Guideline Resource Unit
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Alberta Children's Hospital

Alberta Bone and Marrow Transplant Program:

Pediatric Standard Practice Manual

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Indications

Indications For Allogeneic Blood and Marrow Stem Cell Transplantation

Presented by: Greg Guilcher

Purpose

To facilitate the decision-making process in determining the indication and eligibility for allogeneic hematopoietic cell transplantation (HCT).

Points of Emphasis

Conditions to be considered by the Alberta Blood and Marrow Transplant Program (ABMTP) – Alberta Children's Hospital (ACH):

Donors

- Allogenic donors are selected as per the *Guideline for Criteria of Allogenic Donor Selection*
- Fully matched sibling donors are considered the best option and will be chosen as the first preference based on minimizing risk to recipient and likelihood of achieving a successful outcome.
- Mismatched family and matched and mismatched unrelated donors carry additional risks of graft rejection and treatment-related mortality and will be considered if a matched sibling donor is not available at the discretion of the treating transplant physician. These risks are more applicable to non-malignant disease.
- The transplant physician will consider haplo-identical donors as appropriate donors based on lack of availability of a matched family or unrelated donor (or if appropriate, umbilical cord blood units).
- As haplo-identical techniques have improved in safety and efficacy, the physician may choose a haplo-identical donor as primary preference based on indication, urgency of transplant and available data.

Stem Cell Source

- Stem cell source will be chosen based on the underlying disease and indication for HCT, as supported by the best available evidence. Analysis of local data suggests that peripheral blood stem cells (PBSC) are acceptable for pediatric patients with acute leukemia.
- In the event that a 9/10 donor or related family donor (not sibling donors) is selected, a marrow source will be preferred for malignant diseases or for non-malignant conditions where ATG is being used as serotherapy. Abatacept (in children > 2 years of age) or post-transplant cyclophosphamide should be considered.
- For alemtuzumab based transplants, PBSCs can be used as preferred stem cell source without increased risk of graft-versus-host disease (GVHD) and higher rates of engraftment.
- The final decision is at the discretion of the transplant physician based on available evidence and will be documented.
- All cases will be reviewed by the panel of attending physicians within the pediatric transplant

program.

Conditioning Regimen

- Conditioning regimens will be chosen based on the underlying disease and indication for HCT, as supported by the best available evidence. Reduced toxicity, reduced intensity conditioning (RIC) or nonmyeloablative regimens will be used for non-malignant hematologic conditions considered efficacious to avoid acute and long-term toxicities.
- Clinical trials, if available, will be offered to eligible patients.
    - For patients registered on a clinical trial, all 'clinical trial' procedures and recommendations will be followed.
    - All deviations will be recorded along with the reason for the deviation.
    - Patients may be treated alongside a clinical trial if deemed best practice based on evidence. Such patients will be treated as unregistered patients.
- Consistency in use of regimens is encouraged.
- The indication for allogeneic transplantation continues to increase. As a result:
    - A referral is necessary for any consideration for an allogeneic transplant. Refer to *Pediatric BMT Referral Guideline.*
    - A primary physician will be assigned to each case along with a coordinating nurse.
    - A trainee may be involved in evaluating the referral however, they will work under supervision of the attending physician assigned to the case. The ultimate decision is the responsibility of the attending physician.
    - All cases will be reviewed at the 'work-up meeting'.
    - The primary attending physician assigned to the case (along with the trainee, if applicable) may seek additional opinions from the group of attending transplant physicians.
    - Complex cases may also be discussed in Complex Case Rounds/Tumour Board with referring and multi-disciplinary team members.
    - Final candidacy for transplant and the choice of the conditioning regimen will be made after relevant review, sought opinions and eligibility fulfillment. This is the responsibility of the assigned physician.

Indications for Autologous Blood and Marrow Stem Cell Transplantation

Presented by: Greg Guilcher

Purpose

To facilitate the decision-making process in determining the appropriateness and indication for autologous hematopoietic cell transplantation (HCT).

Points of Emphasis

Conditions to be considered by the pediatric Alberta Blood and Marrow Transplant Program (ABMTP):

Stem Cell Source

- Peripheral blood stem cells (PBSCs) will almost always be prescribed for autologous cellular therapy after high dose chemotherapy. Refer to *Apheresis Procedure Manual* for PBSCs collection procedure.
- A bone marrow source may be used if needed or in addition of PBSCs if additional top-up is necessary based on the discretion of the assigned physician for the case. Refer to *Bone Marrow Harvest Procedure Manual*.

Conditioning Regimen

- Conditioning regimens will be chosen based on the underlying disease and indication for HCT, as supported by the best available evidence. The choice of high-dose chemotherapy and/or radiation therapy is almost always selected to target the specific underlying disease.
    - Clinical trials, if available, will be offered to eligible patients
    - For patients registered on a clinical trial, all 'clinical trial' procedures and recommendations will be followed.
    - All deviations will be recorded along with the reason for the deviation.
    - Patients may be treated alongside a clinical trial if deemed best practice based on evidence. Such patients will be treated as unregistered patients.
- Consistency in use of regimens is encouraged.
- The indications for autologous transplantation continue to increase. As a result:
    - A referral is necessary for any consideration for an autologous transplant refer to *Pediatric BMT Referral Guideline*.
    - A primary physician will be assigned to each case along with a primary nurse.
    - A trainee may be involved in evaluating the referral however they will work under supervision of the attending physician assigned to the case. The ultimate decision will be the responsibility of the attending physician.
    - All cases will be reviewed at the Alberta Children's Hospital (ACH) ABMTP Pediatric Search and Work-Up Meeting.

- The primary attending physician assigned to the case (along with the trainee, if applicable) may seek additional opinions from the group of attending transplant physicians.
- Complex cases may also be discussed in Complex Case Rounds/Tumour Board with referring and multi-disciplinary team members.
- Final candidacy for transplant and the choice of the conditioning regimen will be made after relevant review, sought opinions and eligibility fulfillment. This is the responsibility of the assigned physician.

Management of Complications

Mucositis

Presented by: Greg Guilcher

Summary

Despite continuing evolution of cancer therapy and modalities of treatment, oral mucositis remains as a major morbidity in hematopoietic stem cell transplantation (HSCT). In myeloablative transplant the rate can be as high as 90-100%. Mucositis contributes to toxicity in radiation therapy as well.

Background

There are innumerable studies on mucositis dating back 2-3 decades. Study comparisons are difficult though because researchers use a variety of mucositis scoring systems. Study design variations prevented reproducibility and minimized progress. As well, the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) recognized most mucositis therapies developed from institutional experience rather than from evidence based studies. MASCC/ISOO then created the Mucositis Study Section (MSS) in 1998. In 2000 the MSS under the leadership of Dr. Ed Rubenstein established a panel of experts to develop evidenced based guidelines for oral and GI associated mucositis.

In 2004, Cancer published the "Clinical Practice Guidelines for the Prevention and Treatment of Cancer Therapy-Induced Oral and Gastrointestinal Mucositis." Thirty-six multidisciplinary panellists reviewed literature form 1966-2002. The subtopics involved were terminology, epidemiology, basic oral care and oral care protocols, bland oral rinses, analgesics, cryotherapy, topical anaesthetics, antimicrobial agents, growth factors and cytokines, biologic mucosal protectants, anti-inflammatory agents, complementary and alternative agents, low- energy laser therapy and hemorrhage.

The panelists evaluated the literature based on both level of evidence and grade of recommendation. Draft guidelines were developed using the guideline development method of the American Society of Clinical Oncology. This allowed for two subtypes of guidelines: 1) recommendations and 2) suggestions. The draft guidelines were reviewed in June, 2002 and published in ***Cancer* 2004;100(9 Suppl):2026-2046.** In this paper not many recommendations for treatment or prevention could be made. It did provide a basis for review of future studies.

The panel experts agreed to review the guidelines annually and meet every 3 years to discuss potential changes. The original guidelines were almost immediately out-of-date. Published research on novel targeted agents began to appear. The MASCC/ISOO last updated the guidelines in 2020.

Biologic Basis and Pathogenesis of Mucositis

Injury to the mucosal barrier, both oral and the GI tract, has been described in five phases. The damage occurs quickly and simultaneously in all tissues.

1. Initiation
2. Up-regulation with generation of messengers
3. Signalling and amplification
4. Ulceration with Inflammation
5. Healing

1. Initiation

This phase demonstrates injury to the submucosa tissues by chemotherapy or radiotherapy. There is production of oxidative stress and reactive oxygen species (ROS). Damage to cells, tissues and blood vessels is caused by ROS which are capable of stimulating transcription factors. This is the hallmark of the initiation phase leading to further biologic activities. Studies have shown that mucosal injury can be minimized by agents that block or scavenge oxygen-free radicals.

2. Up-Regulation and Generation of Messengers

ROS causes DNA damage and clonogenic cell death in the epithelial layer. Transcription factor nuclear factor-κB (NF-κB) is activated by radiotherapy or chemotherapy and is able to up- regulate many genes that can elicit a wide variety of tissue responses. This results in the production of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 which leads to tissue injury and apoptosis. The up-regulation of other genes causes expression of adhesion molecules, activation of cyclooxgenase-2 path and consequent angiogenesis.

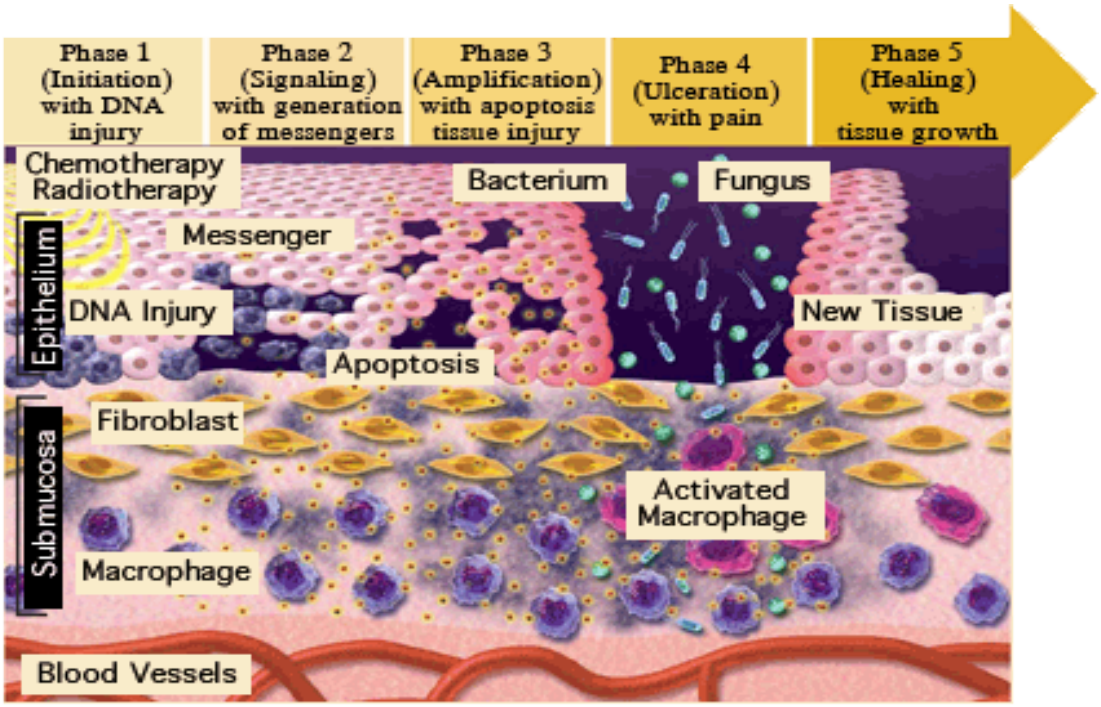
Other pathways may be involved in tissue apoptosis. ROS may activate sphyngomyelinase. Chemotherapy may activate ceramide synthase and the ceramide pathway also induces apoptosis of both submucosal and basal epithelial cells. Fibronectin break-up also occurs. Macrophages are then activated causing metalloproteinases to then cause tissue injury and then causing more TNF-α. There are simultaneous events in all tissues at all levels.

3. Signaling and Amplification

Pro-inflammatory cytokines play an indirect role in amplifying mucosal injury caused by radiation and chemotherapy. The result of mediators released in response to the insult is a series of positive feedback loops that amplify and extend tissue injury. This occurs through the effects of transcription factors and on the ceramide and caspase pathways. The destructive processes are based in the submucosa and basal epithelium therefore the clinical appearance of the mucosa appears normal.

4. **Ulceration**
   This phase is associated with mucositis. The injury and death of the basal epithelial cells result in atrophic changes that cause mucosal deterioration. This phase is the most symptomatic and has an inflammatory infiltrate comprised of polymorphonuclear and round inflammatory cells. The ulcerative mucosa provides a base for bacterial colonization. The bacterial cell wall products penetrate the submucosa resulting in continued production of pro-inflammatory cytokines. During neutropenia the patient is at increased risk of bacteremia and sepsis.

5. **Healing**
   A signal from the extracellular matrix initiates the healing phase of mucositis. The epithelium begins to proliferate and differentiate. The local microbial flora is re-established. In HSCT the healing phase is also marked by recovery of the leukocytes. After healing has occurred the mucosa appears normal but the mucosal environment is still altered and subject to increased risk of further breakdown with subsequent oncolytic therapy.



Foundation of Care

Basic Oral Care

There is no consistent definition of what constitutes basic oral care. A review of the literature showed that different institutions and studies employ a wide spectrum of oral care methods. As a result, there is no guideline for basic oral care related to mucositis prevention or treatment.

Although clear scientific evidence is lacking to define basic oral care guidelines, oral care is important for mucosal health, integrity and function. The purpose of basic oral care is to minimize the impact of oral microbial flora, reduce pain and bleeding, and prevent soft tissue infections that may become systemic. The ability to maintain basic oral hygiene will also minimize the risk of dental complications.

Oral Care Protocols and Patient Care Education
The 2020 guidelines of the MASCC/ISOO suggested that oral care protocols include patient education in an attempt to reduce the severity of mucositis from HSCT (*level of evidence,III;).*

The goal of an oral care protocol is to prevent and manage mucositis with a focus on feasibility, compliance, and patient education about mucositis and oral care. Patients who are educated about mouth care and follow an institutional based oral care protocol are more prepared to manage their symptoms and have improved oral status. Our program recommends the use of chlorhexidine for all patients receiving chemotherapy with a central line in an effort to reduce central line-associated bloodstream infections. Oral bicarbonate may also be used due to safety, despite limited evidence.

Pain Management (including palliative care)
An important component of patient care is pain management. Various combinations of systemic analgesics, individual agents, palliative mixtures of agents, coating agents and topical anesthetics/analgesics have been used.

The 2002 panel guideline recommends patient-controlled analgesia (PCA) with morphine as the treatment of choice for oral mucositis pain in patients undergoing HSCT (level of evidence, I; grade of recommendation, A). There has been little evidence to recommend its use in other patients and settings. Pediatric populations can use PCA efficiently. The 2005 update states that regular oral pain assessment using validated instruments for self-reporting is essential.

Topical preparations that had been used for pain management include viscous lidocaine, benzocaine, milk of magnesia, kaolin, pectin, chlorhexidine, and diphenhydramine. Topical analgesics to be considered include benzydamine and morphine. There is no significant evidence of effectiveness or tolerability of topical agents which have been compounded into mixtures. The lack of evidence prevents the panel from recommending any palliative mixture for therapeutic effect in mucositis. The 2020 update had no new recommendations on the use of topical agents in the HSCT recipient.

High-Dose Chemotherapy with or without TBI plus HSCT: Prevention

Palifermin
The 2020 panel update recommended the use of Keratinocyte growth Factor-1 (Palifermin) in adult autologous HSCT recipients with hematogic malignancies who receive a high dose chemotherapy or total body irradiation. No pediatric recommendation is made.

GM-CSF Mouthwash
The 2020 panel update suggests that GM-CSF mouthwashes not be used for the prevention of oral mucositis in patients undergoing HSCT.

Cryotherapy
The 2020 panel update suggests the use of cryotherapy to prevent oral mucositis in patients receiving high-dose melphalan.

Photobiomodulation (PBM)
PBM requires expensive equipment and specialized training. The panel in 2002 and 2005 was encouraged by the supportive evidence in support of PBM. It was suggested that centers equipped with PBM should use it to reduce the incidence of oral mucositis and associated pain in patients who are receiving high-dose chemotherapy or chemoradiotherapy prior to HSCT (*level of evidence, II; grade of recommendation, B*). PBM promotes wound healing and minimizes pain and inflammation.. PBM appears to have no toxicity and no associated trauma although the equipment is expensive and treatment can be lengthy. The 2020 guidelines state that while the limited data in pediatric patients is encouraging, no guideline can be provided based on existing studies.

Therapies and Associated Supportive Evidence

Acyclovir
The 2002 and 2005 panel recommends that acyclovir and analogues not be used to routinely prevent mucositis (*level of evidence,II; grade of recommendation,B)*. Oral mucositis continues to develop in patients receiving acyclovir prophylaxis suggesting that HSV infection plays little role in causing mucositis. However, refractory or severe mucositis may be complicated by HSV infection.

Topical Mucosal Coating Agents
Recent randomized and controlled studies have shown no difference between sulcrafate rinses and placebo.

Due to lack of efficacy, the 2020 panel recommends against the use of sucralfate for the treatment of radiotherapy-induced oral mucositis; (*level of evidence: II).*

Systemic Analgesia
An important component of patient care is pain management. Various combinations of systemic analgesics, individual agents, palliative mixtures of agents, coating agents and topical anesthetics/analgesics have been used.

The 2002 panel guideline recommends patient-controlled analgesia (PCA) with morphine as the treatment of choice for oral mucositis pain in patients undergoing HSCT (*level of evidence, I; grade of recommendation, A*). There has been little evidence to recommend its use in other patients and

settings. Pediatric populations can use PCA efficiently. The 2005 update states that regular oral pain assessment using validated instruments for self-reporting is essential.

All patients undergoing myoloablative or reduced-toxicity HSCT should have a baseline consultation with the Acute Pain Service during conditioning or close to Day 0.

Systemic Nutritional Supplements

Glutamine is an amino acid essential for cell mitosis. Many studies have examined the effects of glutamine supplementation on the prevention and treatment of mucositis. The results have been conflicting.

In view of the serious side effects the panel suggest against the use of parenteral glutamine.

Mouth Care Protocol for Hematopoietic Stem Cell Transplant Patient

Basic Oral Care

1. All patients to have a pre-admission dental consult. This should be done ideally one month prior to HSCT in order to address any significant oral issues.
2. Start oral care protocols in the outpatient setting if appropriate.
3. Soft toothbrushes to be used and should be replaced every 2 weeks when patient is neutropenic or has active mucositis.
4. Use foam swabs if patient does not have teeth or has trauma with soft toothbrush.

Patient Education

1. Primary caregivers should have comprehensive education prior to initiation of chemotherapy or radiotherapy.
2. Education should include the causes of mucositis, complications (pain, inability to eat, drink or swallow, systemic infections, airway obstruction), the use of oral care protocols and oral assessment scales, and pain management.
3. Ideally this education would start in the outpatient setting in order to encourage good mouth care practice prior to start chemotherapy or radiotherapy. The oral care protocol would be reviewed with patient and primary caregivers on admission for HSCT.
4. CTCAE grading of mucositis will be used.

Oral Care Protocol

1. Initial and ongoing oral assessment using CTCAE grading including patient/caregiver self report and professional exam on a daily basis. Continue until mucosits resolved.
2. Soft toothbrush to be used and replaced every 2 weeks during periods of neutropenia or mucositis.

3. Toothbrush to be rinsed thoroughly after use with water and allowed to air dry.
4. Teeth to be brushed a minimum of twice a day but ideally after each meal. Each brushing should be 90 seconds.
5. The use of a fluoridated toothpaste is encouraged.
6. If child does not have teeth, swab the oral cavity four times daily with Chlorhexidine 0.12 % solution.
7. Chlorhexidine 0.12% solution (10-15 mls) is encouraged to be swished and expectorated four times daily ideally after meals or snacks.
8. If Chlorhexidine is not tolerated, it may be diluted with water or replaced with Club Soda mouth rinses. It is important that the mouth is kept moist with whatever solution is tolerated.
9. Use of Akabutus mouth wash is encouraged. Swish and spit of an age appropriate volume is recommended, however if the child swallows the fluid in small amounts, there is no associated harm.
10. Fluconazole (3-5 mg/kg/day PO or IV) should be used for fungal prophylaxis.
11. Valacyclovir/acyclovir prophylaxis will be used as per separate guidelines.
12. Eucerin lip cream (or equivalent) should be applied as needed to keep lips moist.

Oral Cryotherapy

1. Suggested for patients receiving high dose melphalan (140 mg/m^2).
2. Patient to place ice chips in mouth 5 minutes before chemotherapy starts and to continue this procedure for 30 minutes minimum or until chemotherapy has been infused.

Pain Management

1. Acute Pain Service (APS) for the use of Patient Controlled Analgesia (PCA) will be consulted on all patients admitted for HSCT (except nonmyeloablative conditioning).
2. Regular oral pain assessment using age appropriate assessment scales. Reference the most current Commitment to Comfort materials.
3. Oral morphine may be offered for initial analgesia in cases of mild mucositis if patient able to tolerate oral medications.
4. PCA analgesia will be instituted if patient unable to tolerate oral analgesia.
5. PCA-Morphine is the narcotic of choice initially however if morphine is not tolerated or effective then PCA-Fentanyl or other narcotic agents can be used.
6. Once mucositis has improved, efforts will be made to transition patient to oral analgesia.

Management of Severe Mucositis (Grade 3-4)

1. Continue with oral care protocol and pain management as previously outlined.
2. A toothette may be substituted for the toothbrush if this is more comfortable.
3. If brushing causes further tissue trauma or pain, plaque control can be obtained with regular use of Chlorhexidine mouth rinses.
4. Ensure patient has oxygen saturation monitoring (this should be in place if already using PCA analgesia).

5. Ensure adequate suctioning devices available at bedside.
6. Instruct patient or caregiver how to use suctioning devices.
7. Ensure patient is adequately hydrated. Replacement of suctioning losses may be indicated.
8. Ensure that nutritional demands are met. Total parenteral nutrition will be required.
9. If patient is unable to maintain or clear an airway easily (copious or thick secretions which are difficult to suction, inability to open mouth or cough), ICU should be consulted re airway assessment and need for transfer to ICU.
10. If HSV mucositis is suspected, consult Infectious Disease service and follow guidelines "Prophylaxis and Treatment of HSV Infections."

Oral Mucositis: Assessment Scale

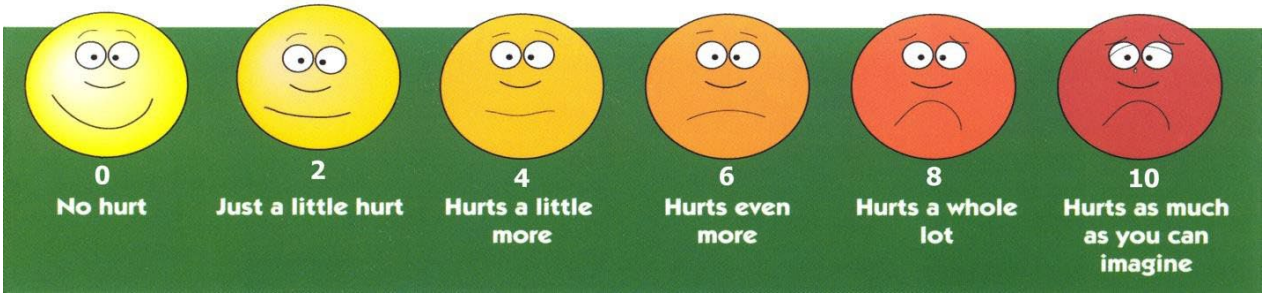
FLACC (3 months – 4 years)

CATEGORIES	0	1	2
FACE	no particular expression or smile	occasional grimace or frown, withdrawn, disinterested	frequent to constant quivering chin, clenched jaw
LEGS	normal position or relaxed	uneasy, restless, tense	kicking or legs drawn up
ACTIVITY	lying quietly, normal position, moves easily	squirming, shifting back and forth, tense	arched rigid or jerking
CRY	no cry (awake or asleep)	moans or whimpers, occasional complaint	crying steadily, screams or sobs, frequent complains
CONSOLABILITY	content relaxed	reassured by occasional touching, hugging or being talked to, distractible	difficult to console or comfort

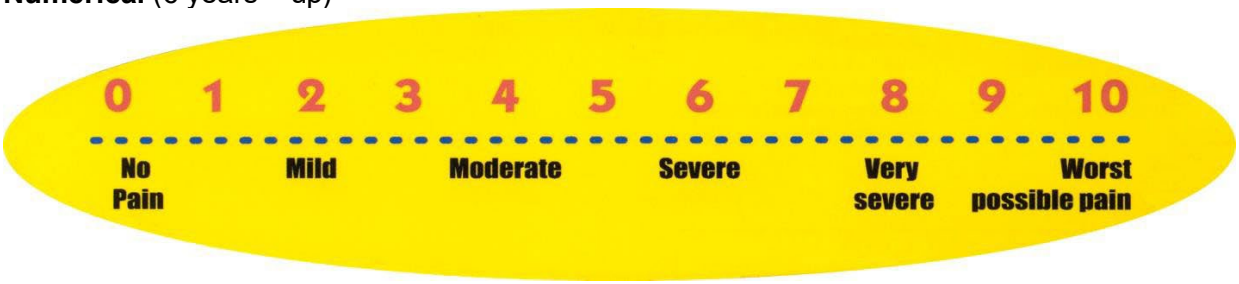
Each of the 5 categories (F) face, (L) Legs, (A) Activity, (C) Cry, (C) Consolability is scored from 0 – 2, which results in a total score between 0 – 10.

taken from Willis, Martha H.W.; Merkel, Sandra I.; Voepel-Lewis, Terri; Malviya, Shobha. (2003). "FLACC Behavioral Pain Assessment Scale: A Comparison with the Child's Self-Report. " Pediatric Nursing 29(3): 195-198.

Faces (3 – 7 years)

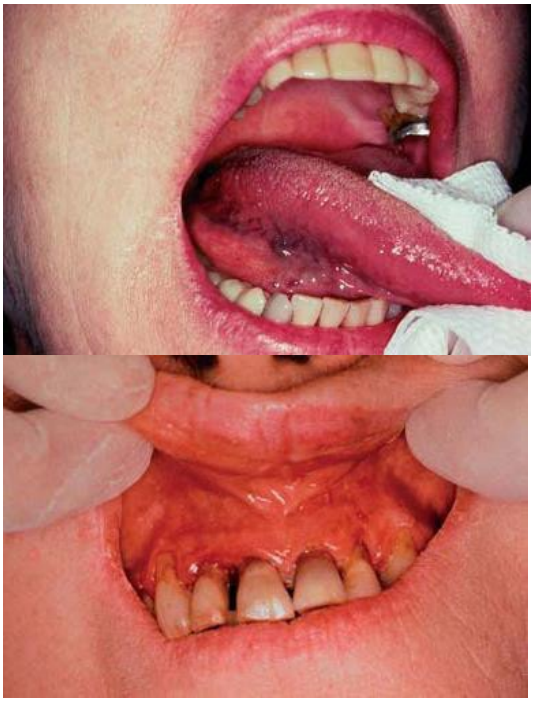


Numerical (6 years + up)



Clinical Assessment Guide

Grade 0 – No ulceration, no erythema and no oral pain.



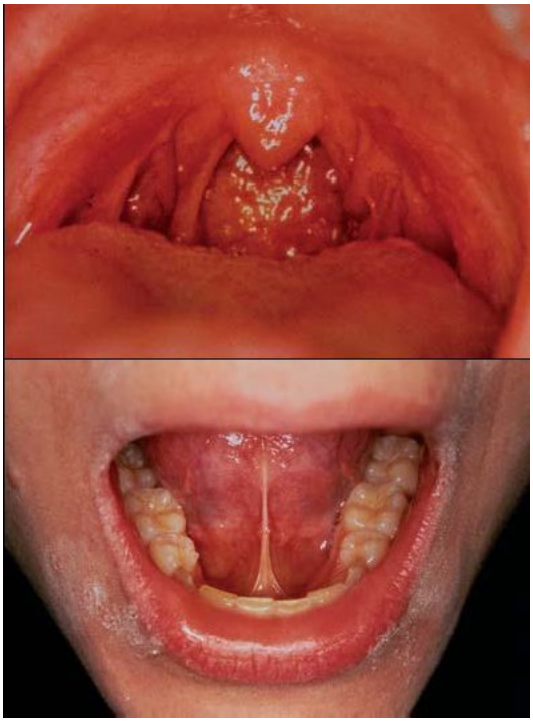
Right lateral and ventral of the tongue.

- no pain, still eating solids
- it is useful to use gauze when examining the tongue, so you can gently move the tongue from side to side.

Upper Lip

- no soreness and can eat solids
- no ulcers are present

Grade 1 – Erythema of the mucosa, minimal symptoms with normal diet



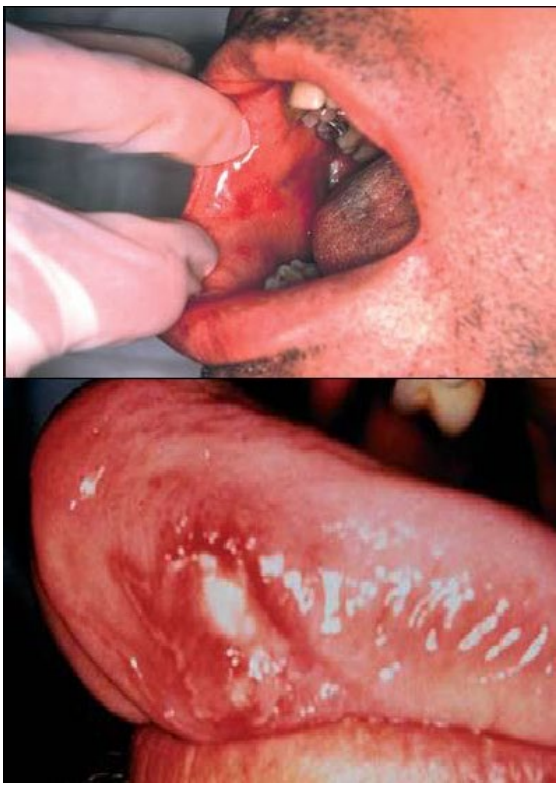
Soft Palate

- erythema and soreness
- no ulcers are present
- able to eat solids

Floor of the mouth

- mild erythema and soreness
- no ulcers present, saliva is normal
- liquid diet due to mouth pain
- the floor of the mouth is the best place for assessing saliva

Grade 2 - Patchy ulcerations or pseudomembranes; symptomatic but can eat and swallow modified diet



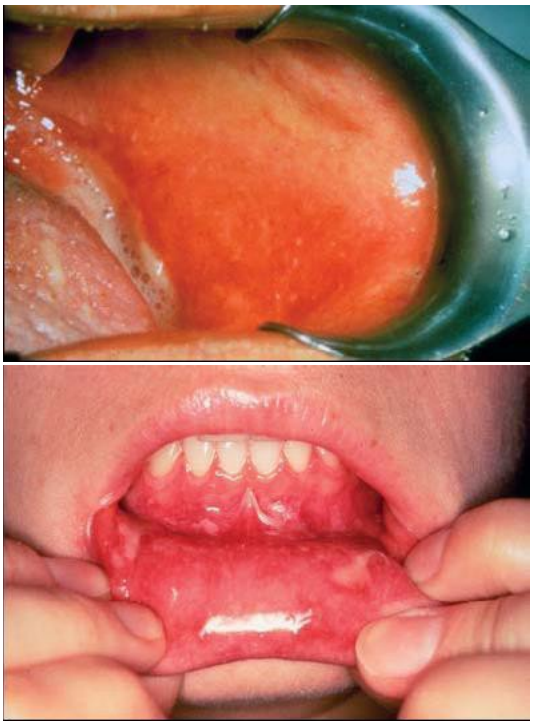
Right cheek

- can eat solids
- on po analgesics due to mouth pain
- ulceration and erythema
- tongue is parched/ dry looking due to lack of saliva

Left lateral and ventral of the tongue

- pain and is taking po medication
- ulceration is present
- patient can eat solids

Grade 3 – Confluent ulcerations or pseudomembranes; bleeding with minor trauma. Symptomatic and unable to adequately aliment or hydrate orally



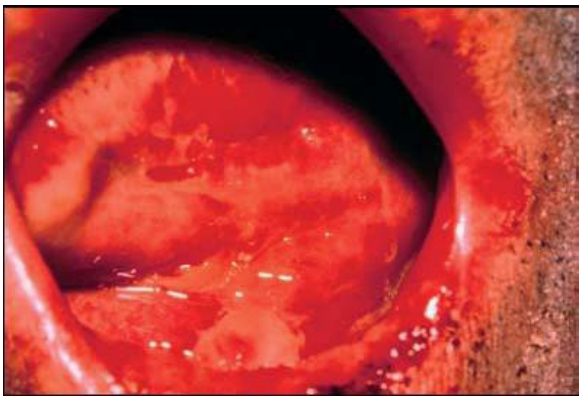
Left cheek

- some pain and discomfort
- liquid diet due to mouth pain
- ulceration and saliva is starting to thicken

Lower lip

- some pain
- liquid diet due to mouth pain
- erythema and ulceration is present

Grade 4 – Tissue necrosis; significant spontaneous bleeding; life threatening consequences
Symptoms associated with life-threatening consequences



Tip of the tongue

- erythema and ulcerations present
- the muscle under the tongue has been completely obliterated
- saliva is normal
- some spontaneous bleeding

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Related Documents

Alberta Health Services (2018) Provincial Clinical Knowledge Topic: Mouth Care to Prevent and Treat Mucositis, Pediatric-Inpatient. (V1). Retrieved from Clinical Knowledge Topics (A- Z) | Insite (albertahealthservices.ca)

Prophylaxis, Prevention and Treatment of Herpes Simplex Virus and Varicella Zoster Virus Infection in the Cellular Therapy Product Recipient

Presented by: Geoff Cuvelier and Carsten Kruger

Purpose

To provide guidance on the prophylaxis, prevention, and management of Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) infection in cellular therapy product (CTP) recipients (includes autologous and allogeneic hematopoietic cell transplant and CAR-T cell therapy).

Background

- Primary HSV-1 infections usually occur in young children < 5 years of age. Immunocompetent individuals are usually either asymptomatic or present clinically with herpes labialis (cold sores).
- Seroprevalence (the development of HSV-1 IgG antibodies) is 90% by the fifth decade of life.
- Throughout life, some immunocompetent individuals will have periodic reactivations of the HSV-1 virus, usually presenting as recurrent herpes labialis. Similar can happen in immunocompromised patients.
- Immunocompromised individuals (particularly those with ongoing T- and NK-cell lymphopenia, patients who received serotherapy with alemtuzumab or ATG, patients on calcineurin inhibitors and high dose systemic corticosteroids, patients with concurrent acute and/or chronic GVHD, particularly those with oral chronic GVHD and on systemic steroids +/- prolonged second and greater lines of GVHD therapy, umbilical cord blood transplants and ex-vivo T cell depleted transplants including alpha-beta TCR / CD19 B cell depleted haploidentical PBSC transplants) can also have HSV-1 reactivations presenting as single or multiple oropharyngeal ulcerative lesions, esophagitis, and potentially disseminated disease (viremia, hepatitis, encephalomeningitis, pneumonitis and the triggering of post-transplant hemophagocytic lymphohistiocytosis).
- HSV-2 antibodies begin to appear in puberty and generally correlate with past sexual activity.
- In CTP recipients, HSV infections (usually occurring as HSV-1 reactivations from a previous primary infection, although new primary infections can also occur) tend to occur early in the neutropenic / pre-engraftment phase and sometimes continue after engraftment and beyond Day +100. The risk is highest in the first month after transplant, particularly when mucositis is present.
- Mucosal damage from the conditioning regimen (mucositis) increases the risk of HSV-1 reactivations. Mucositis from the conditioning regimen and HSV-1 infection in the oropharynx can co-exist and may be difficult to differentiate on appearance alone. A high index of suspicion for HSV-1 infection in the oropharynx is needed and swabbing for HSV PCR of mouth lesions is highly recommended when mucositis exists.
- There is no evidence that HSV-1 or HSV-2 is transmitted from the donor cellular therapy product (bone marrow or peripheral blood stem cells).

- Primary VZV infections in immunocompetent individuals tend to occur in seronegative young children as chicken pox (prodrome of fever, headache, malaise 10-21 days after exposure to the index case, with the development of crops of vesicular lesions that can be widespread throughout the skin).
- In Alberta, most children are eligible to receive two varicella vaccinations (live, attenuated vaccination) as part of the Measles-Mumps-Rubella-Varicella (MMRV) Provincial Immunization program at 12-months and 18-months of age. Catch up programs with the Varicella vaccine are also available for those who missed immunizations.
- Risk of acquiring primary VZV infection (chickenpox) is directly related to titres of VZV IgG, with the risk being greatest (to lowest) in individuals: (1) who are VZV seronegative; (2) who received only 1 varicella vaccination (risk is 7.2% over a 10-year period); (3) who are >5 years from their varicella vaccinations (still low risk); and (4) who had a previous case of true wild-type VZV infection (i.e., chickenpox) (almost no risk of a second primary VZV infection).
- Although many children have been immunized against VZV (and have seroconverted with a positive VZV IgG), it is important to remember that some children remain unvaccinated due to vaccine hesitancy. Furthermore, although breakthrough VZV infections can still occur even in fully vaccinated children (i.e., two doses), this is rare given the varicella vaccination remains very effective. Primary wild-type chicken pox disease therefore still occurs in Alberta, primarily from unvaccinated individuals.
- Individuals with a previous wild-type (non-vaccine) VZV infection are at risk of reactivation of the virus from the dorsal root ganglion. This manifests as herpes zoster (HZ) (also known as shingles). Crops of vesicles (often with painful neuropathic pain and risk of secondary infection) reactivate down one or more dermatomes. Risk of herpes zoster is a function of existing VZV-specific T-cell populations, as opposed to titres of VZV IgG (Laing et al *J Infect Disease* 2018: Suppl 2: S68-S74). Even when vesicles have crusted over and have disappeared, post-herpetic neuralgia remains a major cause of patient morbidity following HZ. HZ incidence rates tend to increase as individuals age (risk is greatest >50 years of age) and is less common in people <18 years of age. A second vaccination (Shingrix®) is available throughout Canada to prevent HZ reactivation for individuals generally >50 years but is not given to children.
- A less intense varicella rash with the vaccine-strain of varicella will occur in 170-183 cases per million varicella vaccinations administered in immunocompetent individuals.
- To date, only a small number of HZ cases in the literature exist where it was proven that the HZ was VZV vaccine related (OKA strain). In a recent review, between 1995-2017 in the USA, there were only 117 cases of HZ, and 39 cases of disseminated VZV due to the Varicella vaccine strain reported as part of post-marketing surveillance (Woodward et al. *Open Forum Infectious Disease* 2019: 6(8)). Given the very high number of people worldwide who have received the varicella vaccine to date (hundreds of millions), this suggests the Varicella vaccine has potential but likely only rarely causes later HZ or disseminated VZV. A few cases of vaccine-associated disseminated VZV and HZ have been reported in both primary immune deficiency patients and cellular therapy patients who received the VZV vaccination, which is why the vaccine is generally contraindicated

in these scenarios until cellular immunity has improved after transplant (usually ≥24 months). Overall, the risk that the VZV vaccination will result in either disseminated VZV or HZ appears low. Data is now most consistent with the VZV vaccine reducing the incidence of HZ later in life.

- Like HSV, there is no evidence that VZV is transmitted from the donor cellular therapy product (bone marrow or peripheral blood stem cells).
- CTP patients who are immunocompromised are at risk for both: (1) primary VZV (as in the situation where a CTP patient is exposed to someone with active wild-type chickenpox, and either the recipient was not previously seropositive, or they lost protective IgG immunity to VZV after transplant); and (2) reactivation of VZV as HZ due to abrogation of VZV-specific T cell populations. VZV infection in immunocompromised CTP patients can be a potentially life-threatening infection that includes multi-dermatomal HZ (and risk of post-herpetic neuralgia and secondary bacterial infection), VZV viremia, HZ ophthalmicus, hepatitis, myocarditis, pneumonitis, meningoencephalitis with risk of stroke, and the triggering of a hemophagocytic lymphohistiocytosis post-transplant.
- The risk of developing disseminated vaccine-related VZV or HZ in an immunocompromised CTP patient who previously received varicella vaccinations but who never experienced a primary VZV infection is unknown. Given the paucity of cases in the literature, while this is a potential risk, the risk is suspected to be very low.
- Risk of VZV reactivation is highest 2-12 months post-cellular therapy, although VZV reactivation and infection have been described 4 or more years after cellular therapy.

Determination of HSV and VZV Serostatus Before Allogeneic and Autologous Hematopoietic Cell Transplant and CAR-T cell Therapy

- All transplant recipients should be tested for IgG antibody responses against HSV-1, HSV-2, and VZV before both autologous AND allogeneic CTP.
- Testing of the donor for HSV and VZV IgG does not play any role in deciding monitoring and prophylaxis approaches (i.e. prescribing either acyclovir or valacyclovir prophylaxis), since HSV and VZV in the CTP recipient are usually reactivations (or primary infections) and are not transmitted with the cellular therapy product. Testing of the donor is often still performed, however, and may help to determine donor T cell immune response after transplant against both these viruses (potentially better in donors who are seropositive).
- For transplant recipients with a HSV and/or VZV IgG seropositive result, a single positive test performed any time before conditioning begins should be considered as being positive (i.e. recipient is seropositive), unless there are other circumstances that may have resulted in a false positive test (e.g., use of IVIg in the previous 6-12 months, infant in the first 6- months of life where HSV or VZV IgG positivity may reflect transplacental maternal antibody). In these situations, repeating the HSV-1, HSV-2, and VZV IgG within 30-days of the start of conditioning may be warranted. In situations where repeat testing will not be helpful (e.g., patient who remains on regular IVIg up to the point of transplant), then assume the patient is HSV and/or VZV

seropositive, with some exceptions. Exceptions may include young infants (0-6 months of age) who may still have maternal antibody present and/or may be receiving regular IVIg (e.g., patient with severe combined immunodeficiency identified by newborn screening who is on regular IVIg up to transplant). In such situations, physicians may make case by case decisions about the likelihood of being truly seropositive against HSV and/or VZV, which is likely very low, and the patient may be considered seronegative (thus impacting their prophylaxis approach).

- Pediatric Infectious Disease consultation for all recipients of cellular therapy products is routine, and Pediatric ID can help with guidance around interpretation of HSV and VZV IgG positivity in the context of young infants who may have transplacental IgG transfer and proximity to IVIg use. This can help guide decisions around the use of (val)acyclovir prophylaxis.
- Patients with a previous HSV and/or VZV IgG negative result drawn outside of the 30-day window before the start of conditioning, must have the test repeated and results confirmed to be negative within 30-days of the start of conditioning to rule out seroconversion in the intervening time-period.
- It is important for cellular therapy physicians and BMT nurses to ask whether a VZV and/or HSV-1 IgG seropositive recipient of a cellular therapy product either: (1) previously received the varicella vaccination; or (2) received IVIg in the previous 6-12 months, which contains VZV and HSV-1 IgG that may persist between 6-11 months even once IVIg is discontinued (depending upon the dose of IVIg, some patients may still be VZV or HSV IgG positive up to 11 months after the last dose); or (3) is an infant who has passively acquired the VZV and/or HSV-1 IgG through maternal transplacental transfer (usually in the first 6 months of life, IgG against VZV and/or HSV will remain detectable); or (4) was the result of a primary wild-type VZV infection (chickenpox) or HSV-1 (e.g., cold sores) before transplant. In one study of HZ infection in children receiving allogeneic hematopoietic cell transplant, most (86.2%) had a known history of prior wild-type VZV infection (i.e. chickenpox) before transplant, with a history of chickenpox before transplant being one of the most significant risk factors for HZ on multivariable analysis (OR: 3.695). This suggests that primary VZV infection before transplant (as opposed to being seropositive from the vaccine) represents a higher risk scenario for the development of HZ after transplant (Arici et al *Pediatric Transplant* 2024: 28:e14819).
- If a patient's HSV-1, HSV-2, and VZV serostatus was positive before CAR-T cell therapy (e.g., as part of the work up before hematopoietic cell transplant), repeating the testing before CAR-T cell therapy is not necessary, unless there were alternative reasons to be positive (e.g., IVIg use). If a patient's HSV-1, HSV-2, and VZV serostatus was negative previously, then repeating IgG against HSV-1, HSV-2, and/or VZV should be performed within 30 days of CAR-T cell infusion.

Prophylaxis against HSV and VZV with Acyclovir or Valacyclovir after Cellular Therapy

- The prophylactic use of (val)acyclovir after transplant reduces the risk of early HSV reactivation and VZV infection / reactivation with HZ and disseminated VZV disease in seropositive patients.

- Approximately 80% of HSV-1 seropositive patients would reactivate HSV in the early post-transplant period in the absence of anti-viral prophylaxis. It is widely accepted that prophylaxis with either acyclovir or valacyclovir for the prevention of early HSV infection in HSV seropositive individuals undergoing both autologous and allogeneic hematopoietic cell therapy is effective and generally safe, reducing the incidence of HSV infection to <5%. Usually this entails starting (val)acyclovir on day 0 and continuing until day+30, or at least until evidence of engraftment, healing of mucositis, and discharge from hospital, whichever occurs earlier. Some patients may benefit from longer antiviral prophylaxis to prevent HSV infection (see below).
- By comparison, HSV IgG seronegative recipients do not require (val)acyclovir prophylaxis specifically to prevent HSV infection.
- The HSV serostatus of the donor does not impact the decision to start (val)acyclovir prophylaxis.
- Prolonged (val)acyclovir prophylaxis after cellular therapy (1-year or greater), and usually in the context of allogeneic hematopoietic cell transplant, is considered primarily to prevent herpes zoster reactivation in VZV seropositive recipients (either as shingles, or as a disseminated VZV infection in severely immunocompromised recipients). Risk of herpes zoster is primarily related to VZV specific T-cell immunity in the recipient, which may be lost as part of the cell mediated immunodeficiency state after transplant. Other inter-related risk factors for herpes zoster reactivation include graft-versus-host disease, delayed immune reconstitution, need for immunoglobulin replacement, use of serotherapy in the conditioning regimen, use of total body irradiation, and recipient age >10 years after transplant (de Berringer et al. Cancer Reports, 2024). (Val)acyclovir prophylaxis may also prevent primary VZV infection in susceptible individuals who are exposed to an individual with VZV (e.g., transplant recipients who are VZV seronegative or who have lost humoral immunity / VZV IgG against VZV after transplant), although this is usually considered a secondary intent of prophylaxis.
- The VZV serostatus of the donor does not impact the decision to start (val)acyclovir prophylaxis.
- The risk of VZV reactivation as herpes zoster in children receiving CTP may be different compared to adults. Studies of VZV prophylaxis specifically in children are all retrospective, single centre, do not generally differentiate between seropositivity due to varicella vaccination compared to primary VZV infection, and are of lower quality evidence. Randomized controlled studies specifically in Pediatric CTP recipients that help to determine the optimal prophylaxis agent, dose, duration, and relative efficacy of prophylaxis in VZV seropositive patients due to either previous varicella vaccination (which appears to be lower risk) compared to wild-type infection (which appears to be higher risk) are lacking.
- Prophylactic strategies with (val)acyclovir to prevent VZV are controversial and varied. Not all Pediatric centres approach this similarly, in terms of antiviral agent used (or not used), dose, and duration. Current ASBMT (Tomblyn et al 2009) and European Blood and Marrow Transplant (Ifversen et al, 2021) recommend either oral acyclovir or valacyclovir prophylaxis until 1-year post transplant in all VZV seropositive recipients of allogeneic HCT, although neither differentiate those who are VZV seropositive due to previous wild-type VZV infection

(chickenpox) versus those who are seropositive due to vaccination. Some Pediatric centres do not routinely prescribe prophylaxis with (val)acyclovir to prevent VZV, whereas others routinely provide prophylaxis to all VZV seropositive patients until 1-year (or greater) post-transplant.

- In autologous HCT patients, long-term prophylaxis with (val)acyclovir past day +30 to prevent VZV is generally not indicated, regardless of VZV serostatus. Prophylaxis in autologous HCT is intended more to prevent HSV in the early post-transplant period. In autologous HCT patients, (val)acyclovir can be discontinued on day +30 or upon neutrophil engraftment and healing of mucositis, whichever occurs first. One recent retrospective Pediatric-specific study (Kang et al, BBMT, 2020), however, showed that the 2-year cumulative incidence of VZV infection after autologous stem cell transplant was 14% in the absence of prolonged VZV prophylaxis. This risk of VZV infection was greatest in older autologous transplant recipients (HR 2.88 if ≥5 years versus <5 years, p=0.008), with the highest rate in patients 15-19 years of age (2-year cumulative incidence 28% versus 10% age 0-4 years, p=0.03), suggesting that prolonged VZV prophylaxis to 1-year post-transplant may be considered in older autologous transplant recipients as well. This would be more consistent with 2009 ASBMT guidelines (CII level of evidence for autologous recipients) (Tomblyn et al, 2009, BBMT). Physicians may make this decision to provide VZV prophylaxis for VZV seropositive autologous transplant recipients on a case-by-case basis.
- For allogeneic HCT recipients, the following guidelines attempt to balance the risk of HSV and VZV infection/reactivation and potential benefits of (val)acyclovir prophylaxis with avoidance of antiviral prophylaxis medications that may contribute to toxicity (e.g., renal dysfunction, nausea, rash), emergence of HSV / VZV antiviral resistance, along with the additional burden of prolonged oral medication administration in Pediatric patients.
- It is important to recognize that in any situation (i.e., regardless of serostatus and the use of prophylaxis), HSV and/or VZV clinical infection can still occur after transplant, so a high index of suspicion and appropriate investigation for HSV / VZV disease is always required.
- BMT physicians should document in their CTP / transplant admission history and physical examination note their reasons for or against prescribing (val)acyclovir prophylaxis and the expected duration, acknowledging that there may be variation in prophylaxis patterns between physicians.
- Use the following **PROPHYLAXIS TABLE AND GUIDELINES** as general principles for allogeneic transplant recipients and CAR-T cell patients around HSV and VZV prevention and exposures:

Recipient HSV IgG	Recipient VZV IgG	Guideline
NEGATIVE	NEGATIVE	- Do not start (val)acyclovir prophylaxis after HCT. - At risk of acquiring primary HSV and VZV infection if exposed. Avoid contact with anyone with active VZV (chickenpox) as best possible and contact transplant team if exposed to someone with VZV for VarIg. - Consider immunizing VZV-seronegative close contacts with varicella vaccination as far in advance of the transplant as is possible, and at least 4 weeks before transplant. - Recommend varicella vaccinations post-transplant at appropriate time (≥24 months post-transplant) (see immunization guideline).
NEGATIVE	POSITIVE and result is due to a confirmed history of receiving the Varicella vaccination and NOT wild type VZV chickenpox infection	- As the risk of vaccine-strain VZV reactivation after varicella vaccination is believed to be significantly less compared to wild-type VZV infection, it is suggested to not start (val)acyclovir prophylaxis after HCT. - Since data specifically in CTP patients is not entirely clear on this risk however, physicians may still decide to start at day +30 and continue (val)acyclovir prophylaxis to 1-year post-transplant as if the patient were seropositive for VZV due to a wild-type VZV infection, on a case-by-case basis. - Recipient is at risk of acquiring primary VZV infection if exposed. Avoid contact with anyone with active VZV (chickenpox) as best possible and contact transplant team if exposed to someone with VZV for VarIg. - Consider immunizing VZV-seronegative close contacts with varicella vaccination as far in advance of the transplant as is possible, and at least 4 weeks before transplant. - Recommend varicella vaccinations post-transplant at appropriate time (≥24 months post-transplant) (see immunization guideline).

Recipient HSV IgG	Recipient VZV IgG	Guideline
NEGATIVE	NEGATIVE	- Do not start (val)acyclovir prophylaxis after HCT. - At risk of acquiring primary HSV and VZV infection if exposed. Avoid contact with anyone with active VZV (chickenpox) as best possible and contact transplant team if exposed to someone with VZV for VarIg. - Consider immunizing VZV-seronegative close contacts with varicella vaccination as far in advance of the transplant as is possible, and at least 4 weeks before transplant. - Recommend varicella vaccinations post-transplant at appropriate time (≥24 months post-transplant) (see immunization guideline).
NEGATIVE	POSITIVE and result is due to a confirmed history of receiving the Varicella vaccination and NOT wild type VZV chickenpox infection	- As the risk of vaccine-strain VZV reactivation after varicella vaccination is believed to be significantly less compared to wild-type VZV infection, it is suggested to not start (val)acyclovir prophylaxis after HCT. - Since data specifically in CTP patients is not entirely clear on this risk however, physicians may still decide to start at day +30 and continue (val)acyclovir prophylaxis to 1-year post-transplant as if the patient were seropositive for VZV due to a wild-type VZV infection, on a case-by-case basis. - Recipient is at risk of acquiring primary VZV infection if exposed. Avoid contact with anyone with active VZV (chickenpox) as best possible and contact transplant team if exposed to someone with VZV for VarIg. - Consider immunizing VZV-seronegative close contacts with varicella vaccination as far in advance of the transplant as is possible, and at least 4 weeks before transplant. - Recommend varicella vaccinations post-transplant at appropriate time (≥24 months post-transplant) (see immunization guideline).

Recipient HSV IgG	Recipient VZV IgG	Guideline
POSITIVE and result is due to history of previous primary HSV disease (or if uncertain about previous HSV)	POSITIVE and result is due to a confirmed past history of receiving the Varicella vaccination and NOT wild type VZV chickenpox infection	- Start IV acyclovir or oral valacyclovir on day 0 and continue until day +30, or until neutrophil engraftment and complete healing of oropharyngeal mucositis occurs, whichever happens first. Anti-viral prophylaxis may be discontinued after this, with consideration to potential indications to extend prophylaxis (see below). - As the risk of VZV reactivation after varicella vaccination is likely less compared to wild-type VZV infection, but since data specifically in CTP patients is not entirely clear on this risk, physicians may or may not decide to continue (val)acyclovir prophylaxis to 1-year post-transplant as if the patient was seropositive for VZV, on a case-by-case basis. - Recipient is at risk of acquiring primary VZV infection if exposed. Avoid contact with anyone with active VZV (chickenpox) as best possible and contact transplant team if exposed to someone with VZV for VarIg. - Consider immunizing VZV-seronegative close contacts with varicella vaccination as far in advance of the transplant as is possible, and at least 4 weeks before transplant. - Recommend varicella vaccinations post-transplant at appropriate time (≥24 months post-transplant) (see immunization guideline).
NEGATIVE	POSITIVE and result is due to past history with wild type chicken pox infection (and not because of Varicella vaccination) or vaccination status / previous chickenpox infection is uncertain / unknown.	- Prophylaxis with (val)acyclovir starting on day +30 and until at least 1-year post-transplant. - At risk of acquiring primary VZV infection if exposed. Avoid contact with anyone with active VZV (chickenpox) as best possible and contact transplant team if exposed to someone with VZV for VarIg. - Recommend varicella vaccinations post-transplant at appropriate time (≥24 months post-transplant) (see immunization guideline).

Recipient HSV IgG	Recipient VZV IgG	Guideline
POSITIVE but result is likely because of maternal transplacental passage of HSV IgG (infants <6 months)	Negative	- Suggest to not start (val)acyclovir prophylaxis after HCT, although physicians may decide to make individual case by case decisions to start (val)acyclovir prophylaxis until day +30 as if the recipient is truly seropositive for HSV due to a past infection. - At risk of acquiring primary VZV infection if exposed. Avoid contact with anyone with active VZV (chickenpox) as best possible and contact transplant team if exposed to someone with VZV for VarIg. - Consider immunizing VZV-seronegative close contacts with varicella vaccination as far in advance of the transplant as is possible, and at least 4 weeks before transplant. - Recommend varicella vaccinations post-transplant at appropriate time (≥24 months post-transplant) (see immunization guideline).
POSITIVE but result is likely because of maternal transplacental passage of HSV IgG (infants <6 months)	POSITIVE but result is likely due to maternal transplacental passage of VZV IgG (infants <6 months)	- Suggest to not start (val)acyclovir prophylaxis after HCT, although physicians may decide to make individual case by case decisions to start (val)acyclovir prophylaxis until 1-year post-transplant as if the recipient is truly seropositive for both HSV and VZV due to past infections. - At risk of acquiring primary VZV infection if exposed. Avoid contact with anyone with active VZV (chickenpox) as best possible and contact transplant team if exposed to someone with VZV for VarIg. - Consider immunizing VZV-seronegative close contacts with varicella vaccination as far in advance of the transplant as is possible, and at least 4 weeks before transplant. - Recommend varicella vaccinations post-transplant at appropriate time (≥24 months post-transplant) (see immunization guideline).

Recipient HSV IgG	Recipient VZV IgG	Guideline
POSITIVE but result is likely because of IVIg exposure in the previous 6-months before testing.	POSITIVE but result is likely because of IVIg exposure in the previous 6- months before testing.	- Consider repeating HSV and VZV serologies within 30 days of the transplant, if the patient can come off IVIg for at least 6-months before transplant. If repeat serology comes back negative for both, (val)acyclovir prophylaxis can be avoided. If one or both come back positive, provide prophylaxis accordingly. - If the patient remains on IVIg within 6-months before transplant, conservatively assume the patient is seropositive for both HSV and VZV and provide prophylaxis with (val)acyclovir until 1-year post-transplant. Exceptions to this may be made, with physicians able to make case by case decisions such as when the patient is a young infant (0-6 months where maternal transplacental passage is also likely as opposed to primary infection); or SCIDs patients receiving regular IVIg who do not have a known history of HSV or VZV disease. In these situations, physicians may make decisions to prescribe prophylaxis or not on a case-by-case basis.

Acyclovir and Valacyclovir Prophylaxis Doses

- Valacyclovir has better oral bioavailability with similar safety profile comparted to oral acyclovir, therefore allowing simpler dosing interval, consequently improving compliance and possibly efficacy. Therefore, whenever possible, oral valacyclovir should be used for HSV and VZV prophylaxis if the patient is able to take oral medications. Otherwise, intravenous acyclovir is also acceptable. These doses may be used at any point post- transplant for HSV / VZV prophylaxis.

- Valacyclovir Dosing:
  - Less than 12 kg: 20 mg/kg/dose PO BID (50 mg/mL suspension with 21-day stability is available)
  - 12 to 39.9 kg: 250 mg PO BID
  - 40 kg or greater: 500 mg PO BID

- Acyclovir Dosing:
  - Less than 40 kg: 250 mg/m^2/dose IV q8hours
  - 40kg or greater: 250 mg/m^2/dose IV q12hours or 5mg/kg/dose IV q12 hourly

Guidelines for Extending HSV or VZV Prophylaxis

- Some patients may experience HSV stomatitis (or other HSV related disease, either primary or recurrent) after day +30.
- VZV infection / reactivation after transplant is also noted to occur past 1-year post- transplant, particularly when prophylaxis ends and in patients with graft-versus-host disease.
- Some recommend that if starting VZV prophylaxis, not to discontinue this prophylaxis until 3- to 6-months after fully discontinuing immunosuppression, even if >1-year post- transplant.
- Some seropositive patients may potentially benefit from prolonged valacyclovir prophylaxis for either (or both) HSV and VZV infection / reactivation. Physicians may make a case-by-case decision and should record this decision in the patient medical record. As a guideline, extended prophylaxis is generally recommended in:
    1. Patients with breakthrough HSV infections despite receiving (val)acyclovir prophylaxis, or patients who develop new HSV infections after prophylaxis is discontinued. The exact duration of extended prophylaxis in these situations is unknown, but generally suggested until 1-year post-transplant.
    2. Patients with oral graft-versus-host disease.
    3. Patients with acute graft-versus-host disease who are on >1 mg/kg/day prednisone for at least 4-weeks, or patients with steroid dependent / steroid refractory acute GVHD, particularly those requiring second line acute GVHD therapies (e.g. ruxolitinib).
    4. Patients with chronic graft-versus-host disease, particularly those with NIH moderate-severe and who require prolonged steroids and other second line immunosuppressant medications (e.g., ruxolitinib, belumosudil).
    5. Patients who received serotherapy (rabbit ATG, alemtuzumab) and who remain with prolonged CD4 T-cell lymphopenia <0.2 x 10e9/L (200 cells/uL).
    6. Patients receiving an alpha-beta TCR / CD19 B cell depleted haploidentical peripheral blood stem cell transplant or an umbilical cord blood stem cell transplant with delayed T-cell immune reconstitution.

Diagnosis and Treatment of HSV and VZV Infection and Disease

- Both HSV and VZV infection and disease can occur after cellular therapy, regardless of the recipient's pre-CTP serostatus and the use of (val)acyclovir prophylaxis. Seronegative patients may develop infections with both viruses due to primary infection; or due to reactivation if their pre-transplant seronegative status was falsely negative. Seropositive patients may develop infections with both viruses due to failure of prophylaxis to prevent reactivation, or non-compliance with prophylaxis. As result, a high index of suspicion for HSV and VZV disease should occur for all cellular therapy patients.
- HSV disease presents as stomatitis, esophagitis, viremia, hepatitis, a hemophagocytic syndrome post-transplant, and encephalomyelitis.
- VZV disease presents as chickenpox, herpes zoster (shingles – either limited to one or two

dermatomes, or more widely disseminated across multiple dermatomes in immunocompromised patients), viremia, hepatitis, myocarditis, pneumonitis, a hemophagocytic syndrome post-transplant, and encephalomyelitis with risk of stroke.
- PCR tests (blood, CSF, mouth swabs, bronchoalveolar lavage, tissue) are the primary method to diagnose HSV and VZV infection.
- Swabs from mouth and epithelial lesions should be sent using the appropriate swabs found along with Universal Transport Media (pink fluid). Lesions or vesicles need to be de-roofed as best possible with the swab and the ulcer vigorously swabbed.
- Checking IgM serology against HSV and VZV to look for an acute infection after transplant has no role in diagnosing infection, given the immunocompromised state.

Treatment of HSV Stomatitis
- Acyclovir 10 mg/kg/dose IV q8h for severe infections or if compliance with oral valacyclovir is a concern.
- Valacyclovir 20 mg/kg/dose PO TID (maximum 1000mg per dose) may be used for those with less severe disease and able to tolerate oral medications.
- Treat mucocutaneous involvement for 7-14 days (7 days if less severe involvement).
- Switching from intravenous acyclovir to oral valacyclovir at 20 mg/kg/dose PO TID (maximum 1000 mg per dose TID) for mucocutaneous disease, is possible based on the patient's clinical status and ability to tolerate oral medication. There is no minimum duration of intravenous therapy.

Treatment of Non-CNS HSV Disease (e.g., viremia, esophagitis, hepatitis)
- Acyclovir 10 mg/kg/dose IV q8h for 10-14 days.
- Consultation with Pediatric Infectious Disease is suggested.

Treatment of Suspected or Proven HSV Meningoencephalitis
- IV acyclovir:
  - ≤12 years: 20 mg/kg/dose IV q8 hours
  - > 12 years: 10 mg/kg/dose IV q8 hours
- Treatment is generally for 14-21 days.
- Consultation with Pediatric Infectious Diseases indicated to help guide duration of therapy.
- Needs repeat LP to become negative for HSV-PCR.

Treatment of Varicella (ChickenPox) in CTP Patients
- The goal of IV acyclovir in CTP recipients with varicella is to stop the development of progressive varicella and to prevent the onset of varicella pneumonia which has a high rate of mortality. CTP recipients should generally be admitted to hospital and placed in airborne and contact precautions to initiate IV acyclovir.
- Primary VZV infections occurring in the first-year post-transplant should receive intravenous

therapy as soon as possible and preferably within 72 hours after the lesions appear, to minimize risk of dissemination. This is particularly important for patients with acute or chronic GVHD, those still on immune suppression, and those with delayed cellular immune reconstitution.

- Infants <1 year: Acyclovir 10-20 mg/kg/dose IV every 8 hours for 7-14 days based on clinical response
- Children ≥ 1 year: 500mg/m^2/dose IV every 8 hours or 10 mg/kg/dose IV every 8 hours for 7-10 days
- Select patients (those with good oral compliance, when no new lesions are appearing, clinically stable and no evidence of organ dysfunction) may be transitioned to oral valacyclovir at 20 mg/kg/dose PO TID (maximum 1000 mg per dose) to complete their course.

Treatment of Herpes Zoster (Shingles)

- Infants <1 year: 10 mg/kg/dose IV every 8 hours for 7-14 days based on clinical response.
- Children ≥ 1 year: 500mg/m^2/dose IV every 8 hours or 10 mg/kg/dose IV every 8 hours for 7-10 days.
- Treatment should continue for at least 2 days after the development of new lesion formation has ended and all lesions are crusted over
- On average, early therapy allows elimination of acute pain within 4 days, crusting of lesions by 7 days and complete healing in 2-3 weeks
- Oral valacyclovir at 20 mg/kg/dose PO TID (maximum 1000 mg per dose) may be considered for select patients who have localized zoster occurring in the late post-transplant period.

Dose Adjustments of IV Acyclovir in Renal Impairment

- Cl_{cr} >50 ml/min/1.73m^2: No dose adjustment required.
- Cl_{cr} 25-50 ml/minute/1.73m^2: administer normal dose every 12 hours
- Cl_{cr} 10-25 ml/minute/1.73m^2: administer normal dose every 24 hours
- Cl_{cr} <10 ml/minute/1.73m^2: 50% decrease in dose, give every 24 hours
- Patient on Continuous Renal Replacement Therapy: IV acyclovir 10mg/kg/dose IV q12hours
- Patient on Intermittent Hemodialysis (acyclovir is dialyzable; 60% reduction after a 6-hour IH) 5 mg/kg/dose IV q24 hours, administered after hemodialysis.

Exposure Prevention of VZV (Recommendation Only)

- Vaccinate prospective contacts (caregivers, siblings, related donors) without a history of chicken pox or VZV vaccination. Ideally the vaccination schedule should be completed with as much lead time before transplant as possible and at least 4-weeks prior to cellular therapy.
- If not contraindicated (e.g., due to primary immunodeficiency or immunocompromising therapy), two doses of VZV containing vaccinations should be provided a minimum of 4- weeks apart, with no dose being provided within 1-month of initiation of immunocompromising

therapy.

- If a seronegative household member or close contact of the CTP recipient is exposed to VZV, then that household member / close contact might undergo VZV vaccination. If ineligible for vaccine, then the exposed household member / close contact should receive valacyclovir. Contact between the exposed household member / close contact and the CTP recipient should be minimized as much as possible for the first 21 days after exposure (or first 28 if VarIg was given to the household member).

Post Exposure Prophylaxis of VZV with VarIg

- Immunocompromised CTP recipients may develop VZV infection as result of contact with another individual with varicella or herpes zoster, although the risk profile is different. A telehealth consultation with Pediatric Infectious Disease may be done to discuss any potential exposure where there is uncertainty about the exposure and/or how to manage post-exposure prophylaxis with VarIg.
- Post-exposure prophylaxis of the CTP recipient with VarIg is indicated in many but not all situations, and only if this exposure is considered significant.
- Significant exposure of the CTP recipient for varicella includes: (1) Continuous household contact (that is, living in the same dwelling) with a person with varicella; (2) Being indoors for more than 1-hour with a person with varicella; (3) Being in the same hospital room for more than 1-hour with an individual with varicella; (4) Being in face-face contact for more than 15 minutes with a person with varicella; or (5) Touching the lesions or articles freshly soiled by discharges from vesicles of a person with active varicella. In any of these situations, the CTP recipient should receive VarIg.
- If the CTP recipient has a significant exposure to another individual who develops a **varicella rash following varicella vaccination**, if the rash appears within the first 2-weeks of that individual having received the vaccination, then the CTP recipient **should receive VarIg,** as it is impossible to know whether the individual acquired wild-type VZV before they were able to mount a vaccine response. If the rash occurs after 2-weeks following vaccination, so long as the CTP recipient has not touched the vesicles, then the rash is most likely vaccine-strain varicella which does not have airborne transmission. In this situation, the CTP recipient **does NOT** require VarIg.
- Significant exposure to herpes zoster includes: (1) Continuous household contact (that is, living in the same dwelling) with an immunocompromised person with herpes zoster or a person with disseminated herpes zoster prior to or within the first 24 hours of antiviral therapy; (2) Being indoors for more than 1 hour with an immunocompromised person with herpes zoster or person with disseminated herpes zoster prior to or within the first 24-hours of antiviral treatment; (3) Being in the same hospital room for more than 1-hour with an immunocompromised person with herpes zoster or a person with disseminated herpes zoster prior to or within the first 24 hours of antiviral therapy; (4) Being in face-face contact for more

than 15 minutes with an immunocompromised person with herpes zoster or a person with disseminated herpes zoster prior to or within the first 24 hours of antiviral therapy; or (5) Touching the lesions or articles freshly soiled by discharges from vesicles of a person with active herpes zoster. In any of these situations, the CTP recipient should receive VarIg.

- **Note**: The CTP recipient who is in contact (even close contact) with an immunocompetent individual who develops localized herpes zoster and so long as the CTP recipient has not touched the lesions or articles of clothing freshly soiled by discharge, the CTP recipient **DOES NOT** require VarIg, as there is no airborne transmission with localized herpes zoster. If the immunocompetent individual, however, develops disseminated herpes zoster (multiple non-contiguous dermatomes, hepatitis, CNS involvement, pneumonitis) then the CTP recipient should receive VarIg.
- Regardless of their pre-CTP VZV IgG result, any CTP recipient < 24 months after allogeneic CTP infusion or patients ≥ 24 months after allogeneic CTP infusion and who are still on immunosuppressive therapy and/or have chronic GvHD, should receive VarIg (ideally within 96 hours of exposure, but the earlier the better) after exposure to either chickenpox or shingles as detailed above. If VarIg is not available, a treatment course of IV acyclovir or oral valacyclovir for 3 weeks should be given. Use of post exposure antiviral agents are not supported by clinical trials and some experts recommend these agents only if VARIG is not available.
- VarIg is ordered through the Blood Bank at Alberta Children's Hospital (ACH) (403-955- 2332). The dosage is as follows: *1 vial = 125 U IM*

≤ 10 kg: 1 vial

>10-20 kg: 2vials

≥20.-30 kg: 3 vials

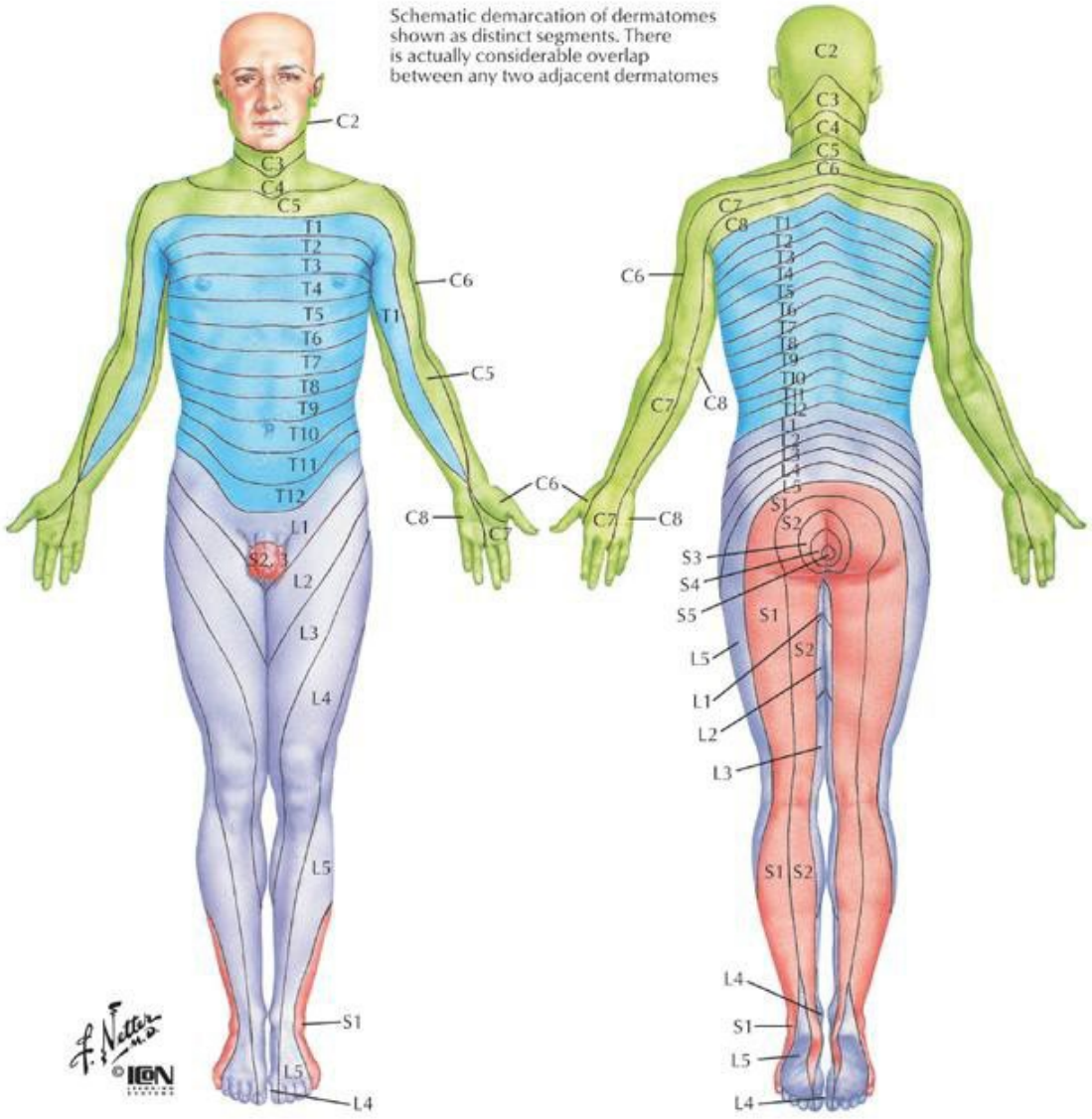
≥30.-40 kg: 4 vials

> 40 kg: 5 vials

- If patient is receiving induction or maintenance doses of ganciclovir, foscarnet or cidofovir, one does not need to add (val)acyclovir as these agents are active against VZV
- If patient has received IVIG within 3 weeks of exposure, *may* elect not to give VarIg.
- If a seronegative post CTP recipient is off all immune suppression for > 6 months, and > 24 months from CTP infusion, then observe closely.

Appendix A:

Dermatome Map of the Body



Levels of principal dermatomes

C5	Clavicles
C5, 6, 7	Lateral parts of upper limbs
C8, T1	Medial sides of upper limbs
C6	Thumb
C6, 7, 8	Hand
C8	Ring and little fingers
T4	Level of nipples
T10	Level of umbilicus
T12	Inguinal or groin regions
L1, 2, 3, 4	Anterior and inner surfaces of lower limbs
L4, 5, S1	Foot
L4	Medial side of great toe
S1, 2, L5	Posterior and outer surfaces of lower limbs
S1	Lateral margin of foot and little toe
S2, 3, 4	Perineum

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Pneumocystis jiroveci Pneumonia Prophylaxis and Treatment in the Hematopoietic Stem Cell Transplant Patient

Presented by: Greg Guilcher

Purpose

To provide guidance on the prophylaxis and management of *Pneumocystis jiroveci* pneumonia (PJP) for patients who receive cellular therapy product (CTP) infusions.

Points of Emphasis

- *Pneumocystis jiroveci* is an opportunistic pathogen that causes a severe respiratory infection, PJP.
- Patients at most risk for infection can be identified by a CD4+T-lymphocyte count < 200 based on studies of AIDS patients.
- Main risk factors for PJP include the use of corticosteroids and defects in cellular immunity
- Diagnosis is based on identification of *P. jiroveci* on a bronchoalveolar lavage (BAL) specimen
- Trimethoprim-sulfamethoxazole (TMP-SMX) has been found to be most effective drug compared to other drugs in the prevention and treatment of PJP.
- In CTP recipients, local guidelines use pentamidine intravenous (IV) as the first-line agent for prevention of PJP until stable engraftment.
- Pentamidine is continued until the patient has sustained engraftment, at which time pentamidine should be discontinued and TMP-SMX initiated if the patient can tolerate.
- PJP prophylaxis should be continued until the patient has been off all immune suppression for 3 months.
- Consider awaiting CD4 count recovery above 200 before discontinuing prophylaxis and using this threshold to identify patients at risk.
- Patients with chronic GVHD require PJP prophylaxis.

Background

Pneumocystis jiroveci (previously *P. carinii*) is an opportunistic micro-organism, which resembles *Ascomycetous fungi*. The host range is wide and includes humans and mammals such as rabbits, dogs, goats, swine, cats, primates and horses. It was shown to cause human disease in 1951.

Epidemiology

Literature has shown that before the use of PJP prophylaxis, 5 -16% of allogeneic blood and marrow transplant recipients developed PJP post transplant with a mortality of 76%. With the effective use of TMP/SMX prophylaxis PJP has become rare. Recent Center for International Blood and Marrow Transplant Research (CIBMTR) analysis showed that overall 0.63% of allogenic and 0.28% of

autologous recipients of first transplant developed PJP. However, the mortality remains much higher in HIV negative patients compared to the HIV positive cohort.

The recommended use of TMP/SMX has not been associated with breakthrough PJP infections in at risk populations, though Trimethoprim resistance mutations in clinical isolates of *Pneumocystis jiroveci* has been shown in laboratory.

Risk Factors

The main risk factors of PJP infection are:

- deficiencies in cellular immunity
- use of corticosteroids

Other risk factors are:

- Invasive cytomegalovirus (CMV) enhances the virulence of *Pneumocystis.*
- Use of agents such as Alemtuzumab, Rituximab, TNF blockade (Infliximab, Etanercept), lymphodepleting chemotherapy (e.g Cyclophosphamide, Fludarabine) confers risk for PJP
- Patients with chronic graft dysfunction or graft versus host disease (GvHD) who need ongoing immune suppression require prolonged PJP prophylaxis.
- The risk of PJP in autologous CTP is unknown although cases have been reported.

Clinical Manifestations

- Patients present with acute onset of respiratory symptoms over days (unlike weeks in HIV positive patients), including dry cough, fever with sweats, and difficulty in taking a deep breath. Hemoptysis may be present.
- Examination often reveals tachypnea, tachycardia, cyanosis, and fine crackles on auscultation. Hypoxia is often present as assessed by oxygen saturation or blood gas analysis.
- Chest X-ray may be normal or may show diffuse bilateral infiltrates or multiple nodules. CT scan may show diffuse interstitial and nodular parenchyma even though CXR appears normal. Serum LDH is typically elevated (>300) though this is non-specific.

Diagnosis

BAL is generally used to obtain samples to be identified for PJP.

- The sample is processed using a cytospin technique and stained using a monoclonal antibody in the past, but replaced by PCR nowadays.
- PCR is 97% sensitive, 99% specific and has nearly 100% negative predictive value. It is useful for ruling out PJP, but differentiating colonization from true infection requires clinical judgement.
- BAL provides a diagnosis of PJP in >80% of patients. The use of BAL with transbronchial biopsy increases the diagnostic yield to >90%.
- Sputum samples or tracheal aspirates are generally not suitable.

- The gold standard is open lung biopsy, but this is rarely performed in current clinical practice.

Diagnosis

1. Trimethoprim-Sulfamethoxazole

TMP-SMX is the most effective agent against *Pneumocystis,* with almost no breakthrough cases with adherence to recommended prophylaxis

- TMP inhibits dihydrofolate reductase (DHFR) and SMX inhibits dihydropteroate synthetase (DHPS).
- Toxicities include fever, rash, headache, marrow suppression, hepatitis, anaphylaxis, nephrotoxicity, hyperkalemia, and hypoglycaemia. Significant toxicities generally occur in the first month but can be seen many months into therapy. G6PD deficiency is a contraindication for use of TMP-SMX
- In CTP recipients however, the use of TMP-SMX is occasionally associated with bone marrow suppression and delayed engraftment. Evaluating the cause of skin rashes and elevated LFTs is complicated with the use of TMP-SMX in the early engraftment phase.
- Due to the risk of marrow suppression and other potential side effects (elevated LFTs) TMP-SMX may be substituted by pentamidine in the first month post-transplant. After that, every attempt should be made to transition the patient to TMP-SMX, typically BID twice a week. Even a single (BID dosing) weekly administration was shown to be extremely effective in preventing PJP in cancer/leukemia patients.

2. Pentamidine

Pentamidine mechanism of action is unknown and it may be given IV or by inhalation. Alberta Children's Hospital (ACH) is not set-up to administer pentamadine via inhalation, therefore only IV delivery is used. Side effects include hypo/hyperglycemia, vomiting, diarrhea, fever, megaloblastic anemia, increased liver enzymes, nephrotoxicity, hypocalcemia, granulocytopenia, hypotension, and allergic reactions. Select patients may be referred to adult hospitals for inhaled pentamidine administration.

After TMP-SMX, there appears to be more evidence to support the use of aerosolized Pentamidine and Atovaquone compared to Dapsone and IV Pentamidine. However, the pediatric Alberta Blood and Marrow Transplant Program (ABMTP) has found IV pentamidine successful for PJP prophylaxis in the pediatric allogeneic CTP recipient. IV pentamidine has been well tolerated and conveniently delivered. Breakthrough PJP infections with IV Pentamidine are rare post CTP therapy, as supported by our local experience and a large series published by Lurie Children's Hospital (Chicago).

Pentamidine is initiated for all allogeneic CTP patients just prior to conditioning. It is expected that many of these patients will receive a 2nd dose (typically given one month apart) which should provide *Pneumocystis* propylaxis for the first 6-8 weeks post-transplant. Once robust engraftment has occurred then the previous PJP prophylaxis regimen will be resumed as soon as tolerable – preferably TMP-SMX.

Guideline and Procedures

- For all allogeneic CTP patients (peripheral blood stem cell, marrow, cord blood or immune effector cell recipients), pentamidine 4 mg/kg/dose ; maximum dose 300 mg IV will be given at time of admission (unless given within the previous 28 days). This will usually happen on the in-patient unit at the time of admission but can be administered in the outpatient setting as well.
- Document on CTP admission orders the date of the next scheduled pentamidine dose.
- Change to TMP-SMX as soon as possible unless there are very convincing reasons to continue with Pentamidine. Ease of administration should not be the only reason to continue with Pentamidine given that TMP-SMX is the recommended first-line prophylactic agent. In addition, the risk of PJP rises after the first month of transplantation.
- If patient develops a significant adverse reaction to pentamidine, discontinue and resume pre-admission prophylaxis.
- If Pentamidine was continued for any reason ensure that at the time of discharge, the reason for continuing and date of the next pentamidine dose are clearly documented.
- Continue PJP prophylaxis until patient has been off all immune suppression for 3 months.
- For tandem autologous transplants, continue Pentamidine until completion of all transplants and then switch to the pre-admission prophylaxis.
- Patients with chronic GVHD require PJP prophylaxis.

Treatment of PJP Infection

- TMP-SMX remains the recommended first-line therapy for treatment of mild, moderate and severe PJP infection. Therapy should be promptly initiated without deferral for investigations.
- For severe cases, IV formulation is preferred and can be switched to oral once symptoms improve. Trimethoprim component 15- 20 mg/kg/day in 3-4 divided doses is the recommended dosage.
- Treatment duration is 21 days or as directed by the infectious disease consultants.
- Initial deterioration in first 3-5 days is common. If no clinical response in 8 days, treatment failure is suspected, and repeat investigations are recommended to identify coinfections.
- Persistent positive PCR in BAL is not an indication of treatment failure as the organism may persist longer in the respiratory tract.
- In the case of intolerance to allergy to sulphonamides, alternatives include intravenous pentamidine, combination of primaquine and clindamycin, or atovaquone
- The use of corticosteroids as adjunctive therapy has been shown to have benefit in hypoxemic HIV patients and has been used in post-transplant recipients as well, but there are no trials for steroid use in non-HIV children. Consider use of steroids in severe patients who are hypoxemic with multi-disciplinary discussion.
- Secondary prophylaxis is indicated in all patients thereafter, and the agent is chosen as for primary prophylaxis.

- Monitoring is required for myelosuppression, liver and renal toxicities; dosage adjustment may be required for renal impairment.

Drug Dosing for PJP Prophylaxis

SMX-TMP

- Contraindicated in infants < 2 months old
- Administer TWICE daily on two days of each week (for example: on Saturdays and Sundays)

Weight (kg)	Adult Tablets (80 mg TMP/tab)	Oral Suspension (8 mg TMP/ml)	Pediatric Tablets (20 mg TMP/tab)
5-7.4	-	2 ml BID	-
7.5-11.9	-	2.5 ml BID	1 ped. tab BID
12-19.9	½ tablet	5 ml BID	2 ped. tabs BID
20-29.9	-	7.5 ml BID	3 ped. tabs BID
>30	1 tablet	10 ml BID	4 ped. tabs BID

Pentamidine

- Pentamidine 4 mg/kg/dose (maximum 300mg) intravenously every 2 – 4 weeks

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Management of Hepatic Sinusoidal Obstructive Syndrome (formerly Veno-Occlusive Disease)

Presented by: Greg Guilcher

Purpose

To provide guidance on the diagnosis and management of hepatic sinusoidal obstructive syndrome (SOS).

Points of Emphasis

- Hepatic sinusoidal obstructive syndrome (SOS), previously known as hepatic veno- occlusive disease (VOD), is a disorder of the liver that classically presents with tender hepatomegaly, hyperbilirubinemia, refractory thrombocytopenia, ascites, and weight gain.
- Patients undergoing stem cell transplantation should be assessed for risk factors leading to SOS, be referred for GI consultation as needed, and considered for prophylactic therapies such as defibrotide.
- Prevention of SOS involves identifying patients at risk for SOS, routine use of volume- restricted IV fluids and medications, close monitoring of weights and laboratory indicators.
- The only established treatment for SOS is defibrotide. Early diagnosis and treatment with defibrotide has been shown to result in improved outcomes.

Background

Incidence

The median incidence of SOS in children after hematopoietic stem cell transplant (HSCT) is 20% (range 0%-70%), depending on patient characteristics, diagnostic criteria, risk factors and the conditioning regimen employed. Regimens with busulfan, cyclophosphamide and TBI greater than 1200 cGy are associated with higher risk.

There has been a decline in the incidence and severity of SOS due to newer non-myeloablative regimens, avoiding the use of cyclophosphamide-based regimens, a decrease in chronic Hepatitis C viral infections in transplant patients, and the use of IV busulfan (with pharmacokinetics) in regimens containing busulfan and cyclophosphamide.

Risk Factors

1. Pre-existing liver disease (hepatitis C, hepatic fibrosis, cirrhosis)
2. Previous exposure or use of a myeloablative regimen
3. Past history of SOS
4. High dose of total-body irradiation or liver irradiation
5. Use of high dose alkylating agent (e.g. cyclophosphamide)

6. Administration of cyclophosphamide after busulfan (particularly if the interval between last dose of Busulfan and first dose of cyclophosphamide is less than 24 hours)
7. Oral or fixed dose of busulfan (irrespective of plasma concentrations)
8. Use of specific agents such as gemtuzumab, ozogamicin, and inotuzumab
9. Patient heavily pre-treated with transfusion or chemotherapy, prior to HSCT
10. Presence of an identified risk polymorphism
11. Underlying disease known to increase risk (e.g. thalassemia major, familial HLH, osteopetrosis)
12. Infant age

Pathophysiology and Histology

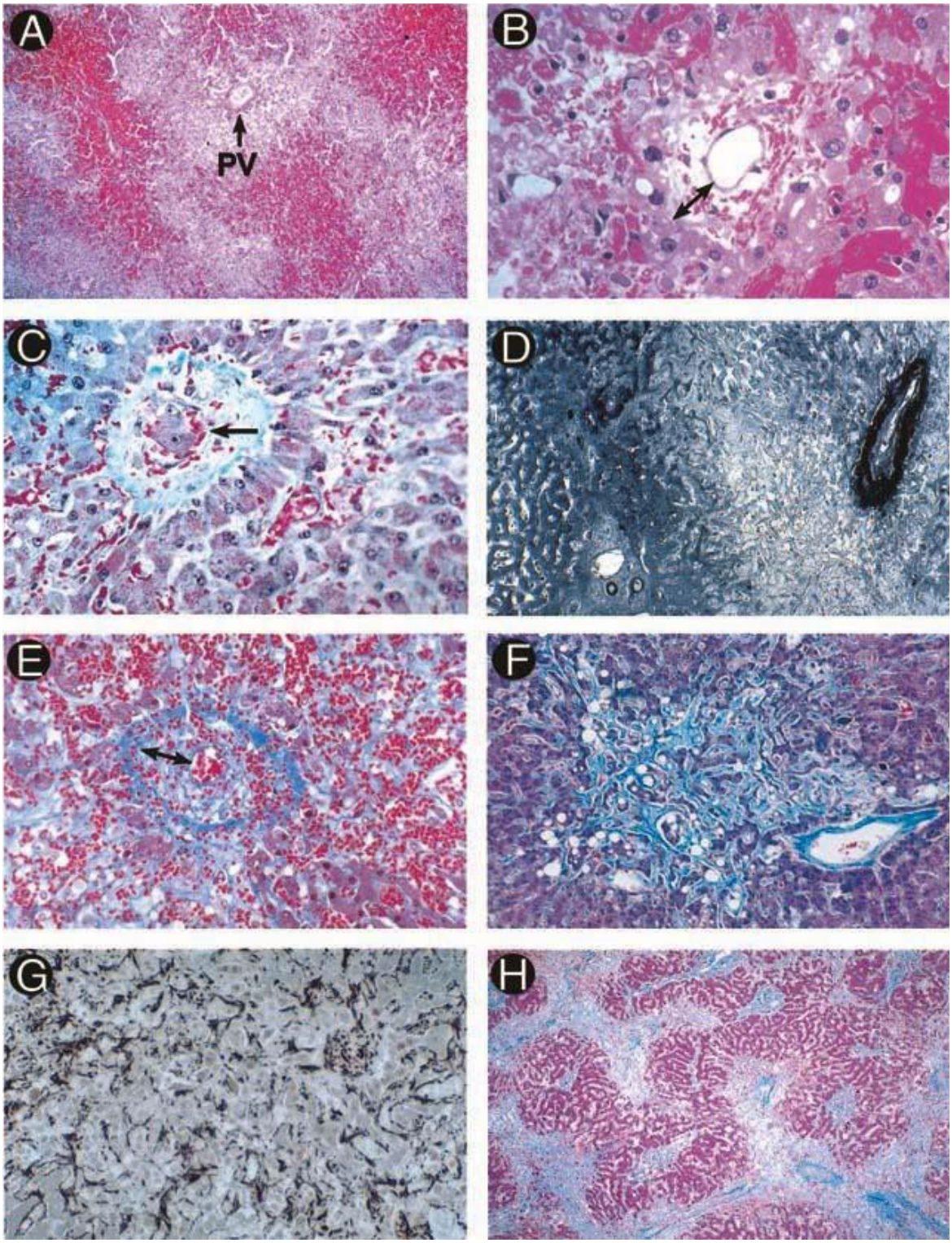
Hepatic SOS is a disorder of the liver that classically presents with tender hepatomegaly, hyperbilirubinemia, refractory thrombocytopenia, ascites and weight gain. The name has been altered from VOD, as the disease can develop without venular involvement and the obstruction has been shown to begin in the sinusoids. SOS generally presents as portal hypertension followed by parenchymal dysfunction. Occlusion of the central venules by subendothelial edema, hemorrhage or fibrosis is easily detected which resulted in the disorder initially being called veno-occlusive disease. Venule occlusion, though common in severe disease is not essential for diagnosis. Sinusoidal involvement has been confirmed by experimental and clinical studies, resulting in the new name of sinusoidal obstructive syndrome.

In vitro cellular studies show that toxins and drugs causing SOS are more toxic to the hepatic sinusoidal endothelial cells (SECs) than to hepatocytes. One of the earliest morphological change is SECs rounding up, followed by development of gaps within the sinusoidal barrier. Red blood cells then enter into the space of Disse dissecting the sinusoidal lining. The detached cells from this lining then embolize downstream.

Several factors are involved in the development of SOS:

1. Glutathione depletion
2. Nitric oxide (NO) depletion
3. Increased matrix metalloproteinases (MMP)
4. Increased vascular endothelial growth factor (VEGF)
5. Possibly clotting factors

Histological Abnormalities of SOS



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Evolution of Histological Abnormalities of SOS

A. Fatal SOS 23 days post autograft (H and E stain). Hemorrhagic necrosis of zone 3 with sparing of zone 1 (PV, portal vein).
B. High power showing early changes of concentric venular luminal narrowing by a widened subendothelial zone (double arrow) containing trapped red cells. The surrounding changes include anuclear clusters of necrotic hepatocytes, disrupted sinusoids and hemorrhage into the space of Disse.
C. Severe SOS 21 days post allograft. Hepatocyte dropout, sinusoidal hemorrhage and embolization of a cluster of hepatocytes (arrow) into a partially collagenized venule.
D. Immunostained liver section of early SOS showing intense perivenular and adventitial staining., loss of hepatocyte staining in zone 3 and preservation of portal and zone 1 anatomy.
E. Fatal SOS 31 days post allograft. A small sublobular venule is nearly occluded by loose extracellualr matrix and red cells within the widened subendothelial zone (double arrows). Extensive necrosis has obliterated the liver cords which are replaced by strands of connective tissue admixed with red cells.
F. Fatal SOS 37 days post transplantation. Extensive zone 3 sinusoidal fibrosis adjacent to a nonoccluded sublobular venule.
G. Same specimen as F showing proliferation of activated hepatic stellate cells lining perivenular sinusoids.
H. Fatal SOS 76 days post allograft showing a pattern of reverse cirrhosis with confluent bridging between collapsed, fibrotic perivenular zones containing venules occluded by fibrous matrix.

Clinical Findings

SOS is characterized by weight gain caused by fluid retention and ascites, tender hepatomegaly, refractory thrombocytopenia and hyperbilirubinemia which follows cytoreductive therapy in the absence of other causes. In conditioning regimens containing cyclophosphamide the syndrome presents 10-20 days after the start of conditioning. A later onset may occur with other regimens. Some studies have described a “late SOS” after therapy with busulfan where signs of liver disease are first seen after day 30.

The differential diagnosis of SOS is broad and includes:

1. Acute liver GVHD
2. Fungal infiltration of liver
3. Viral hepatitis
4. Cholangitis lenta, e.g. during sepsis
5. Drug-induced liver disease (CSA, Septra, penicillins, azoles, methotrexate)
6. Constrictive pericarditis and right congestive heart failure
7. Persistent tumor infiltration of the liver
8. Pancreatic ascities and chylous ascites
9. Total Parenteral Nutrition
10. Hemolysis
11. Renal failure

12. Transplantation-associated microangiopathy (TMA)

Laboratory Findings

Studies have shown that patients with SOS may have:

1. An increase in serum bilirubin (although ~30% of children have normal bilirubin) and AST
2. An increase in levels of von Willebrand factor and thrombomodulin, suggesting endothelial injury
3. An increase of coagulation activation markers such as protein fragments 1+2 and thrombin ± antithrombin complexes
4. A decrease in concentrations of natural anticoagulants such as protein C and antithrombin III
5. An increase in procoagulants such as factor VIII and fibrinogen
6. A decrease in the activity of von Willebrand factor protease Elevated bilirubin is a sensitive but non-specific index of SOS

Endothelial damage can be suspected prior to the presence of clinical or laboratory signs by elevated serum levels of PAI-1, procollagen III and its precursor P-III-P in children. Elevated serum P-III-P and low levels of protein C prior to conditioning can predict patients who will develop SOS.

Plasminogen activator inhibitor 1 (PAI-1) has been found to be significantly elevated at the time of increased bilirubin in SOS when compared to GVHD or other causes of liver damage. It can permit a correct differential diagnosis of SOS in patients without sepsis.

Impaired activity of plasma von Willebrand factor-cleaving protease may predict the occurrence of SOS after SCT. Serum CA-125 also appears to be an early and accurate predictive marker in the pediatric population.

All the above tests are not used routinely and are often only used in a research setting.

Radiographic Findings

Ultrasound of abdomen and liver with Doppler is the imaging of choice, but findings may not appear until late in the disease process and the test has poor negative predictive value. The common findings include ascites, hepatomegaly, attenuated hepatic flow, hepatic vein or biliary dilatation. Ultrasound can also exclude extrahepatic biliary obstruction or malignant infiltration of the liver. Gall-bladder wall thickness has been shown to correlate with hepatic venous pressure gradient (HVPG) which may have prognostic importance. These signs however are non-specific for diagnosis and must be interpreted with clinical findings.

Doppler ultrasound may be a prognostic tool rather than diagnostic. It may show a decreased or reversal of portal blood flow which is a relatively late finding in SOS. Significant elevation of the hepatic artery resistive index may be a sensitive indicator of liver damage related to SOS. In infants a segmental portal flow reversal has been shown to be strongly associated with early SOS.

Hemodynamics
A transjugular hepatic venous pressure gradient (HVPG) with liver biopsy is an invasive study and indicated only when the patient is deteriorating, when diagnosis is uncertain and when therapy may be hazardous. HVPG is the difference between occluded hepatic venous pressure and the non-occluded pressure on the hepatic veins. Absence of a significant gradient (< 6 mmHg) along the hepatic veins and in the IVC can exclude anatomical causes of outflow obstruction. HVPG > 10 mmHg is > 90% specific and 60% sensitive for SOS and helps to differentiate SOS from GVHD. HVPG greater than 20 mmHg correlates with poor prognosis.

HVPG and liver biopsy are rarely used in the pediatric population due to the risks of the procedures.

Prevention
Severe SOS has a very high mortality rate therefore emphasizing the importance of minimizing the risk of SOS.

Identify patients at risk:
See prior list of risk factors

Minimize exposure to risk factors.

Other measures (variable proven efficacy):
Ursodeoxycholic acid

At the Alberta Children's Hospital (ACH), patients at risk for SOS are assessed by the GI service. Ursodeoxycholic acid (ursofalk) is started on all patients routinely. Patients at higher risk for SOS may be eligible for prophylactic defibrotide. Ursofalk may help in decreasing biliary sludging which also may be associated with multiple morbidities.

Careful attention is paid to the patient's fluid balance and total fluid intake particularly after the stem cells have been infused. Generally by day +1 the total fluid intake is decreased from the hyperhydration state to maintenance.

Guidelines for the Diagnosis and Management of SOS:

Clinical Diagnosis

The diagnosis of SOS is based on clinical criteria after ruling out other conditions as previously listed above. The EBMT have published the most currently acceptable clinical criteria, which are more appropriate for pediatric patients. Historically, the Seattle and Baltimore criteria have been used.

Table 1: Proposed EMBT diagnostic criteria for hepatic SOS/VOD in children

Pediatric Criteria
• No limitation for time of onset of VOD/SOS
• Presence of ≥2 of the following*:
• Unexplained consumptive and transfusion-refractory thrombocytopenia†
• Otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics or a wight gain > 5% above baseline value
• Hepatomegaly‡ (best if confirmed by imaging) above baseline value
• Ascites‡ (best if confirmed by imaging) above baseline value
• Rising bilirubin from a baseline value on 3 consecutive days or bilirubin ≥ 2 mg/dL within 72h

CT indicates computed tomography; MRI, magnetic resonance Imaging.
*With the exclusion of other potential differential diagnoses.
† ≥1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines
‡ Suggested: imaging (ultrasound, CT, or MRI) immediately before HSCT to determine baseline value for both hepatomegaly and ascites
(Bone Marrow Transplant 208 Feb; 53(2): 138-145) ***Study based criteria should be used in case an open study is available

SOS can be divided into 3 categories of disease severity

Mild: The disease is clinically obvious but resolves without treatment. There is no adverse effect from liver disease, no therapy is needed and the illness is self-limited.

Moderate: There is adverse effect from the liver disease. Treatment such as diuretics, sodium restriction and analgesics is required. Eventually there is complete resolution of all signs of liver damage.

Severe: The disease requires treatment, is life-threatening, and involves mulit-organ failure.

Table 2: Severity grading thresholds of sinusoidal obstructive syndrome among children, adolescents, and young adults. (Mahadeo et al. Lancet Haematol. 2020 Jan; 7(1): e61-e72)

	Mild	Moderate	Severe	Very Severe
ALT, AST, GLDH (mg/dL)	≤ 2 x normal	2-5 x normal	2-5 x normal	>5 x normal
Bilirubin (mg/dL)	< 2	< 2	≥ 2	Bilirubin doubles in 48h
Coagulopathy (not responsive to vitamin K administration; INR)	< 1.5	1.5-1.9	> 2	Need for replacement of coagulation factors
Ascites	Mild (minimal fluid by liver, spleen or pelvis)	Moderate (<1 cm fluid)	Severe (fluid in all three regions with >1cm fluid in at least two regions)	Requires paracentesis
Weight gain (from baseline)	2.5%	5-10% despite diuretic use	>10%	Persistent rise
Renal function score	KDIGO 1: serum creatinine 1.5-1.9 x baseline or ≥ 0.3 mg/dL (≥26.5 mmol/L) increase or urine output < 0.5 mL/kg/h for 6-12h	KDIGO 2: serum creatinine 2.0-2.9 x baseline or urine output < 0.5 mL/kg/h for ≥12h	KDIGO 3: serum creatinine 3.0 x baseline or increase in serum creatinine ≥4.0 mg/dL (≥353.6 mmol/L) or initiation of renal replacement therapy or decrease in eGFR to < 35 mL/min per 1.73 m^2 (patients <18 year) or urine output <0.3mL/kg/h for ≥24h or anuria for ≥ 12h (patients < 18 years)	Persistent need for renal replacement therapy
Encephalopathy	CAPD <9	CAPD<9	CAPD ≥9	CAPD ≥9
Persistent RT	<3 days	3-7 days	--	> 7 days
Pulmonary function	<2 L	<2 L	NIV/IMV	IMV

ALT=alanine aminotransferase. AST=aspartate aminotransferase. GLDH=glutamate dehydrogenase. INR=international normalized ratio. KDIGO=Kidney Disease: Improving Global Outcomes score. CAPD=Cornell Assessment of Pediatric Delirium. RT=refractory thrombocytopenia. NIV=non-invasive ventilation. IMV=invasive mechanical ventilation.

Management

Mild

1. If weight gain is persistently > 5% above baseline weight, 24-48 hours or greater post stem cell infusion, reassess fluid intake and minimize fluid intake (IV and PO) where possible.
2. Begin twice daily weights.
3. Obtain daily bilirubin, ALT, AST, lytes, Bun, Cr.

Moderate

1. If weight gain remains > 5% increase of baseline weight, and bilirubin > 34 µmol/L, with or without hepatomegaly/tender liver, obtain liver ultrasound with doppler.
2. If weight gain > 5% above baseline despite fluid restriction, begin sodium restriction and diuretic therapy.
3. Consider twice daily lytes, BUN, and Cr if using diuretic therapy.
4. Consult GI service.
5. Begin use of Ursofalk if not currently being used.

6. Consider the use of defibrotide – see below.
7. May need to consider liver biopsy is diagnosis is unclear.

Severe

1. Multi-organ failure (MOF) as defined as either an oxygen requirement with an oxygen saturation < 90% on room air and/or ventilator dependence, and /or renal dysfunction (defined as doubling of baseline creatinine and/or dialysis dependent) and /or encephalopathy. In order for MOF to be SOS related it needs to be present within 28 days after the diagnosis of SOS.
2. Continue supportive care with fluid and sodium restriction, diuretics.
3. Ascites may need to be treated with paracentesis for discomfort or shortness of breath.
4. Correct any coagulopathy.
5. Consult ICU.
6. Mechanical organ support may be needed when renal or respiratory failure develops.
7. Begin use of defibrotide – see below.
8. Consider alternative therapies – see below.
9. The Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) and the Pediatric Transplant and Cellular Therapy Consortium have published comprehensive consensus reviews on the supportive and critical care management of severe SOS.

Recommendations for Management of Fluid, Electrolyte, and Renal Dysfunction in Patients with Veno-Occlusive Disease (Mahadeo et al. Biol Blood Marrow Transplant. 2017 Dec; 23(12):2023-2033)

1. Avoid acute fluid overload (FO) in all patients undergoing hematopoietic stem cell transplantation (HCT); restriction of fluid and diuretics may be indicated in patients exhibiting evidence of FO at any time.
2. Patients with veno-occlusive disease (VOD) invariably have acute FO, and fluid management should be adjusted to achieve the patient's baseline weight
3. A stepwise gradual incremental increase in diuretic dosage may be helpful for achieving the patient's baseline body weight.
4. The use of medications specifically for the promotion of renal perfusion is not currently recommended for management of VOD.
5. For patients with VOD and a serum albumin level ≥ 3 g/dL, albumin administration is not recommended. For patients with hypoalbuminemia, 5% or 25% albumin (1g/kg/dose) may be followed by administration of a diuretic.
6. Continuous renal replacement therapy should be considered if progressive FO occurs despite fluid restriction and aggressive diuresis or if electrolyte imbalances result from underlying disease, including acute kidney injury, which cannot be corrected by medical management.
7. Special recommendations for younger children should be followed.
8. The enteral route is preferred over parenteral nutrition in patients undergoing HCT.

Defibrotide Therapy

Defibrotide is a large single stranded polydeoxyribonucleic acid derived from porcine and bovine mucosa. It has antithrombotic, anti-ischemic, anti-inflammatory and thrombolytic properties without major systemic anti-coagulant effects. It also decreases leukocyte rolling and adherence to the endothelium as well as decreasing thrombin generation and lowering circulating levels of PAI-1.

It has a short circulating half-life from 10-30 minutes with IV administration. It has been used in peripheral vascular disease, microvascular thrombotic states and chemotherapy-related hemolytic uremic disease. Defibrotide is well tolerated with adverse effects including mild systolic hypotension, nausea and abdominal discomfort.

Recommendations

- Consider enrolling on any open studies that allow use of defibrotide in eligible patients.
- Consider prophylactic defibrotide in patients at high risk of developing SOS.

Defibrotide is given at a dose of 6.25 mg/kg every 6 hours for 4 doses a day (total dose, 25 mg/kg/day) based on baseline weight, defined as weight on the date of admission to the transplantation unit for conditioning.

Earlier intervention for severe SOS results in better outcomes. Defibrotide is administered IV in 5% dextrose in water, mixed to a maximum concentration of 4 mg/mL, with the dose rounded to the nearest 10 mg. Due to expense, consider dose rounding in consultation with pharmacy.

During therapy, wherever possible, maintain platelets ≥ 20,000/μL a(30,000 for those on thrombolytic therapy and haemoglobin ≥ 70 g/L. Frozen plasma and cryoprecipitate are recommended for bleeding patients with abnormal coagulation studies, but not for correction of laboratory abnormalities in the absence of bleeding.

Treatment is typically 21 days duration. If SOS *and* multi-organ failure resolve sooner, many experts discontinue therapy earlier with a low risk of recurrence. There is no consensus as to what parameter should be primarily used for treatment response (e.g. platelet refractoriness, bilirubin [if elevated at diagnosis], weight).

Response has been defined as clinical improvement with fluid mobilization, decrease in bilirubin, decrease in hepatomegaly or right upper quadrant (RUQ) pain, improvement in coagulopathy, and/or reduction in other end-organ dysfunction.

Alternative Therapies

There is no other standard medical therapy.

Transjugular intrahepatic portosystemic shunt insertion (TIPS) can relieve portal hypertension and prevent renal failure in patients with SOS. A review paper did not recommend TIPS for SOS associated with HSCT as it did not change prognosis. It may be useful in patients with SOS following liver transplantation.

Liver transplantation has been reported as a treatment for SOS. The presence of malignancies and MOF contraindicates the use of ortothopic liver transplantation.

Many other treatment modalities have been tried including N-acetylcysteine, methylprednisolone and charcoal hemofiltration. These have only been presented in case reports.

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Graft Versus Host Disease – Prophylaxis and Management

Presented by: Greg Guilcher and Tony Truong

Purpose

To provide guidance on the prophylaxis and management of acute graft versus host disease (GVHD) in pediatric patients undergoing allogeneic stem cell transplantation.

Points of Emphasis

- Acute GVHD is a major cause of transplant-related mortality and morbidity.
- The incidence and severity are multifactorial.
- Prophylaxis method, donor/recipient matching, conditioning regimen and graft composition are important considerations.

Background

There are 3 phases in the pathophysiology of acute GVHD:

1. Tissue damage due to previous therapy and conditioning regimen
2. Donor T-cell activation after interaction with antigen presenting cells (APC)
3. Cytokine and cell-mediated target tissue damage

GVHD Diagnostic Difficulties

GVHD damage can be difficult to differentiate from tissue injury caused by other processes. Definitive diagnosis is the demonstration of GVHD in tissue biopsy specimens but it is often difficult to obtain specimens i.e. liver, bowel or skin biopsy. Tissue samples still may be difficult to diagnose histologically as appearances of acute GVHD may be like that seen with damage due to by radiation, drugs, infections and microangiopathy.

Staging/Clinical Description

The original grading system was proposed by Glucksberg in 1974.GVHD is characterized by manifestations of skin, liver and gut.

- **Skin -** flushing of face, ears, palms and soles which is actually a fine maculopapular rash that may become severe. Severe skin involvement is characterized by bulla formation and desquamation. May need to distinguish from rashes caused by bacterial, viral, fungal infections or drugs.
- **Liver** - obstructive hyperbilirubinemia primarily but may also see elevation of liver enzymes. Transaminitis is seen notably with weaning of immune suppression. Degree of liver involvement is defined by total bilirubin level. Must distinguish from venous occlusive disease (VOD), biliary stones, drug toxicity and infection. Liver biopsy shows bile duct damage and lymphocytic infiltration.

Gut – diarrhea is the most common symptom. Severity is based on stool volume. May also see anorexia, nausea, vomiting, abdominal pain, bloody stools and ileus. Differential includes infection, malabsorption and mucosal toxicity. Bowel biopsy may show lymphocytic infiltration and crypt cell necrosis.

Criteria for Staging Acute GVHD

Category	Stage	Description	
Skin	0	No rash	
	1	Maculopapular rash < 25 % of body surface area	
	2	Maculopapular rash 25-50% of body surface area	
	3	Maculopapular rash > 50% of body surface area	
	4	Generalized erythroderma with bullous formation and desquamation	
Liver*	0	Bilirubin < 34 µmol/L	
	1	Bilirubin 34-50 µmol/L	
	2	Bilirubin 51-100 µmol/L	
	3	Bilirubin 101-250 µmol/L	
	4	Bilirubin > 250 µmol/L	
Gastro-Intestinal (diarrhea)**		Adults	Children
	0	<500 ml/day	<10 ml/kg/day
	1	500-999ml/day	10-19.9 ml/kg/day
	2	1000-1499ml/day	20-29.9 ml/kg/day
	3	>1500 ml/day	>30 ml/kg/day
	4	Severe abdominal pain/ileus Bloody stool regardless of volume	Severe abdominal pain/ileus Bloody stool regardless of volume

* If patient has documented GVHD of the liver and documented veno-occlusive disease of the liver then downstage liver GVHD by 1 stage.
** If patient has documented GVHD of the gut and documented alternative cause of diarrhea (severe mucositis, CMV enteritis, or C. difficile infection), then downstage gut by 1 stage.

Clinical Grading of Severity of Acute GVHD

Overall GRADE	SKIN Stage	LIVER Stage	GUT Stage
0 (None)	0	0	0
I (Mild)	+1 to +2	0	0
II (Moderate)	0 to +3 and	+1 and/or	+1
III (Severe	+2 to +3	+2 to +3 and/or	+2 to +3
IV (Life Threatening)	+4 or	3 to +4 and/or	+4

Grading Index of Acute GVHD Grading

	Grade A	Grade B	Grade C	Grade D
Skin	1	2	3	4
Gut	0	1-2	3	4
Upper GI	0	1		
Liver	0	1-2	3	4

Risk Factors for aGVHD

1. Source of Stem Cells and Graft T-cell content
2. Degree of HLA Matching
3. Donor Characteristics
4. Conditioning Regimen

Stem Cell Source

- Most studies show no differences between using cryopreserved or fresh marrow.
- More centers are using (peripheral blood stem cell) PBSC, which have 10 times as many T lymphocytes compared to marrow. Most studies have shown little increase in aGVHD, although some studies show increased frequency and severity of chronic GVHD (cGVHD).
- Ex vivo graft manipulation and T-cell depletion can reduce the risk of GVHD, notably for haploidentical transplantation.
- Cord blood transplants (CBT) are being used less with the advances in haploidentical BMT. There is a decreased incidence of aGVHD in mismatched (0-2 HLA loci) CBT compared to marrow controls. This may be due to the immunologic immaturity of the fetal lymphocyte. Matching at 8 loci has become a more recent standard (previously only 6)

Degree of Match

- Incidence and severity of a GVHD correlates to degree of HLA mismatch.
- HLA mismatch at any locus increases the risk of aGVHD.
- Increase in grade III/IV aGVHD and mortality seen with mismatch at DRB1 locus.
- Increase in severe aGVHD with mismatch at one or more antigens at the class I loci but no significant increase seen with class II mismatch, (other than DRB1).
- In addition to major HLA loci, “minor antigens” play a role in aGVHD as matched related transplants do better than matched unrelated transplants.

Donor Characteristics

- Increased risk of aGVHD seen with increased donor age.
- Increased incidence and severity of aGVHD is seen with increased recipient age, notably donors greater than 13 years of age
- Increased risk of aGVHD is seen with the use of a female donor for a male recipient.
- Increased risk of aGVHD may be seen with cytomegalovirus (CMV)/herpes simplex virus

(HSV) seropositivity of the donor.

Conditioning Regimen

- Increased risk of aGVHD is associated with more intense conditioning regimens and more advanced disease.
- Intense conditioning causes increased tissue damage resulting in exposed host antigens and an increase in cytokine release.

Medications for Prophylaxis and Treatment of aGVHD

1. *Nonselective Agents (Cytotoxic*) –Methotrexate, Steroids, Cyclophosphamide
2. *T-Cell Inhibition* – Cyclosporine (CSA), Tacrolimus (FK506), Sirolimus (rapamycin), Mycophenolate Mofetil (MMF)
3. *Antibody Therapy*- Antithymocye Globin (Thymoglobin), Alemtuzumab (Campath-1H), Infliximab (Anti-Tumor Necrosis Factor)
4. *Targeted Therapy* – Ruxolitinib (JAK/STAT inhibition)

Methotrexate

- Useful for prophylaxis only
- Generally used in combination with CSA
- Initial dose of 15 mg/m^2 (IV or PO) on day +1 and 10 mg/m^2 on day +3, +6 and +11.
- Toxicity includes nausea, vomiting, myelosuppression, mucositis, rash, hepatotoxicity

Steroids

- Used for treatment
- Variable dosage range
- Can suppress number and function of lymphocytes
- Oral, parenteral, topical, and inhaled forms
- Toxicity includes hypertension, hyperglycemia, hypertriglyceridemia, gastric ulcerations, osteoporosis, osteonecrosis

Cyclophosphamide

- Used for prophylaxis and given post-transplantation
- Typically used for haploidentical transplantation but may be used with other alternative donor regimens.
- **MUST NOT GIVE CORTICOSTEROIDS FOR ANY REASON BETWEEN GRAFT INFUSION AND CYCLOPHOSPHAMIDE TO AVOID COMPROMISING EFFICACY**

Cyclosporine

- Single agent or use in combination
- Calcineurin inhibitor which interferes with T-lymphocyte function

- Frequently used in prophylaxis starting day -1 given orally or IV
- Dose adjustments made based on trough levels
- Toxicity includes hypertension, renal toxicity, hepatotoxicity, hypomagnesemia, leukoencephalopathy, seizures

Tacrolimus
- Macrolid lactone that inhibits T-cell activation by down regulation of IL-2 gene expression. It forms a complex with FK-binding protein which inhibits calcineurin.
- Used in prophylaxis starting day -1 given orally or parenterally
- Dose adjustments made on trough levels
- Toxicity similar to CSA but may include myelotoxicity

Sirolimus
- Similar in structure to CSA and tacrolimus
- Inhibits signal transduction and cell cycle progression by binding to FK-binding proteins and may have some anti-leukemic effect in Pre-B ALL
- Currently undergoing randomized trials

Mycophenolate Mofetil
- Potent competitive inhibitor of purine synthesis, particularly the synthesis of guanine nucleotides
- Used for prophylaxis and treatment of aGVHD given orally or parenterally
- Toxicity includes myelotoxicity, GI toxicity, diarrhea, nausea, hepatotoxicity
- Dosing starting at 45 mg/kg/day divided q8h, starting Day -3 or Day 0 through to Day +45

Antithymocyte Globulin
- Horse or rabbit serum given parenterally that contains pan anti-T-cell antibodies
- Used in conditioning and second line treatment of aGVHD
- Toxicities includes high frequency of allergic reactions and serum sickness

Alemtuzumab
- Recombinant humanized monoclonal antibody directed against CD52 + cells found on lymphocytes, NK cells, macrophages, monocytes and some granulocytes
- Used in prophylaxis and treatment of aGVHD but optimal dose and timing has yet to be established. Timing is highly relevant to engraftment and GVHD prevention.
- Given parenterally and toxicities include rash hives, infection, headache, vomiting and diarrhea

Infliximab
- Recombinant humanized monoclonal antibody directed against tumor necrosis factor (TNF).

- Activity has been demonstrated in treating steroid resistant aGVHD especially gut GVHD
- Concern regarding increased risk of invasive fungal infections
- Toxicities include infection, headache, tremor, seizures, stroke, GI bleeding nausea and vomiting

Ruxolitinib

- Recent landmark paper showed improved durable responses in adults and children over 12 years of age with steroid-refractory aGVHD.
- Toxicities include cytopenias, weight gain, GI bleeding, and CMV infection.

Protocols from Prophylaxis of Acute Graft Versus Host Disease

All patients undergoing allogeneic HSCT will receive GVHD prophylaxis

- Prophylaxis may be dependent on the underlying condition requiring transplant, stem cell source, and conditioning regimen to be used.
- Below are some institutional protocols for prophylaxis, however, these will be substituted with 'study based prophylaxis' as needed.

Matched/Mismatched Sibling Allogeneic Transplant Using PBSC or Marrow
Matched/Mismatched Unrelated Donor Transplant Using PBSC or Marrow

- CSA/Methotrexate

All Cord Blood Transplants

- CSA + mycophenolate mofetil

Methotrexate (MTX) Protocol

- MTX: Initial dose of 15 mg/m^2 (IV or PO) on day +1 (at least 24 hours following infusion of product) and 10 mg/M^2 on day +3, +6 and +11.
- If stem cells are given two days apart (Day 0 and Day 1), then MTX will be given 1 day later that the usual protocol (i.e. 15 mg/m^2 on Day +2, and 10mg/m^2 on Day +4, +7, and +12).
- MTX may be adjusted for hepatic and renal dysfunction – see below
- MTX might not be given if patient has severe mucositis (> Grade 3) on the day MTX is scheduled. All attempts should be made to ensure this dose is given
- MTX will not be given or MTX levels will be monitored if patient has a large 3rd space fluid collection
- Septra should not be given on days MTX is scheduled

Dosage Reduction for Impaired Hepatic Function

Direct Bilirubin (micromoles/Litre)	% Methotrexate Dose Reduction
34	0
34-50	25
51-100	50
>100	100

Dosage Reduction for Impaired Renal Function

Calculated Creatinine Clearance (mls/min)	% Methotrexate Dose Reduction
>85	0
65-84	25
50-64	50
<49	100

Dosing and Monitoring Guidelines for GVHS Prophylaxis

Cyclosporine Protocol

- CSA dosing 2.5 mg/kg/dose IV every 12 hours starting day -1. If able to tolerate oral form, start at 6.25 mg/kg/dose every 12 hours
- CSA dose is monitored by trough levels which are done Mon/Wed/Fri morning prior to morning dose. If CSA levels are required on the weekend or statutory holidays, they must be ordered stat for those days.
- CSA dose will need to be adjusted or held based on renal or hepatic impairment.
- CSA level is generally between 150-200 for malignant conditions and 200-300 for non-malignant conditions (as no graft versus leukemia (GVL) effect is desired).
- Once patient is able to tolerate oral medications, can switch to oral CSA regimen.
- Oral CSA dosing is 2.5 times the IV dosing.

Tacrolimus Protocol

- Often used if there is CSA intolerance.
- IV dosing of tacrolimus has historically been given as a continuous infusion (rather than bolus dosing) at 0.02 mg/kg/day. Alternatively, tacrolimus may be given intravenously every 12 hours starting at 0.02 mg/kg/day divided every 12 hours and infused over 2 hours
- Oral dosing is 0.2 mg/kg PO divided every 12 hours
- Trough levels will be drawn prior to morning dose on Mon/Wed/Fri as per CSA protocol Level range is 8-12
- Oral dosing is 4 times the IV dosing
- To convert from cyclosporine: the dose of tacrolimus is 1/50 the dose of oral cyclosporine.

Tacrolimus can be started 12 hours after the last oral cyclosporine dose.

Sirolimus Protocol

- Used primarily for sickle cell disease protocols
- Oral administration only
- Loading doses required when initiated and when fluconazole discontinued to reach appropriate steady state levels quickly. When fluconazole is discontinued and levels are within range, consider increasing the next sirolimus dose to 3x the current sirolimus dose for 1 day, thereafter increase the sirolimus dose to 2x the current dose (e.g. If current sirolimus dose is 2 mg PO daily, stop fluconazole, then increase sirolimus to 6 mg PO x 1 day, then 4 mg PO daily thereafter). Continue weekly levels.
- Level range is 8-12

Post-Transplant Cyclophosphamide

- Used primarily for unmanipulated haploidentical allografts
- IV dose of 50 mg/kg/day on Days +3 and +4
- Mesna administered as per standard practice
- Cytokine release syndrome common between unmanipulated haploidentical stem cell infusion and first dose of cyclophosmide
- **MUST NOT GIVE CORTICOSTEROIDS FOR ANY REASON BETWEEN GRAFT INFUSION AND CYCLOPHOSPHAMIDE TO AVOID COMPROMISING EFFICACY**

Tapering of Immune Suppression if No aGVHD

- Tapering of immune suppression is variable and dependent on disease process and type of transplant.
- MTX is completed by day + 11 with no weaning is required.
- See table below for timing of CSA/tacrolimus/sirolimus taper if no aGVHD

Disease	Donor	Start Taper Day
ALL AML	Any	Day 42-45 if no GVHD
Other malignant high risk leukemia	Any	Day 45 if no GVHD
Non-Malignant*	Any	Day 180 Aplastic Anemia patients continue immune suppression for 9 months before tapering.
Sickle Cell Disease (NIH protocol)	Matched sibling	1 year or donor T-cell chimerism >50%, whichever is later

Cyclosporine Wean Example: Baseline dose of 100 mg po bid

1. Decrease CSA by 10 % from baseline dose x one week → 90 mg po bid
2. Decrease CSA by 25 % from baseline dose x one week → 75 mg po bid
3. Decrease CSA by 50 % from baseline dose x one week → 50 mg po bid
4. Decrease CSA by 75 % from baseline dose x one week → 25 mg po bid and then stop

- Taper schedule is not absolute and depends on patient's clinical condition. However, one should attempt to stick to the protocol as much as possible to ascertain treatment failure and need for additional treatments.
- If patient develops moderate aGVHD, will need to return to previous higher level.

Management of Acute Graft Versus Host Disease

- All patients should have weekly documentation of GVHD grade within the in-patient setting.
- Ideally this has been suggested for Mondays of every week and will also be updated for team information at the weekly BMT meeting.
- The BMT staff will update GVHD grading on Tuesday for a 'holiday Monday' in case the covering staff is not a BMT physician.
- If grade of GVHD changes during the week, it should be updated in the daily note.
- Outpatient GVHD grading should be updated at each patient visit in the GVHD flowsheet or in the physician note.

First Line Treatment for Acute Graft vs Host Disease

MILD-Skin GRADE I, stage 1-2 only:

- Continue GVHD prophylaxis with CSA.
- Maintain CSA levels 150-200 for patients with malignant disease.
- Maintain CSA levels 200-300 for patients with non-malignant disease.
- Start topical betamethasone 0.1% tid to affected areas on body (hands, feet, limbs, and torso).
- Start topical hydrocortisone 1% to affected areas on face and perineal area.
- If skin rash progresses within 7 days or shows no improvement after 7-10 days, then proceed to MODERATE therapy.

MODERATE- Grade II or greater, skin stage 3, and/or liver 1-4 and/or GIT 1-3 and/or UGI:

- Continue CSA/tacrolimus and maintain levels 200-300 range.
- Start prednisone 2 mg/kg/day (60 mg/m$^{2/}$day) PO divided BID (or methylprednisolone 1.6 mg/kg/day (48 mg/m^2/day) IV divided q8h/tid) for 7 days.

- Start GERD prophylaxis if needed.
- If continual improvement, then proceed to "Taper Schedule" after one week.
- If after 4 days, GVHD progresses by one stage (steroid resistant) → 2nd line treatment.
- If after 7 days GVHD has not improved by one stage (steroid resistant) → 2nd line treatment.
- If after initial response, develops recurrent/progressive GVHD, while on steroids, increase dose to prednisone 2 mg/kg/day (60 mg/m^2/day) PO divided BID (or methylprednisolone 1.6 mg/kg/day (48 mg/m^2/day) IV divided q8 h/tid) for 7 days and → 2nd line treatment.

Response Criteria:
- **Partial**-Reduce stage by one or alternate diagnosis
- **Mixed-** Reduce stage in one organ while increasing stage in another organ
- **Stable-** No change in any organ
- **Progressive-** Increase in any organ by one stage

Second Line Treatment for Acute Graft vs Host Disease
The first choice for patients already on CSA is to add steroids in doses stated above as full dose steroids. If no response to treatment over the next 5-7 days, any of the following options might be considered as there are no specific option that are proven to be better than others, aside from recent data supporting the use of ruxolitinib.

***Ruxolitinib** should be considered for GVHD refractory to steroids and calcineurin inhibitors
***Infliximab** should be considered in isolated or predominant gut GVHD requiring additional line of treatment.

Option 1 – ruxolitinib:
- Continue on present dose of CSA and steroids
- Start ruxolitinib 10 mg po bid (children 12 years of age or older). Reduced dosing is required for smaller children – consult a pharmacist
- Steroid wean may begin if GVHD responsive.
- Start CSA taper 30 days after patient is off steroid therapy for GVHD**.**
- Wean ruxolitinib at day 56 of therapy if no active GVHD**.**

Option 2- Antithymocyte Globulin (ATG):
- Continue present dose of CSA. Start CSA taper 30 days after patient is off steroid therapy for GVHD.
- Continue methylprednisolone 48mg/m^2/day IV divided bid for 7 days. This should be given as the pre-medication for ATG and should be timed for the start of ATG.
- Rabbit antithymoglobulin 3 mg/kg/dose IV over 4 hours every 24 hours for 3-5 days. Pre-medicate ATG with steroid as above, diphenhydramine 1 mg/kg IV Max 50 mg and acetaminophen 10-15 mg/kg (max 1 gram) orally.
- If patient develops ATG reaction, can use further diphenhydramine and meperidine 1 mg/kg IV

(max 50 mg) and slow infusion rate as per physician.
- Once ATG course completed, give single dose prednisone 60 mg/m^2/day for 7 days; then taper over 8 weeks.

Option 3 – High dose Steroid Pulse:
- CSA and ATG as above.
- High dose methylprednisolone 250 mg/m^2/day IV divided q12h for 5 days. Then decrease to methylprednisolone 48 mg/m^2/day IV divided q12h for 7 days and then start tapering schedule.

Option 4 – Etanercept:
- Etanercept 0.4 mg/kg/dose (max 25 mg) subcutaneously twice weekly, each dose separated by 72-96 hours.

Option 5 – Extracorporeal photopheresis:
- Extracorporeal photopheresis is an in vivo method to inactivate T cells via ultraviolet irradiation while minimizing systemic complications seen with other treatments.
- Lymphocytes are removed from the patient by leukapheresis and treated with UVA and Psoralen. There are few systemic effects with re-infusion of the cells.
- Useful in patients with predominantly skin GVHD.
- Patient size (less than 25 kg) may be prohibitive.

Option 6 – Cyclophosphamide:
- For isolated skin graft versus host disease, a single dose of IV cyclophosphamide 1000 mg/m2 with MESNA protection and IV hydration may given and repeated every 3-4 weeks dependent on count recovery.

ACH HOT BMT PROGRAM IMMUNOSUPPRESSANT TAPERING SCHEDULE for MALIGNANT Conditions

Patient Name: _____
Taper Start Date: _____
BMT Day #: _____
Weight used for taper: _____
Baseline immunosuppressant and dose: _____

Date	Taper Week	Dosing level	Immunosuppressant	Dose	Morning	Afternoon	Supper	Bedtime
	WEEK 1 (Day 42-49)	90% of baseline dose						
	WEEK 2 (Day 50-57)	75% of baseline dose						
	WEEK 3 (Day 58-65)	50% of baseline dose						
	WEEK 4 (Day 66-73)	25% of baseline dose						
		STOP						

Immunosuppressant Agents:

Cyclosporine supplied as: 10 mg capsule, 25 mg capsule, 50 mg capsule, 100 mg capsule, 100 mg/mL oral liquid Tacrolimus supplied as: 0.5 mg capsule, 1 mg capsule, 5 mg capsule, 1 mg/mL oral suspension
Sirolimus supplied as: 1 mg tablet, 1 mg/mL oral liquid

Immunosuppressant Tapering Schedule for NON-MALIGNANT Conditions

Patient Name: _____
Taper Start Date: _____
BMT Day #: _____
Weight used for taper: _____
Baseline immunosuppressant and dose: _____

***For sirolimus patients:** *use IMMUNOSUPPRESSANT TAPERING FOR SIROLIMUS*

Date	Taper Week	Dosing level	Immunosuppressant	Dose	Morning	Afternoon	Supper	Bedtime
	WEEK 1 (Day___-___)	90% of baseline dose						
	WEEK 2 (Day___-___)	80% of baseline dose						
	WEEK 3 (Day___-___)	70% of baseline dose						
	WEEK 4 (Day___-___)	60% of baseline dose						
	WEEK 5 (Day___-___)	50% of baseline dose						
	WEEK 6 (Day___-___)	40% of baseline dose						
	WEEK 7 (Day___-___)	30% of baseline dose						
	WEEK 8 (Day___-___)	20% of baseline dose						
	WEEK 9 (Day___-___)	10% of baseline dose						
		STOP						

Immunosuppressant Agents: Cyclosporine supplied as: 10 mg capsule, 25 mg capsule, 50 mg capsule, 100 mg capsule, 100 mg/mL oral liquid Tacrolimus supplied as: 0.5 mg capsule, 1 mg capsule, 5 mg capsule, 1 mg/mL oral suspension

Prepared by:
Approved by:
Date:

Immunosuppressant Tapering Schedule Following Treatment for GVHD

Patient Name: _____
Taper Start Date: _____
BMT Day #: _____
Weight used for taper: _____
Baseline immunosuppressant and dose: _____

Date	Taper Week	Dosing level	Immunosuppressant	Dose	Morning	Afternoon	Supper	Bedtime
	WEEK 1 (Day___-___)	90% of baseline dose						
	WEEK 2 (Day___-___)	80% of baseline dose						
	WEEK 3 (Day___-___)	70% of baseline dose						
	WEEK 4 (Day___-___)	60% of baseline dose						
	WEEK 5 (Day___-___)	50% of baseline dose						
	WEEK 6 (Day___-___)	40% of baseline dose						
	WEEK 7 (Day___-___)	30% of baseline dose						
	WEEK 8 (Day___-___)	20% of baseline dose						
	WEEK 9 (Day___-___)	10% of baseline dose						
		STOP						

Immunosuppressant Agents:

Cyclosporine supplied as: 10 mg capsule, 25 mg capsule, 50 mg capsule, 100 mg capsule, 100 mg/mL oral liquid Tacrolimus supplied as: 0.5 mg capsule, 1 mg capsule, 5 mg capsule, 1 mg/mL oral suspension
Sirolimus supplied as: 1 mg tablet, 1 mg/mL oral liquid

Date Reviewed/Comments:

ACH HOT BMT PROGRAM STEROID TAPERING SCHEDULE Following Treatment for GVHD

Patient Name: _____
Taper Start Date: _____
BMT Day #: _____
Weight used for taper: _____

Steroid Agents:

- □ ***Oral: Prednisone (Supplied as: 50 mg tablets, 5 mg tablets, 1 mg tablets, 5 mg/mL oral suspension)***
- □ ***IV: Methylprednisone injection*** ***Steroid conversion: Prednisone 5 mg = Methylprednisone 4 mg***

Date	Taper Week or Duration	Dosing level	Steroid Agent	Dose	Morning	Afternoon	Supper	Bedtime
	WEEK 1 (Day 1-7)	PREDNISONE 2 mg/kg/day divided TWICE daily						
	WEEK 2 (Day 8-14)	PREDNISONE 1.8 mg/kg/day divided TWICE daily						
	WEEK 3 (Day 15-21)	PREDNISONE 1.6 mg/kg/day divided **ONCE daily**						
	WEEK 4 (Day 22-28)	PREDNISONE 1.4 mg/kg/day divided ONCE daily						
	WEEK 5 (Day 29-35)	PREDNISONE 1.2 mg/kg/day divided ONCE daily						
	WEEK 6 (Day 36-42)	PREDNISONE 1.0 mg/kg/day ONCE daily						
	For 5 days (Day 43-47)	PREDNISONE 0.8 mg/kg/day ONCE daily						
	For 5 days (Day 48-52)	PREDNISONE 0.6 mg/kg/day ONCE daily						

Date	Taper Week or Duration	Dosing level	Steroid Agent	Dose	Morning	Afternoon	Supper	Bedtime
	For 5 days (Day 53-57)	PREDNISONE 0.4 mg/kg/day ONCE daily						
	For 5 days (Day 58-62)	PREDNISONE 0.2 mg/kg/day ONCE daily						
	For 5 days (Day 63-67)	PREDNISONE 0.1 mg/kg/day ONCE daily						
	For 5 days (Day 68-72)	PREDNISONE 0.1 mg/kg/day **EVERY OTHER DAY**						
		STOP						

Date Reviewed/Comments:

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Hemorrhagic Cystitis

Presented by: Ravi Shah

Hemorrhagic cystitis (HC) is a well-recognized complication of hematopoietic stem cell transplant (HSCT) in children and adolescents. Many modalities, both invasive and non- invasive, are used to treat moderate to severe HC, but none are consistently effective. Few studies compare various therapeutic options to guide the treatment of this challenging condition. This guideline is limited to managing hemorrhagic cystitis post-stem cell transplant.

Definition

- Presence of hematuria AND urinary tract irritability (dysuria, frequency, urgency) in the absence of other conditions such as vaginal bleeding, generalized bleeding diathesis, and bacterial or fungal urinary tract infection.
- Early-onset HC: Typically, within 48-72 hours after end of the conditioning regimen and it is due to direct toxic effect of drugs or radiation on bladder mucosa.
- Late-onset HC: It usually occurs 2 weeks after HSCT and up to 3 months after transplant. The aetiology is varied and includes infections.
- BK HC or BKPyV-HC:
    - Presence of hematuria [≥grade 2]
    - Clinical Symptoms/signs of Cystitis [Dysuria, increased urine frequency, lower abdominal pain]
    - High load BKPyV viuria [>10*7 copies/ml]

Etiology

- Damage to bladder transitional epithelium and blood vessels by toxins, viruses, radiation, drugs, or disease
- Early-onset HC is frequently associated with cyclophosphamide and/or busulfan, especially the former, whose liver metabolite [acrolein] accumulates in the bladder. Late- onset HC often results from various viral infections, especially polyomaviruses (BKPyV, JC), adenovirus type 11 or CMV, and busulfan exposure in the conditioning phase of transplant. BKPyV persists latently in the renal tubular epithelial and urothelial cells and can replicate during an immunosuppressive state.
- A higher degree of immune suppression may predispose allogeneic HSCT recipients to HC
- Myeloablative conditioning has a higher risk than reduced intensity conditioning
- Cord stem cell transplant and HHV-6 viral infection are also risk factors, according to some studies

Pathogenesis

- The cause of post-HCT HC is multifactorial. It includes the combined effects of the extensive

viral cytopathic damage of the bladder mucosa, the chemical or actinic damage induced by the conditioning regimen and the immune donor-derived alloreactivity targeting bladder mucosa. In patients receiving allogeneic HCT, BKPyV viruria >10^7 genomic copies/ml and BKPyV viremia >103 genomic copies/ml are predictive factors for BKPyV-HC.

- Mesna administration with PTCY helps prevent or reduce the severity of HC. There is no consensus on the optimal dosing schedule for mesna administration in HSCT recipients receiving PTCy-based GVHD prophylaxis. Intermittent mesna dosing schedules have not proved to be beneficial in reducing the incidence of HC among allogeneic HSCT recipients. In a recent study by Arango et al. the continuous infusion of mesna was found to be more useful than recurrent bolus administration in preventing HC among haploidentical HSCT recipients receiving PTCy as GVHD prophylaxis.

In the late-onset HC, BKPyV replication has a key role in exacerbating the damage of bladder mucosa through its cytopathic effect and in inducing the donor immune alloreactivity targeting the bladder mucosa.

Clinical Presentation

- Microscopic/macroscopic hematuria
- Urinary frequency, urgency, dysuria, incontinence
- Suprapubic pain (bladder spasms)
- Back or flank pain uncommon and may indicate upper urinary tract disease
- Clot retention and obstructive uropathy

GRADING of Hematuria

1	Microscopic hematuria
2	Macroscopic hematuria
3	Macroscopic hematuria with clots
4	Macroscopic hematuria with urinary obstruction or renal dysfunction due to urinary obstruction

Approach to Persistent Microscopic Hematuria post HSCT

Early Onset
<2-week post HSCT
Usually due to conditioning regimen

Delayed Onset >2-week post HSCT
Usually due to other causes

1. Urine routine and micro, culture
2. Evaluate for Clinical cystitis and radiological cystitis [if appropriate]
3. Send urine samples for BK and Adeno PCR. If urine positive test for serum. DO Serum CMV PCR, we do not have CMV PCR urine testing available
4. Consider w/u for TA-TMA if there is proteinuria or other signs of TA-TMA
5. Ensure patient is well hydrated and use hyperhydration [1.2-1.5 X maintenance]
6. Keep platelets >10 [for asymptomatic] and do CBC monitoring as appropriate
    a. Regular platelet transfusions may augment developed of clots and sustain/enhance HC.

Management of Hemorrhagic Cystitis

General Principles

1. Keep Platelet count >20-30 [for low grade cystitis] and in Severe cases, try a higher cut off [>50] as it has been found beneficial in some studies
2. Correct any coagulopathy
3. Maintain Hb level ≥ 8 g/L
4. Hyperhydration [1.5-2 x maintenance if permitted clinically]
5. Forced Diuresis if urine output is <2/3rd of the Input
6. Symptom control
    a. Oxybutynin or tolterodine [bladder spasms]
    b. Phenazopyridine [dysuria]
    c. Parenteral opioids
7. Suspect obstruction if Urea/creatinine increases or urine output falls
    a. If urinary obstruction or persistent clots occur, Bladder Irrigation [UROLOGY] is recommended. It is no more effective than hyperhydration, so the EBMT guideline does not recommend it but can be considered on a case-by-case basis.
8. Monitor for nephropathy
9. Reduce immune suppression if Viuria/viremia + and if it is safe to do so from the Gvhd point of view
10. Consult UROLOGY for refractory cases

Refractory Cystitis

The literature includes many alternative therapies, both invasive and non-invasive. However, there is no consensus on the best treatment modality. Often, interventions can take days or weeks to show a meaningful response.

- Consider HYPERBARIC oxygen, consult early, as it takes time to set it up. [Appendix]
- Consult Urology- consider cystoscopy for clot removal and local therapy for bleeding sites [Fibrin glue]
    - Cystoscopic application of fibrin glue to the damaged bleeding bladder mucosa has been associated with a response rate of 83%, with most cases resolved with one or two applications
- Consider use of IV Cidofovir (for susceptible viruses) as below and decreasing immune suppression if no active AGVHD – Appendix 1
    - For refractory cases, intravesicular cidofovir has been used and might be considered.
- Adoptive transfer of donor-derived virus-specific T cells (VSTs) has shown efficacy, but access is limited
- Surgical options

  - Supravesical urinary diversion using a bilateral nephrostomy. Supravesical urinary diversion prevents urokinase, which is secreted from renal cells, from reaching the bladder wall, thereby promoting hemostasis.
  - In case of life-threatening bleed: Selective arterial embolisation [vesical or internal iliac arteries]
- Some results have been reported with leflunomide [no Pediatric studies], an antimetabolite drug with immunomodulatory and antiviral activity. **Anecdotal use** of other agents (conjugated oestrogen, oral cipro or levofloxacin, FXIII concentrate, intravesical sodium hyaluronate and oestrogens) is reported in the literature. The evidence supporting the use of these agents is poor, and we do not recommend using them routinely.

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Appendix 1: Use of Cidofovir in Hemorrhagic Cystitis

Generally, HC due to BK infection is considered a self-limited complication. However, it prolongs hospitalisation, may cause significant morbidity, and may be fatal, especially if it causes BK nephropathy. Cidofovir has a limited role in treating BKV-related HC, especially given the risk of drug-related tubular nephrotoxicity. Cidofovir can be used for adenovirus-related refractory cystitis. Grades 3 and 4 BK-related refractory HC or BK nephropathy warrant treatment with IV cidofovir.

- Document viruria and viremia with either adenovirus or BK
- Obtain BUN, Cr, Cr clearance (GFR if available), urinalysis R/M
- Cautions:
  - Hypersensitivity to cidofovir or probenecid
  - Serum Cr > 130 or 1.5 x baseline
  - Creatinine clearance < 55 ml/min
  - Patients receiving other nephrotoxic drugs
- Drug Interactions:
  - Aminoglycosides, amphotericin B, foscarnet, vancomycin, pentamidine and NSAIDS increase nephrotoxicity
- Dosage:
  - Must be used with concomitant oral probenecid and IV NS hydration. Probenecid reduces the risk of nephrotoxicity by decreasing the concentration of cidofovir in the proximal tubular cells
  - Cidofovir (Children) 1 mg/kg/dose IV three times/week or 5 mg/kg/dose once weekly for three weeks, then every two weeks. Oral probenecid 1.25 g/m^2/dose 3 hours before and 1 hour and 8 hours after completion of each 1-hour cidofovir infusion. NS bolus equal to 3 times the maintenance fluid is given for 1 hour before cidofovir infusion and 1 hour after, then decreased to 2 times the maintenance fluid for the subsequent 2 hours
  - Renal Impairment: If serum creatinine increases by 1.25 x baseline, reduce cidofovir dose to 3 mg/kg; discontinue cidofovir for increases 1.5 x baseline or 3+ proteinuria
  - Cidofovir can be administered INTRAVESICALLY to reduce the risk of nephrotoxicity, at the dose of 5 mg/kg/body weight/week and left in situ for 1–2 h after clamping the vesical catheter, the response rate being about 50%
- Monitor BUN, Cr, urinalysis R/M, CBC and diff, electrolytes, Ca, Mg, Phos, uric acid, and LFTs

Appendix 2: Hyperbaric Oxygen Therapy

Hyperbaric Oxygen Therapy (HBOT) was initially used in patients with radiation-induced HC, and more recently used for chemotherapy-induced HC.

High-pressure oxygen generates a high oxygen gradient between the damaged urothelium and the surrounding healthy tissues. This oxygen gradient promotes macrophage invasion into the damaged tissues and stimulates angiogenesis and tissue healing via the secretion of cytokines by macrophages.

HBOT is non-invasive and may help preserve bladder function, so it should be considered early in patients with refractory HC. It is an attractive approach because of the non-invasive nature of therapy. Ideally, it should be considered before using bladder instillations of chemicals, which may result in a fibrotic, contracted and non-compliant bladder.

Patients should be hemodynamically stable enough to be heplocked and confined to a hyperbaric chamber for daily 2-hour sessions**. [No procedural sedation and the patient needs to be alone in the chamber]**. The patient breathes 100% oxygen in a pressure chamber, which increases the pressure to 2.4-2.6 atmospheric pressure. The therapy may be required for several weeks. The only contraindication is an untreated pneumothorax. Currently, in Alberta, the cost is generally covered by Alberta Health Care.

Counsel patients for the risk of ear barotrauma or pressure intolerance and claustrophobia episodes during the procedure.

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Evaluation Of Donor Chimerism and Engraftment in Pediatric Recipients of Cellular Therapy Product

Presented by: Greg Guilcher

Purpose

To provide guidance with the evaluation of donor chimerism and engraftment in allogeneic cellular therapy product (CTP) patients.

Points of Emphasis/Background

Evaluation of donor chimerism is helpful in routine documentation of donor engraftment, assessment of graft failure, evaluation of persistence of donor cells and monitoring for risk of recurrent malignancy or recurrence of underlying non-malignant disease and associated complications.

Donor chimerism refers to the presence of allogeneic donor hematopoietic or lymphoid cells in a CTP recipient. Full donor chimerism is achieved when all hematopoietic and lymphoid cells are derived from an allogeneic donor (defined as >95% donor cells detected). Partial or mixed chimerism occurs when recipient hematopoietic or lymphoid cells persist together with donor cells after CTP infusion (defined as at least 5% or 10% donor cells respectively). Absent donor chimerism occurs when there are no detectable donor hematopoietic/lymphoid cells (defined as <5 % donor cells).

Lineage-specific chimerism can be measured by sorting bone marrow or peripheral blood cells by flow cytometry to give specific T, B, myeloid, and NK-cell chimerisms. This is particularly useful for assessing the effect of particular conditioning regimens (T-cell depleted, reduced intensity or non-myeloablative), assessing the probability of GVHD and GVL effects (donor T- cell chimerism) and can be helpful in confirming the diagnosis of recurrent malignancy (disease- specific lineage chimerism). Split chimerism occurs when donor cells are present within some hematopoietic or lymphoid lineages but not in others. Details of split chimerism should be clearly documented, e.g., myeloid cells are 100% host and T cells are 100% donor.

Poor graft function has been defined by some experts as mixed donor chimerism with the need for transfusion or G-CSF support.

In allogeneic CTP, donor and recipient cells can be distinguished by testing informative genetic markers. This is accomplished by PCR analysis of common genetic polymorphisms (variable number of tandem repeats [VNTR] or short tandem repeats [STR]). Blood samples from the donor and recipient are required pre-CTP in order to determine informative alleles for chimerism testing post-CTP.

Evaluation of Engraftment

- Chimerism studies will be drawn from peripheral blood on day +21 if there are signs of early engraftment. Absence of any lymphocytes in peripheral blood will lead to results showing 'insufficient cells for evaluation.
- If there are no signs of engraftment, delay chimerism studies until day +28, at which time a sample for engraftment analysis should be sent regardless of neutrophil count.
- In malignant disorders (non-cord blood CTP) a bone marrow evaluation should be considered at this point for evaluation of remission status. In such cases bone marrow samples should be sent for engraftment studies. This may also be considered for non- malignant diseases to assess cellularity, as indicated.
- Only one sample (bone marrow or peripheral blood) should be sent for evaluation at a given time point.
- In cases of malignant disorders, if day +21 chimerism studies show complete donor chimerism, then repeat studies at day +100, or follow disease-specific protocol as applicable.
- If day +21 chimerism studies are less than complete donor chimerism repeat studies at day +60.
- Malignant CTP recipients undergo bone marrow aspirate +/- trephine biopsy at around day +100. Only one of the sources - preferably bone marrow cells - should be examined for chimerisms.
- For malignant CTP recipients chimerisms should be repeated at 6 months post-CTP. Beyond that time point, chimerism testing is at the discretion of the primary physician.
- For non-malignant disorders, metabolic disorders, as well as hematopoietic stem cell transplant (HSCT) using T-cell depleted, non-myeloablative, or reduced intensity conditioning, or novel GVHD prophylactic regimens, obtain chimerism studies at day +21-28, day +60, day +100, day +180. and 1 year post CTP infusion. Beyond the 1-year time point chimerisms may be obtained at the discretion of the primary physician.
- Disease or patient specific considerations may influence the frequency of testing. Often correlate testing (HPLC or immune functional testing) is timed with some of these evaluations of donor chimerism.

Chimerism Testing Procedure

- All chimerism study samples will be forwarded to the Flow Cytometry department.
- Chimerisms will be tested on 'sorted' samples with measurements of T-cells, lineage specific cell line (B or myeloid) and other cell lines as indicated by the disease process e.g. NK cells, B-cells for immunodeficiency CTP recipients. Haploidentical recipients will often have all cell lines evaluated.

- The donor episode must be linked to the recipient episode in the medical record, and "Selected for Donation".

- **Bone Marrow Specimens:**
  - The bone marrow requisition will accompany all samples and the physician will confirm if Chimerism Studies are required.
  - Specimens will be collected in Flow Bone Marrow Media (BMM) and 0.5 ml of marrow is needed.
  - A separate BMM is required if Flow Cytometry is requested.
- **Peripheral Blood Specimens:**
  - Pediatrics: 1 x 2.7 ml Na Citrate
  - Adults: 1 x 8.5 ml ACD-A
  - All samples to be accompanied by a Flow Cytometry requisition with the Chimerism Investigation section completed.

Management of graft failure

The management of graft failure (primary or secondary) and falling donor chimerisms is complex and patient/disease specific.

Primary graft failure typically results in marrow aplasia, which requires urgent intervention with another CTP. This product may be from the same donor or from a new donor. The requirement for conditioning depends on the patient's clinical status and the CTP. Early intervention to prevent life-threatening infections should be considered. In the event of autologous marrow recovery, the approach may be different and more time might be taken to consider a second CTP, depending on the patient's condition and urgency.

Secondary graft failure may be associated with aplasia or autologous marrow recovery. Interventions for secondary graft failure, poor graft function or decreasing donor chimerism depend on the clinical status of the patient, underlying disease, availability of donors/additional CTPs and urgency for curative therapy.

Patients with primary or secondary graft failure should undergo appropriate workup to determine a possible cause (such as viral infection, e.g. CMV) and those with a history of malignancy should be evaluated for disease recurrence. Relapsed malignancy may require chemotherapy and/or radiation therapy.

Interventions for graft failure and/or decreasing donor chimerism may include:

- Decrease in immune suppression (malignant diseases)

- Increase in immune suppression (non-malignant diseases)
- Donor stem cell boost (typically non-malignant diseases in the setting of some donor T-cell engraftment), with or without lymphodepletion
- Donor lymphocyte infusion (malignant diseases)
- Re-transplantation with full conditioning (usually deferred for at least 6 months from prior CTP, especially if the patient received myeloablative conditioning)

Definitions

Neutrophil Engraftment:

- The first day of 3 days when the absolute neutrophil count (ANC) is > 500 cells/μL
- The first of the 3 days is referred to as the "date of engraftment"

Platelet Engraftment:

Platelet count is > 20,000 platelets/μL without transfusion for one week

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Pre-Emptive Therapy, Prophylaxis and Treatment of Cytomegalovirus Infections in Cellular Therapy Product Infusion Recipients

Presented by: Geoff Cuvelier

Purpose

To provide guidance on the pre-emptive therapy, prophylaxis and treatment of cytomegalovirus (CMV) in cellular therapy product (CTP) infusion patients. This guideline applies to both hematopoietic cell therapy and CAR-T cell therapy patients.

Points of Emphasis

- This revised guideline incorporates the following new changes:
    - Risk stratification to guide CMV pre-emptive therapy
    - CMV maintenance therapy may stop after the **SECOND** negative PCR
    - Oral valganciclovir may be used for CMV induction and maintenance therapy
    - Lower thresholds of CMV viremia to initiate repeat testing and/or pre-emptive therapy
- CMV can cause a primary infection in previously unexposed patients or can reactivate in previously infected patients during immunosuppressed states.
- CMV primary infection or reactivation occurs more commonly with allogeneic than autologous transplant recipients.
- CMV disease mortality is high >50% and routine monitoring with pre-emptive therapy is the standard approach.
- The CMV testing method in the BMT program is real time quantitative PCR, using the Real Star assay (Altona), with viral load expressed as IU/mL of plasma.

Definitions

In the pre-transplant evaluation donors and recipients are tested for CMV serologic status: CMV positive or negative status is determined by CMV IgG.
In the post-transplant period (beginning with the start of conditioning for the recipient), CMV status may change as follows:

CMV Infection (primary infection or reactivation): Evidence of CMV virus in plasma or whole blood (CMV viremia, as detected by PCR) without clinical signs of disease. CMV primary infection occurs in patients who were previously CMV IgG negative. CMV re-activation applies to previously CMV-positive patients, but in this guideline, are considered synonymous with CMV infection.

CMV disease: CMV infection (evidence of CMV virus in plasma/blood) AND CMV end-organ involvement (retinitis/colitis/pneumonitis/hepatitis/encephalitis) + demonstration of CMV/histology (when available) in an appropriate clinical specimen.

- Early CMV disease occurs within the first 100 days after transplant and late CMV disease is after Day 100.
- Detection of CMV by PCR alone is insufficient for the diagnosis of CMV pneumonia and CMV GI disease (Ljungman et al. Clin Infect Dis. (2002)).
- CMV disease (esp. lung or GI) can occur without positive blood PCR.

Primary Prophylaxis: Preventive therapy to reduce the risk of CMV infection or reactivation.

Pre-emptive therapy: Treatment of CMV infection or re-activation before CMV disease develops.

Risk Factors

The main factor affecting CMV infection or disease development is recipient and donor CMV serological status (Table 1).

Table 1: Risk of CMV Infection and Disease by Recipient and Donor CMV Serological Status

Recipient (R) and donor (D) serological status	Infection Risk	Disease Risk (without use of preemptive treatment)
R+/ D-	70%	20-35%
R-/ D+	19-30%	10%
R+/ D+		4-20%
R-/ D-	1-3%	1-2%
R+ (Auto)	25-40%	5-7%

Other risk factors are:

1. Umbilical cord transplant
2. In-vivo T-cell depletion – ATG, alemtuzumab (Campath)
3. Ex-vivo T-cell depletion (e.g. alpha-beta TCR depletion) or CD34 positive selection
4. Haploidentical transplants with post-transplant cyclophosphamide
5. CMV infection prior to conditioning
6. High dose steroids
7. Acute and chronic GVHD

CMV Surveillance

1. CMV Baseline Serological Status

a. Serum CMV IgG must be determined in both recipient and donor within 28 days of transplant.
b. Note for infants <6 months of age, CMV IgG positivity *usually* (but not always) reflects maternal seropositivity and CMV antibody acquired transplacentally from the mother. This has implications particularly when the donor is CMV seropositive, placing the recipient patient at the highest risk for CMV infection after transplant.

c. Note for patients receiving IVIg before transplant, CMV IgG will be positive from IVIg and the true serostatus of the recipient is ideally determined from a pre-IVIg CMV IgG level (if available).

2. CMV Detection Testing Methods

a. Real Star CMV PCR (RT) – current standard since March 2012
   i. Real time PCR with high sensitivity and negative predictive value.
   ii. Test is run on plasma (not whole blood) and BAL fluid.
   iii. Reported in international standard (IU)/mL (WHO standard) allowing comparison across labs.
   iv. Conversion factor from previous Alberta Precision Laboratory (APL) in-house assay (copiesl/ml of plasma) to current APL assay (IU/ml of plasma) is approximately 2 fold. (2 copies/ml = 1 IU/ml). This conversion factors varies from lab to lab, depending on testing methods for copies/ml; it is expected that the adoption of an IU will lead to reliable lab to lab comparisons.
   v. Threshold for detection is 40 IU/mL (below this level, test is reported as "negative"). Levels between 40-150 IU/mL are not reliably quantifiable and cannot be compared. The dynamic range is 150 – 1.2 x 10^{12} IU/mL.
   vi. In quantitative PCR, test variability is common and a 2-3x increase may not represent a significant change. However, a 5x increase in CMV PCR viral load is considered significant (equivalent to 1 log increase in the former units of copies/mL).

3. Routine CMV Viral Load Monitoring by PCR

a. In all allogeneic patients and CAR-T (regardless of the donor/recipient serostatus), weekly CMV PCR starting on admission to hospital (blood draws are usually done on Mondays) until Day +100. Pre-emptive therapy monitoring in CMV IgG Donor negative and Recipient negative situations is controversial and may not be cost effective, however, for simplicity and to avoid confusion, we will do CMV PCR monitoring for all allogeneic recipients regardless of donor/recipient serostatus.
b. In certain situations, it may be advisable to monitor CMV PCR before transplant (e.g., in patients with inborn errors of immunity, or patients who received previous serotherapy e.g. sever aplastic anemia patients not responding to immune suppression therapy who are being prepared for transplant).
c. In the absence of CMV infection before day +100, CMV PCR monitoring can continue to be performed monthly from Day +100 to 6 months post-transplant with routine clinic visits, or more frequently if concern for possible CMV disease exists.
d. Monitoring for late CMV infection: In some situations, more frequent monitoring (every 1- 3 weeks) for CMV infection between days 100-180 is indicated. The exact frequency is patient and physician dependent. These situations include: (1) CMV infection and/or disease was present prior to Day +100, to look for recurrence after day 100, when antiviral pre-emptive

therapy or CMV treatment has been discontinued; (2) Ongoing T- cell lymphopenia (CD3 T cell count <200 cells/uL and / or CD4 T cells <50 cells/uL) from any cause; (3) With active late acute and/or chronic GVHD (particularly when on T-cell immunosuppressants and/or on prednisone ≥0.5mg/kg/day); (4) patients with alpha-beta TCR depleted haploidentical transplants who are known to be at higher risk for CMV infection, including late infection; (5) umbilical cord blood recipients when the recipient was CMV IgG seropositive; or (6) patients who received letermovir prophylaxis (currently not licensed for children, although patients may be on a clinical trial or receiving off label) in the first 100 days after transplant.

e. In autologous patients, CMV will not be monitored unless there is clinical suspicion.

Prevention/Prophylaxis of CMV Disease

Pre-Transplant Strategy

- CMV-safe (leukocyte reduced/filtered) blood products are acceptable in cellular therapy patients.
- When choosing hematopoietic donors, when available and all other factors (e.g, HLA match) are equal:
  - a CMV seropositive (+) donor is chosen for a CMV seropositive (+) recipient.
  - a CMV seronegative (-) donor is chosen for a CMV seronegative (-) recipient.
- Local adult data has shown that for a CMV positive recipient, a matched-unrelated donor (MUD) CMV-positive donor results in better outcomes than a matched-related donor (MRD) CMV-negative donor. These results have not been replicated in pediatrics and do not currently inform donor selection.
- High-dose acyclovir, CMV immunoglobulin or IVIg is not recommended for CMV prophylaxis.
- Letermovir is approved in adults for prophylaxis but is currently under study in pediatric patients.

Pre-Emptive Therapy

The approach to CMV pre-emptive therapy will follow a risk-based stratification.

Thresholds for Initiation of Pre-Emptive Therapy:

Prior to allogeneic HCT or CAR T cell therapy, within 100 days post-infusion and if undergoing active therapy for GVHD: Viral load 150-500 IU/ml- repeat testing within a week. If > 150 then initiate therapy. Viral load > 500 IU/ml- initiate therapy.

Beyond 100 days post infusion and no GVHD: >1000 IU/ml Threshold for intervention may be modified based on individual risk factors.

Duration of Pre-Emptive Therapy:

- Induction therapy
  - Continue Induction therapy for a minimum 2 weeks **and until CMV PCR is negative x 2 consecutive weeks, measured at least 7 days apart** (See Table 2, Induction Therapy).
  - If levels are rising (at least 1 log10 increase in copies or 5x increase in CMV PCR viral load in IU/ml) after 2 weeks, suspect resistance and consider a change in therapy. A 5x increase in CMV PCR viral load is considered significant (equivalent to 1 log10 increase in the former units of copies/mL).
- Maintenance therapy
  - Continue maintenance therapy for at least 2 weeks **until CMV PCR is negative x 2 consecutive weeks, measured at least 7 days apart** (See Table 3 Maintenance Therapy).
  - Minimum 2 week of maintenance therapy.
- These recommendations are for general guidance, but physicians may make individualized decisions in the best interest of their patients.

Treatment Agents:

Table 2. Induction Therapy for CMV Infection

Standard Approach		Special Situations: Before engraftment or for patients with ANC <1.0
1st Choice	Valganciclovir PO (see dosing below) or Ganciclovir 5mg/kg/dose IV Q12hr	Foscarnet 60mg/kg/dose IV Q8h
2nd Choice	Foscarnet 60mg/kg/dose IV Q8h	Ganciclovir 5 mg/kg/dose IV Q12H or Valganciclovir PO(see dosing below)
3rd Choice	Cidofovir 5 mg/kg/dose IV per week	Cidofovir 5 mg/kg/dose IV per week

Table 3. Maintenance Therapy for CMV Infection

Standard Approach		Special Situations: Before engraftment or for patients with ANC <1.0
1st Choice	Valganciclovir PO (see dosing below) or Ganciclovir 5mg/kg/dose IV daily Monday-Friday*	Foscarnet 90mg/kg/dose IV daily
2nd Choice	Foscarnet 90mg/kg/dose IV daily	Valganciclovir PO (see dosing below) or Ganciclovir 5 mg/kg/dose IV daily Monday-Friday* or
3rd Choice	Cidofovir 5 mg/kg/dose IV once every two weeks	Cidofovir 5 mg/kg/dose IV once every two weeks

* Based on local institutional practice for resource considerations and patient quality of life. There is limited evidence for Monday-Friday dosing in CMV retinitis (Holland, Ophthalmology 1987).

Ganciclovir Dosing, and Management of Toxicity

- Discontinue acyclovir prophylaxis while patient on Ganciclovir or Foscarnet.
- If ANC<1.0 x10^9/L on two consecutive determinations or ANC < 0.75 for one day, start G- CSF for at least 3 days (alternatively, GCSF at 5 mcg/kg/dose three times a week on a Monday-Wednesday-Friday may suffice to maintain ANC >1.0 x 10^9/L).
- Consider withholding Septra for 2-4 weeks and initiate IV pentamidine at 4 mg/kg/dose IV q28 days for pneumocystis prophylaxis.
- If ANC has not increased to >1.0x 10^9/L within 3 days of starting GCSF or if ANC remains <0.5/10^9/L, switch ganciclovir to Foscarnet.
- Amphotericin B, cyclosporine, and tacrolimus increase risk for nephrotoxicity.
- Imipenem/cilastatin may increase risk for seizures.
- Ganciclovir should be dosed and frequency reduced with reduced CrCl.
- Renal adjustment dosing (It is highly recommended to consult pharmacy when renal dysfunction is present and ganciclovir is to be prescribed. The Schwartz formula should be used to calculate pediatric GFR into per 1.73 m2):
    - Induction
        - >70 m/min/1,73m^2: 5 mg/kg Q12 hour
        - 50-69 mL/min/1,73m^2- 2.5mg/kg Q12 hour
        - 25-49 mL/min/1,73m^2- 2.5mg/kg Q24 hour
        - 10-24 ml/min/1,73m^2- 1.25mg/kg Q 24 hour
    - Maintenance
        - >70 mL/min/1,73m^2: 5 mg/kg Q24 hour
        - 50-69 mL/min/1,73m^2- 2.5mg/kg Q24 hour
        - 25-49 mL/min/1,73m^2- 1.25mg/kg Q24 hour
        - 10-24 mL/min/1,73m^2- 0.625mg/kg Q 24 hour

Valganciclovir Dosing – Requires good oral intake and absence of diarrhea (no GUT GVHD) for better bioavailability

- Induction: 14 mg/kg/dose PO BID (maximum 900 mg PO BID)
- Maintenance: 14 mg/kg/dose PO QD (maximum 900 mg PO QD)

Each tablet is 225 mg. A liquid preparation (50mg/ml) is available. From time to time, valganciclovir is on back order, and a compounded liquid needs to be made that is 60 mg/mL

OR, use the following dosing table, adjusted for Creatinine Clearance (Villeneuve, Ped Transplantation 2012).

Induction Dosing:

CrCl (mL/min/1.73 m^2)	≥10-15 kg	≥15-20 kg	≥20-40 kg	≥40-50 kg	≥50 kg
≥60	14 mg/kg/dose PO BID	225 mg PO BID	450 mg PO BID	675 mg PO BID	900 mg PO BID
40-59	7-8 PO mg/kg/dose BID	7-8 PO mg/kg/dose BID	225 mg PO BID	7-8 PO mg/kg/dose BID	450 mg PO BID
25-39	7-8 PO mg/kg/dose QD	7-8 PO mg/kg/dose QD	225 mg PO QD	7-8 PO mg/kg/dose QD	450 mg PO QD
10-24	7-8 PO mg/kg/dose every other day	7-8 PO mg/kg/dose every other day	225 mg PO every other day	7-8 PO mg/kg/dose every other day	450 mg PO every other day
<10	Consult pharmacy				

Maintenance dosing:

CrCl (mL/min/1.73 m^2)	≥10-15 kg	≥15-20 kg	≥20-40 kg	≥40-50 kg	≥50 kg
≥60	14 PO mg/kg/dose QD	225 mg PO QD	450 mg PO QD	675 mg PO QD	900 mg PO QD
40-59	7-8 PO mg/kg/dose QD				450 mg PO QD
25-39	7-8 PO mg/kg/dose every other day				450 mg PO every other day
10-24	7-8 PO mg/kg/dose twice weekly				450 mg PO twice weekly
<10	Consult pharmacy				

Note: weight-based dosing of valganciclovir may result in subtherapeutic doses compared to BSA-based dosing. If viral breakthrough or antiviral resistance is a concern, consult pharmacy for alternative BSA- based dosing.

Foscarnet Dosing:

- Foscarnet should be initiated within the in-patient setting.
- Foscarnet dose:
  - INDUCTION: 60 mg/kg/dose IV Q8 hourly; or 90mg/kg/dose IV Q12 hourly
- Usual dosing is 180 mg/kg/day div q8-12 hours.
  - MAINTENANCE: 90 mg/kg/dose IV Q daily
- Fluids:
  - Normal saline flush pre-foscarnet during induction and maintenance.
  - 5-10 ml/kg Normal Saline.
- Initial electrolyte monitoring:
  - K, Phos, Mg, Ca Q 12 hourly x 2 days or until stable.
- May cause peripheral neuropathy, seizures, hallucinations, GI disturbance, increased LFTs, hypertension, chest pain, ECG abnormalities, coughing, dyspnea, bronchospasm, and renal failure (adequate hydration and avoiding nephrotoxic medications may reduce risk). Hypocalcemia

(increased risk if given with pentamidine), hypokalemia, and hypomagnesemia may also occur. Use with ciprofloxacin may increase risk for seizures.
- Consult pharmacy for renal dosing recommendations for foscarnet and cidofovir.

Cidofovir Dosing:
- Note: AHS non-formulary medication, STEDT required for approval for use.
- Dosing: 5 mg/kg/dose IV once per week (alternative is 1 mg/kg/dose IV three times per week); dose must be adjusted in renal dysfunction – consult pharmacy.
- Requires probenecid administration (pre and post infusion – 3 hrs before, 3 and 9 hrs after infusion).
- Requires hydration: 20 mL/kg IV prior to & during cidofovir infusion then 2-3 mL/kg/hr IV or PO for 2 hours after infusion.

Therapy of CMV disease
- Ganciclovir or Foscarnet same as above dosing
- Induction therapy: minimum of 4 weeks, then step down to maintenance, if CMV PCR negative x 2 weeks, measured at least 7 days apart
- Maintenance therapy: duration dependent on disease status
- IVIg or CMV IgG can be used for proven or probable CMV pneumonitis
  - IVIg and CMV-Ig are similar efficacy
  - Dose of IVIg 1 gram/kg (based on adjusted ideal body weight) for two consecutive days, with weekly reassessment of immunoglobulin levels and consideration of weekly re-treatment with IVIg for ongoing hypogammaglobulinemia and/or CMV pneumonitis. This dosing is consistent with the 2022 2nd Edition Prairie Collaborative between Alberta, Saskatchewan, and Manitoba in the guideline "Criteria for the Clinical Use of Immunoglobulin: 2nd Edition, 2022)
  - or 150mg/kg CMV Ig every 48 hour for 2-weeks
  - Once weekly during maintenance therapy
  - If volume overload is an issue, use CMV-Ig can be used because the infused volume of CMV-Ig is lower than IVIg

Anti-Viral Resistance

Persistent PCR positivity or increase in viral load in patient on antivirals
- Initial CMV load may rise/remain persistent in first 3 weeks after start of treatment (up to 40% patients)
- Suspect resistance and switch to second line therapy if increasing viral load (≥ 1 log10 increase in copies/mL or a 5 x increase in CMV PCR viral load) after 2 weeks on antiviral therapy. However, a 5x increase in CMV PCR viral load is considered significant (equivalent to 1 log10 increase in the former units of copies/mL)

- Due to test variability an increase of 2-3x in CMV PCR is allowable
- Send testing for viral resistance testing at the peak of CMV viral load
    - UL97 is the phosphotransferase gene; some mutations are associated with ganciclovir resistance. Since foscarnet and cidofovir do not require phosphorylation, these drugs are not affected by UL97 mutations.
    - UL 54 is the DNA polymerase gene; some mutations affect ganciclovir, foscarnet and/or cidofovir resistance.
    - In some cases, increasing Ganciclovir dose to 15mg/kg/day can be considered with pre-emptive G-CSF use.

Note on antiviral susceptibility testing: this is done by amplification and sequencing on the two genes for UL54 and UL97, at the National Microbiology Laboratory in Winnipeg. The turn- around time is about 10 days. Please also note that because the test requires amplification of the whole genes for sequencing, the sensitivity is lower than the detection assay, and for patients with a low viral load it may not work. The cut-off has not been determined with precision yet but below 50,000 IU /mL it becomes increasingly difficult (personal communication, Dr. R. Tellier, Virologist, ProvLab). Inquiries for this assay should be directed to the Virologist on Call (VOC), Alberta Precision Laboratories and discussed with the Infectious Disease service.

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Pediatric Blood and Marrow Transplant Guidelines for the Prophylaxis and Treatment of Fungal Infections

Presented by: Ravi Shah and Greg Guilcher

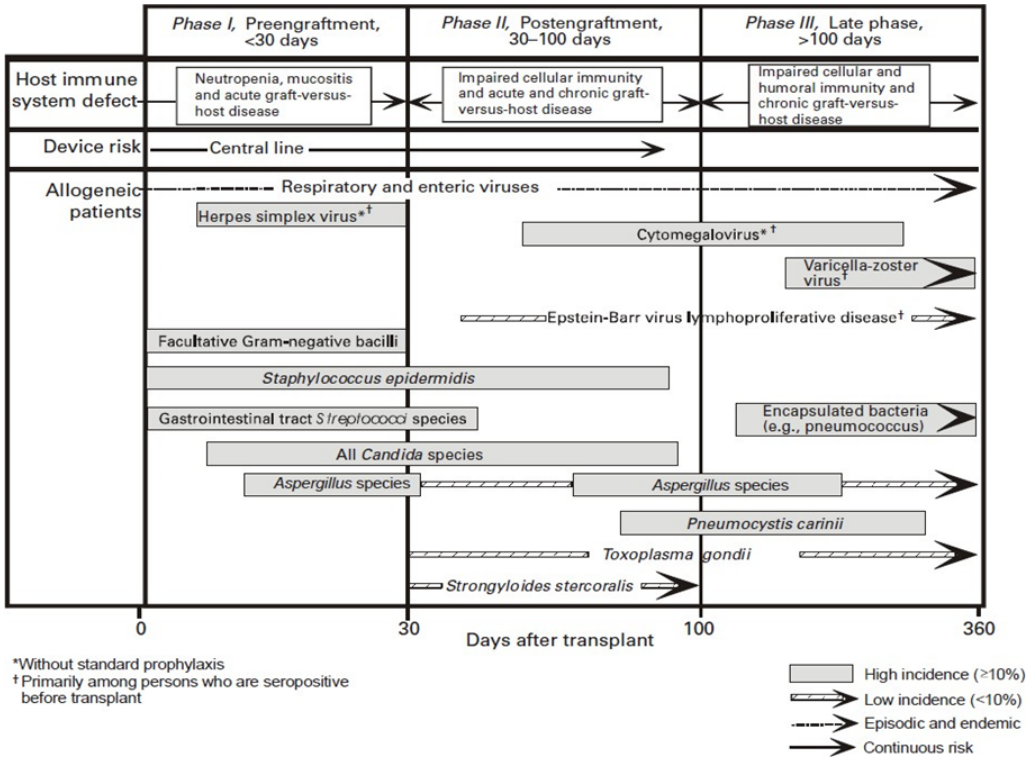
Purpose

To provide guidance on the prophylaxis, prevention, and management of fungal infections in recipients of hematopoietic stem cell transplantation (HSCT).

Points of Emphasis/Background

Epidemiology of Fungal Infection in the HSCT recipient

- Risk of invasive fungal infections (IFI) is higher in HSCT recipients than in other immunocompromised patients.
- The reported incidence of IFI in the hematopoietic stem cell transplant (HSCT) population is between 10-20% in most studies; however significantly higher rates have been reported up to 31.5%.
- Candida species, a type of yeast, and Aspergillus species, a type of mold, account for over 80%of all IFI's following HSCT.
- In the pre-engraftment period, candida and aspergillus infections may occur due to neutropenia and mucositis.
- In the post-engraftment period, aspergillus infections are more common than candida.



Risk Factors

- Studies have proven that mold infections are more common in older adults or adolescent and young adult (AYA) population.
- Allogeneic HSCT.
- In autologous HSCT recipients, the risk of IFI is minimized once neutropenia and mucositis have resolved.
- Children with prolonged neutropenia greater than 7 days.
- Children receiving high dose corticosteroids.
- Other factors influence the risk of IFI:
    - degree and duration neutropenia (higher risk in patients receiving bone marrow or cord blood stem cells vs. peripheral blood stem cells and non-myeloablative transplants)
    - severe mucositis
    - presence of a central venous line
    - acute and chronic GVHD and its therapy

Clinical Manifestations

- Candidal organisms reside on the skin, airways and in the GI tract, which may lead to endogenous dissemination in HSCT patients
- Molds (aspergillus and fusarium species) are known to exist in the air and in water, and water-related surfaces, and gain entry via the nasal or inhalational route
- Dissemination of fungal infection may occur at any tissue in the body
- Mucocutaneous infections
- Skin lesions, esophagitis, dysphagia, nausea and vomiting
- Candidemia
- Lung involvement: nodules, air space consolidation, ground glass opacities, tree-in-bud formation, pleural effusion, and cavitation
- Visceral dissemination: hepatosplenic candidiasis
- Aspergillosis refers to invasive disease. The most common sites of entry are the bronchial tree and paranasal sinuses, leading to pneumonia and sinusitis, necrotic skin or mucosal lesions

Diagnosis

- The diagnosis of IFI's following HSCT is classified into 3 categories: proven, probable or possible [IDSA/EORTC consensus definition, please refer to article reference for details].
    - All patients undergoing HSCT qualifies for at least one host factor which put them at risk of IFI.
- Proven infection – **Isolation or microscopic visualization** of fungus from a **tissue biopsy** or **sterile fluid** or **blood culture** (excluding BAL fluid or a paranasal or mastoid sinus cavity specimen, and urine).
- Probable infection – The presence of at least 1 host factor, a clinical feature AND isolation of fungus from nonsterile specimens (ex. Sputum) or radiographic evidence consistent with IFI

- Possible infection – The presence of at least 1 host factor, a clinical feature AND WITHOUT mycologic evidence
- Mycological evidence [for criteria look at reference 1] includes Galactomannan testing and Aspergillus PCR testing [not available locally]. EORTC Galactomannan cut offs are
    - Single serum or BAL fluid or CSF level ≥1
    - Single serum ≥0.7 *AND* BAL fluid ≥0.8

Clinical features
Pulmonary aspergillosis
The presence of 1 of the following 4 patterns on CT:
Dense, well-circumscribed lesions(s) with or without a halo sign
Air crescent sign
Cavity
Wedge-shaped and segmental or lobar consolidation
Other pulmonary mold diseases
As for pulmonary aspergillosis but also including a reverse halo sign
Tracheobronchitis
Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis
Sino-nasal diseases
Acute localized pain (including pain radiating to the eye)
Nasal ulcer with black eschar
Extension from the paranasal sinus across bony barriers, including into the orbit
Central nervous system infection
1 of the following 2 signs:
Focal lesions on imaging
Meningeal enhancement on magnetic resonance imaging or CT

Clinical Features for Candidiasis

Clinical features
At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:
Small, target-like abscesses in liver or spleen (bull's-eye lesions) or in the brain, or, meningeal enhancement
Progressive retinal exudates or vitreal opacities on ophthalmologic examination

Guidelines

Primary Prophylaxis for Patients Autologous HSCT

Systemic antifungal prophylaxis in patients undergoing >1 autologous HSCT until neutropenia and mucositis have resolved.

Primary Prophylaxis for Patients Allogeneic HSCT or CAR T-Cell Therapy

Fluconazole is the recommended drug for prophylaxis based on local experience, bioavailability and safety profile. It has activity against many candidal organisms including *Candida albicans*, variable activity against *C. glabrata*, but is not effective for *Candida krusei* or molds.

Prophylactic Agents (for Both aAllogeneic and CAR T-Cell Recipients)

- Fluconazole IV or PO as a single daily dose [3-5 mg/kg/dose]. Studies have shown that higher dose fluconazole [>5 mg/kg] prophylaxis does not offer any additional benefit.
- Start prophylaxis at Day 0
    - For CAR-T, Fluconazole can begin with lymphodepletion and continue until sustained neutrophil recovery [ANC ≥1.0 for two consecutive days without use of GCSF]
    - For patients with acute or chronic GvHD who are NOT on antifungal prophylaxis start voriconazole if they are on systemic steroids ≥1 mg/kg/day (prednisone dose equivalent) and if the high dose steroid exposure is expected to be ≥4 weeks.
- For patients who cannot receive fluconazole, an echinocandin can be used alternatively. Micafungin may be considered in cases of prior infections with azole-resistant candida species or in cases of azole-intolerance or other contraindications (abnormal liver function, QTc prolongation).
- Micafungin can be used daily [1 mg/kg] or twice a week dosing [3 mg/kg/dose].
- The optimal duration of fluconazole/voriconazole prophylaxis is not defined but is continued until day 75 post HSCT or as long as the patient is receiving steroids [≥0.3 mg/kg/day} or has neutropenia (ANC <0.5).
- **Voriconazole prophylaxis in patients with**
    - Any patient with history of possible, probable or proven mold/mucor infection in the past [Secondary Prophylaxis]
    - Acute or chronic GVHD and prolonged high dose steroid exposure (see above)
    - Patient with Chronic Granulomatous disease
    - Relapsed AML/MDS as a transplant indication
    - CAR-T cell recipients with prior allogeneic HSCT or CAR-T cell therapy

Empiric Treatment of patients with suspected IFI

- Patients with fever lasting 5-7 days despite administration of empiric antibiotics or with new fever after 5-7 days of empiric antibiotics should be evaluated for IFI, among other infections.

Empiric anti-fungal agents

- Liposomal amphotericin may be considered for patients with abnormal liver function or if there is drug interaction with Azoles.
- Voriconazole may be considered as first line treatment if the suspicion of Aspergillus is high.
- Alternatives: echinocandins (caspofungin/micafungin)
- Obtain consultation from Infectious disease service.

Targeted Therapy:
Once an IFI has been confirmed and a fungus identified, therapy can be narrowed initially based on the identification and later based on sensitivities, if applicable:

Treatment of Candidemia:

- Echinocandin (caspofungin or micafungin)
- Amphotericin B liposomal
- Fluconazole (in patients less critically ill with no recent azole exposure)

Treatment of Aspergillosis:

- Voriconazole, or posaconazole
- Amphotericin B liposomal
- Combination therapy voriconazole **PLUS** Echinocandin may be considered in select patients with Invasive Aspergillosis

Supportive Care considerations:

- Catheter removal should be strongly considered on an individual basis, especially if positive blood cultures for fungus.
- Gastrointestinal tract source is possible and imaging or endoscopic evaluation may be considered.
- Ophthalmology examination required in all patients suspected to have invasive fungal infection. Findings may be minimal until recovery of neutropenia. A dilated fundoscopic exam should be repeated within first week after neutrophil recovery.
- G-CSF may be considered in select patients with persistent candidemia and anticipated protracted neutropenia.

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Management of Respiratory Virus Infection in Cellular Therapy Product Recipients

Presented by: Greg Guilcher and Othman Mosleh

Respiratory Viruses

- Respiratory syncytial virus (RSV)
- Parainfluenza virus 1, 2, 3, 4
- Influenza virus A, B
- Rhinovirus
- Respiratory Enteroviruses
- Adenovirus
- Human metapneumovirus (hMPV)
- COVID-19 virus ((SARS-CoV-2) (clinical diagnostic criteria, isolation precautions and testing practices for COVID 19 are continually changing and providers should reference the most current guidelines in real time). It should be noted that rates of mortality are highest in adult hematopoietic stem cell transplantation (HSCT) recipients, while morbidity and mortality in recipients of immune effector cell therapy is not clearly known

Clinical Manifestations

- Typically, upper respiratory tract infection (URTI).
- Likelihood of progression to pneumonia highest for RSV (30-40%), followed by parainfluenza and influenza viruses. The main risk factors for progression are lymphopenia, Graft vs. Host Disease (GVHD), and immunosuppressive drugs for the prevention and treatment of GVHD.

Prevention/Prophylaxis

- Hand hygiene including handwashing with soap and water or use of alcohol-based hand rub or foam.
- Isolation and use of additional precautions as per Infection Prevention and Control guidelines (including use of appropriate personal protective equipment-PPE).
- For influenza, vaccination of close contacts (family members and friends, health care workers, the related cellular therapy product (CTP) donor) and the patient (greater than or equal to 3 weeks before conditioning and/or greater than or equal to 6 months post- transplant) is recommended. The inactivated vaccine should be chosen.
    - Oseltamivir/zanamivir should be considered early for heavily immunosuppressed patients (on immunosuppressive drugs in addition to routine GVHD prophylaxis) with documented or suspected influenza, URTI or lower respiratory tract infection (LRTI). Confirmatory testing should be performed. For such patients, treatment may be considered even after the 96-hour recommended period to initiate treatment has

expired. Infectious disease (ID) consultation may be sought.

- For RSV prevention, consider palivizumab (FDA-approved for immunocompromised children <2-y-old) during RSV season. New RSV vaccines will soon be available in Canada. Household or close family members 60 years of age or older should strongly consider the Arexyy RSV vaccine. (9)
- Aerosolized ribavirin can be considered in heavily immunosuppressed patients (on immunosuppressive drugs in addition to routine GVHD prophylaxis) with documented RSV, URTI, or LRTI. Special ribavirin precautions are required.

Therapy of Pneumonia

- For influenza, oseltamivir/zanamivir.
- For RSV,
    - Palivizumab prophylaxis for children < 2 years of age.
    - Ribavirin can be considered in consultation with Infectious Disease consultations, and while some publications support its use, data is limited and this is not considered standard of care.
- For impending lower tract disease, early intensive care (Pediatric Intensive Care Unit) consultation should be undertaken. For adenovirus, the benefits and risks of cidofovir should be discussed with the ID service in the absence of viremia. A decision to use cidofovir in such patients should be taken after careful consideration of toxicities in combination with the patient's clinical status.
- For parainfluenza, there is no consensus or proven effective therapy in cellular therapy recipients. ID consultation should be requested.
- To date there is no standard therapy for COVID 19 treatment though several can be considered with ID consultation such as dexamethasone and remdesivir. (7)

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Appendix A- Adenovirus References

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Pediatric Febrile Neutropenia Guidelines: Oncology and Cellular Therapy Product Patients

Presented by: Lucie Lafay-Cousin and Greg Guilcher

Purpose

To provide guidance on the risk stratification and management of pediatric oncology patients and patients who have received cellular therapy product (CTP) with fever and neutropenia.

Rick Stratification

Clinical Criteria for Low-Risk Febrile Neutropenia	
Outpatient at presentation and **EXCLUDING** the following • History of sepsis within the previous 6 months • Age < 12 months • Down Syndrome • Cellular therapy product (CTP) recipients with duration of risk outlined below • Diagnosis of: – AML – BURKITT lymphoma/leukemia or Intensive B lymphoma protocol – ALL **not in maintenance** – High Risk Neuroblastoma – Relapsed Leukemia or progressive/relapsed malignancy with suspected or proven bone marrow involvement	Outpatient at presentation and **EXCLUDING** the following • Presence of any one or more of the following: – Sepsis syndrome – Hypotension – Tachypnea – Hypoxia (O2 saturation (IF checked) < 94% on room air) – New infiltrates on chest X-ray (If x-ray is done) – Altered mental status – Mucositis ≥ grade 3 – Vomiting ≥ grade 3 – Abdominal pain ≥ grade 3 – Clinical typhlitis – Evidence of significant local infection (e.g. tunnel infection, peri-rectal abscess, cellulitis)

Social Criteria for Low-Risk Febrile Neutropenia	
Social Criteria	Requirements
Access to hospital	• Live within 1 hour travel time of ACH • Have access to a vehicle 24 hours a day in the event of a change in the clinical condition of the child
Communication	• Family has a working telephone in the home
Thermometer	• Family has a working thermometer in the home
Caregiver	• Available at home 24 hours a day • English-speaking /able to communicate with the treating team • Available for daily contact (will phone the hospital or receive daily phone calls) • Able to take oral or axillary temperatures as needed and document readings on the log • Able to administer oral medications as scheduled • Agrees to follow-up clinic visit
Child	• Able to tolerate oral medications • Remains home from school/daycare
Adherence	• History of compliance with/adherence to other outpatient treatment

Criteria for High-Risk Febrile Neutropenia Patients

- Not meeting low risk F/N criteria.
  - All CTP recipients are high risk. Autologous CTP recipients are considered high-risk for 3 months following CTP infusion.
  - Allogeneic CTP recipients are considered high-risk for 6 months following CTP and or longer if the following apply: ongoing GVHD, ongoing treatment with immunosuppression.
  - Chimeric antigen receptor (CAR) T-cell recipients are considered high risk for 2 months following CTP infusion.

Initial Investigations

- CBC and differential, electrolytes, creatinine, and urea
- Blood cultures from each lumen of CVC
  - Peripheral site in addition to central line cultures if possible (not mandatory)
  - NOTE: Do not delay antibiotics in order to obtain blood cultures
- Culture from other sites of suspected infection as indicated
  - Stool
  - Urine
  - CSF
  - Skin aspiration/biopsy
  - Respiratory specimens
  - *Bronchoalevolar lavage (BAL) in patients with infiltrate of uncertain etiology
  - *Nasopharyngeal aspirate (NPA)/BAL if symptoms of respiratory tract infection, particularly during outbreaks or during winter
- Chest x-ray (CXR) if respiratory signs/symptoms
- Other tests as indicated: Inflammatory markers: CRP, cytokines as indicated (e.g. IL-6, IL-8)

Blood Culture Follow-Up

- If fevers are persistent, daily blood cultures (via catheter or peripheral)
- If initial defervescence occurs with empirical antibiotics, any recrudescent fever should be evaluated as a new episode of febrile neutropenia

Treatment

A. High Risk Febrile Neutropenic Oncology Patient

Always admit for Empirical Intravenous Antibiotics

- Monotherapy* recommended
  - Piperacillin-Tazobactam
    OR
  - Cefepime
- Add Vancomycin (OR Linezolid) ONLY if:
  - Suspected catheter related infection: defined as pain, redness, pus at catheter site,

or previously diagnosed catheter related infection
    - Skin or soft tissue infection
    - Pneumonia
    - Hemodynamic instability/severe sepsis
    - Vancomycin does not automatically need to be added for gram positive blood culture, but can be considered if the patient has other indications for vancomycin on this list
    - Colonization with Methicillin Resistant Staphylococcus aureus (MRSA), Vancomycin Resistant Enterococcus (VRE), Penicillin Resistant Streptococcus pneumonia (PRSP)
    - **Caution with co-administration with piperacillin-tazobactam due to synergistic nephrotoxicity**
- Add Aminoglycoside (AG) or Fluoroquinolone (FQ) ONLY if:
    - Hypotension
    - Pneumonia (FQ for atypical organisms)
    - Antibiotic Resistant Organism (ARO) suspected or proven (positive BC for Gram Negative Bacteria (GNB) or previous history of ARO)Consider Meropenem + AG/FQ
    - Reassess prior to second dose of aminoglycoside and consider therapeutic drug monitoring
- For patients allergic to Penicillins, consider a combination of Vancomycin and Ceftazidime (should cross-reactivity not be a concern) rather than single agent 'Levofloxacin'. Such patients should ideally have a plan for febrile neutropenia made in advance.

Modification of Antibiotic Regimen:

- Change in antibiotic therapy should be guided by clinical change (deterioration) and/or microbiologic data.
- If patient stable with unexplained persistent fever rarely requires change in antibiotics. Consider fungal workup after 4-7 days of fever on broad-spectrum antibiotics. Workup can include chest x-ray + abdominal ultrasound or CT scan of sinuses (age dependent), chest/abdomen/pelvis. Treatment of possible, probable or proven fungal infection should be discussed with the infectious Disease service.
- If Vancomycin (or other GP coverage) started initially, stop after 2 days if no evidence of GP infection.
- If a patient becomes hemodynamically unstable or remains unstable after 2-4 days of antimicrobial therapy→consider broadening therapy for ARO (MRSA,VRE or resistant GNB), and possibly anaerobic bacteria, and/or fungi.
- E.g. Meropenem +/- AG/FQ +/- vancomycin

Duration of Antimicrobial Therapy

- For clinically or microbiologically documented infections, duration is dictated by particular organism and site; antibiotics should continue for at least duration of neutropenia (ANC ≥ 100 cells/mm^3 and rising) or longer if clinically indicated
- May narrow antibiotic coverage for documented infections after neutrophil recovery and if patient is stable
- If unexplained fever:
    - Antibiotic regimen should continue until clear signs of marrow recovery; ANC ≥ 100 cells/mm^3 and rising
      OR
    - Antibiotic regimen can be discontinued if appropriate treatment course completed (e.g. 10-14 days) and all signs and symptoms of documented infection resolved in patients who remain neutropenic

B. Low Risk Febrile Neutropenia Patient

- Admit to in-patient unit and start IV antibiotics:
    - PIPERACILLIN-TAZOBACTAM 80 mg piperacillin/kg/dose (piperacillin component) IV (max single dose: 4 g) x 1-3 doses
- Admission for 12-24 hours followed by discharge on oral antibiotic
- Oral antibiotic options:
    - LEVOFLOXACIN
        - 1 to < 5 yrs: 10 mg/kg/dose PO BID;
        - ≥ 5 yrs: 10 mg/kg/dose PO as a single daily dose (max single dose: 750 mg)
    - CIPROFLOXACIN 15 mg/kg/dose BID (max single dose 500 mg) & CLAVULIN 4:1 40 mg amoxicillin/kg/day TID ***liquid***

When to re-admit:

- Intolerance of oral antibiotic
- Non-adherence to antibiotic administration schedule or monitoring requirements
- Positive blood culture
- Clinical deterioration
- Remain febrile > 5 days of oral antibiotic administration, ***regardless of clinical status***

Duration of Antimicrobial Therapy:

- STOP ANTIBIOTIC IF
    - Afebrile for 24 hr
    - Clinically well
    - Culture negative at 48 hr
    - Hematological recovery (ANC >100 cells/mm^3)
- STOP ANTIBIOTIC AFTER 7 DAYS IF
    - Afebrile for 24 hr
    - Clinically well

- Culture negative at 48 hr
- No hematological recovery

C. Vascular Devices

An indwelling vascular access device may be left in place except in the following situations:

- Infection recurrent or persistent after ≥ 72 hours of therapy
- Subcutaneous tunnel or port pocket site infection
- Septic thrombosis
- Endocarditis
- Sepsis with hemodynamic instability
- Non-patent catheter
- Organism: *S. aureus*, *P. aeruginosa*, fungal, Atypical mycobacteria require removal

References

1. Alberta Health Services. (2017). *Provincial Clinical Knowledge Topic: Fever and neutropenia, pediatric acute care.* (Version 1.0). Retrieved from: https://extranet.ahsnet.ca/teams/policydocuments/1/klink/et-klink-ckv-pediatric-cancer- fever- and-neutopenia-pediatric-acute-care.pdf

Other Topics

Guidelines For Antibiotic Treatment in Cases of Compromised Product

Presented by: Greg Guilcher

Purpose

To provide guidance on the management of pediatric patients (donors and recipients) receiving cellular therapy products (CTP) with documented or suspected microbial contamination

Points of Emphasis

1) CTP will be considered compromised in the following situations:
    a. A positive microbial culture of the CTP is reported.
    b. Cracks are noted/reported in the CTP.
    c. Breaks occur while retrieving the CTP from liquid nitrogen containers.
    d. Breaks occur during the thawing procedure.
    e. Any violation of the sterile technique while infusing the product.
    f. If the donor was treated for a positive culture immediately prior to or during collection of stem cells. Donors may have been on antibiotics at time of such a collection thus making assessment of negative culture and non-compromise of collected product difficult. In donors/patients who were afebrile and had negative cultures at time of collection the treating physician may or may not choose to treat the recipient with antibiotics at or after product infusion.
2) Compromise of the CTP occurring in any of the above situations will require the following protocol to be followed:
    a. Guidelines followed by Transfusion Medicine will be instituted in cases where 'breaks' occur while retrieving product from liquid nitrogen containers.
    b. For patients within the Alberta Blood and Marrow Transplant Program (ABMTP), refer to SOP *Management of Cellular Therapy Products with Microbial Contamination Collected within the ABMTP* (BMTS20024).
    c. Transfusion Medicine shall be made aware in the case where there is a positive blood or stem cell culture reported.
    d. The CTP shall have aerobic, anaerobic, and fungal cultures drawn and kept in culture for 7-10 days allowing isolation of organisms that show delayed growth. This should be outlined on the requisition.
    e. In the case of a suspected microbial contamination, recipients will be started on vancomycin 15 mg/kg/dose IV every 6 hours for infants and children, vancomycin 15 mg/kg/dose IV every 12 hours for children > 60 kg. Levels will be followed as per institutional guidelines. An alternative antibiotic with comparable microbial coverage will be chosen if the recipient cannot receive vancomycin.
    f. For proven and documented microbial contamination of the CTP, antibiotic choice will be guided by local sensitivity patterns.

   g. Daily blood cultures will be drawn for a minimum of 3 days in cases where the patient remains afebrile.
   h. For febrile patients, cultures will be drawn daily (max 1/day) until fevers resolve, or as otherwise indicated by the Infectious Disease service which shall be consulted as needed.
   i. A minimum of 5 days of treatment shall be given in all situations of compromised stem cell product.
   j. Additional antibiotics or anti-fungal agents shall be added as per fever treatment protocol.
3) The recipient patient and family will be notified by the attending ABMTP physician of:
   a. The nature of the compromise,
   b. The planned action of care and
   c. Any follow-up plans
4) Permission to proceed with use of compromised CTP is not necessary. However, the conversation around the compromised CTP will be documented in the patient's medical record. Refer to Management of Cellular Therapy Products with Microbial Contamination Collected within the ABMTP SOP for documentation requirements.
5) The ABMTP attending physician is responsible for completing and sending the non-conforming product approval form back to CTL (refer to BMTS20024)
6) For sibling/family donors collected at Alberta Children's Hospital (ACH), the attending ABMTP physician responsible for the sibling donor will be notified. The ABMTP physician will be responsible for notifying the donor/family, and document disclosure. It is at the physician's discretion whether the donor will be brought to outpatient clinic/Unit 1 for further assessment.
7) For sibling/family donors being collected at ACH where the recipient is at another hospital (e.g. FMC) the recipient physician will be notified of the compromised product either by the ACH staff if the compromise occurs at the ACH or by CTL if the product is compromised at that site. The recipient physician will have the responsibility of informing the recipient, documenting the information and treating the recipient (as required).
8) Donors collected at the ACH will require assessment as per physician discretion with follow up in the outpatient clinic or by telephone within 24 hours of identification of suspected contamination) and as per Management of Cellular Therapy Products with Microbial Contamination Collected within the ABMTP SOP.

Criteria For Eligibility: Pediatric Allogeneic Cellular Therapy Recipient

Presented by: Tony Truong

Purpose

To establish guidelines to determine the eligibility of potential allogeneic cellular therapy recipients.

Criteria to Consider

Age	• < 18 years of age ○ Unless under special circumstances and with permission from hospital administration

Disease Status	• Disease responsive to therapy
	  ○ In extenuating circumstances and based on evidence patients may be transplanted in the presence of disease.
	  ○ Non-malignant diseases will typically be active at the time of transplant

Cardiac	• LVEF > 45% and SF >27%or as dictated by "study protocol". May be waived based on type of conditioning used or with adequate cardiac care and support.
Respiratory	• DLCO/FEV1/FVC >50% predicted or as dictated by the specific "study protocol" ○ If deviation is necessary, the exact reason needs to be documented.
Renal	• Creatinine Clearance >50% of normal and/or GFR> 45 ml/min/1.73m^2 (or as dictated by protocol) • Appropriate adjustment based on GFR needs to be in consideration ○ If deviation is necessary, the rationale needs to be documented.
GI	• Bilirubin and ALT < 3x Upper Limit of Normal (or as dictated by protocol) ○ If deviation is necessary, the rationale needs to be documented.
Performance Status	• ECOG performance status ≤ 2 • Lansky/Karnofsky score ≥ 50%
Uncontrolled Infection	• Absent • While active infection at the time of hematopoietic cellular therapy is strongly discouraged, if the potential benefits outweigh the risks, individualized decisions can be made with patient/parental disclosure. Infectious Diseases consultation is strongly recommended in these circumstances.
HIV Status	• Negative

Pregnancy Test	• Negative
	  ○ Pregnancy is a contraindication to stem cell transplant.
	  ○ All procedures would be held until after the pregnancy was completed or terminated.
	  ○ All patients undergoing planning for transplantation therapy should be adequately counselled about this requirement. Agreement should be sought that women of childbearing age will use adequate protection or abstain from sexual activity prior to conditioning and during transplantation therapy.

Informed Consent	• Signed, dated, and witnessed (as per AHS guidelines)

These criteria are not absolute. Selection criteria may change if recipient is enrolled in a clinical trial. If a recipient is registered on a clinical trial, the study criteria will take priority.

Criteria For Eligibility: Pediatric Autologous Cellular Therapy Recipient

Presented by: Tony Truong

Purpose

To establish guidelines to determine the eligibility of potential autologous cellular therapy recipients.

Criteria to Consider

Age	• < 18 years of age • unless under special circumstances and with permission from hospital administration
Disease status	• Disease responsive to therapy • Some diseases allow for transplant in cases of stable disease ○ If deviation is necessary, the rationale needs to be documented.
Cardiac	• LVEF > 45% or FS > 25% or as dictated by "study protocol". • May be waived based on type of conditioning used or with adequate cardiac care and support. ○ If deviation is necessary, the rationale needs to be documented.
Respiratory	• DLCO/FEV1/FVC >50% predicted or as dictated by the specific "study protocol" ○ If deviation is necessary, the rationale needs to be documented.
Renal	• Creatinine Clearance >50% of normal and/or GFR> 45 ml/min/1.73m2 (or as dictated by protocol) • Appropriate adjustments will be made based on reduced GFR and documentation shall be completed. ○ If deviation is necessary, the rationale needs to be documented.
GI	• Bilirubin and ALT < 3x Upper Limit of Normal (or as dictated by protocol) ○ If deviation is necessary, the rationale needs to be documented.
Performance status	• ECOG performance status < 2 • Lansky/Karnofsky score ≥ 50%
Uncontrolled infection	• Absent • While active infection at the time of hematopoietic cellular therapy is strongly discouraged, if the potential benefits outweigh the risks, individualized decisions can be made with patient/parental disclosure. Infectious Diseases consultation is strongly recommended in these circumstances.

Pregnancy Test	• Negative
	  ○ Pregnancy is a contraindication to stem cell transplant.
	  ○ All procedures would be held until after the pregnancy was completed or terminated.
	  ○ All patients undergoing planning for transplantation therapy should be adequately counselled about this requirement. Agreement should be sought that women of childbearing age will use adequate protection or abstain from sexual activity prior to conditioning and during transplantation therapy.

Informed Consent	Signed, dated, and witnessed (as per AHS guidelines)

These criteria are not absolute. Selection criteria may change if recipient is enrolled in a clinical trial. If a recipient is registered on a clinical trial, the study criteria will take priority.

Guideline for Criteria of Allogeneic Donor Selection

Presented by: Tony Truong

Purpose

To provide guidance in the process of donor searches and serve as an adjunct for donor eligibility and suitability evaluation and donor selection.

Points of Emphasis

The following criteria should be considered for selection of donors for pediatric allogeneic cellular therapy products (CTP):

- Donors may be related or unrelated to the recipient
- Donors may be pediatric or adult
- All donors must be evaluated, medically and psychologically cleared, and consented prior to CTP collection
    - If the recipient has a genetic condition for which transplant is indicated, related donors must be confirmed NOT to have the same condition
- Donors must not have a medical condition which places them at risk during preparation or collection of CTP
    - Sibling or haploidentical donors with 'diagnosis of trait/carrier status' may be selected at the discretion of the treating physician based on evidence and in cases of absence of risk to the recipient
- Donor clearance and informed consent must be performed by a physician other than the recipient's primary transplant physician
    - Possible conflict of interest must be considered in cases of donors who are minors. This is especially true when a minor donor is being considered for a recipient who is their parent (a Clinical Ethics review may be necessary in some cases)
- Pediatric sibling donors will have a psychosocial evaluation with the Social Worker/ Psychologist prior to collection of stem cells
- All tissue typing for related and unrelated donors will be reviewed by the pediatric Alberta Blood and Marrow Transplant Program (ABMTP) transplant physician and the pediatric ABMTP Coordinator
- When a sibling donor is an HLA-match for more than one recipient in the family, the donor will be approached to donate cells for only one sibling at a given time
    - World Marrow Donor Association standards state that a single donor should donate a maximum of twice regardless of the number of identified recipients. If more than two donations are requested from a single donor appropriate psychosocial and Clinical Ethics review must be undertaken to protect the donor.
- Should a donation be required a second time a sibling donor may be approached

    - Request should be no sooner than 4-6 months from the first donation and at the discretion of the donor physician
    - Products such as donor lymphocyte infusion (DLI) may be obtained earlier if deemed safe by the donor physician
- For recipients with hemoglobinopathies, the donor should be evaluated for hemoglobinopathies prior to administration of the mobilization regimen containing G-CSF
- Female donors of childbearing potential must have a pregnancy test which is documented in the donor medical record
- The donor/guardian should be adequately counselled. A donor advocate should be available to represent allogeneic donors who are minors or who are mentally incapacitated
- Allogeneic donors shall be tested for ABO group and Rh type using two independently collected samples
- These criteria are not absolute. See page 4, "Stem Cell Source for Pediatric Allogeneic Transplants"

Process

1. Recommended Sequence of Donor Search

- Matched sibling donor (MSD) or matched family donors (MFD) are generally preferred.
    - All potential sibling and parent donors should be identified through the HLA consult and have HLA typing complete at high resolution for all 10 loci.
- Siblings less than 8 months of age shall not be considered as donors.
- If there is no MFD/MSD and the disease justifies searching for a matched unrelated donor (MUD), initiate a world donor search.
    - Outcomes from MUD CTP infusion have been shown to be comparable to mismatched or even MFD transplants for some conditions.
- Unrelated donors will be confirmed with high resolution typing at all HLA loci.
- Consider alternate stem cell sources such as umbilical cord blood unit with adequate cell dose or haploidentical donor.
    - As the data using haploidentical donors is maturing and showing equivalence to MUDs and even MSD in some cases, the choice of moving ahead with a haplo-identical donor while superseding MUD is at the discretion of the transplant physician. Haploidentical donors may be desirable if there is urgency to transplant. In these situations, the referral to adult ABMTP should be made as soon as possible.
- Donor selection is discussed weekly with transplant physicians and coordinators at the BMT Search and Assessment Meeting. This forum allows for input and discussion with colleagues.

2. Eligibility Guidelines for Donor Selection

The following criteria are considered when choosing a related or unrelated donor:

HLA Typing:

HLA typing will be performed at a minimum of 8 and possibly 10 loci when available:
Class I – A, B, C
Class II – DR, DQ
Statement: DP permissive mismatches

Note: For malignant conditions, consider the direction of mismatch in the graft versus host disease (GvHD)/graft versus leukemia (GvL) direction vs. graft rejection direction. Also refer to algorithm for donor selection guideline.

Principles of Selection:

- MSD or MFD will take precedence over MUD
- A donor at the age of majority will take precedence over a younger donor if medically equivalent, unless there are significant benefits to choosing the younger donor
- When there is more than one sibling match under the age of majority, the oldest sibling will be selected unless there are contraindications or if there are significant benefits to choosing the younger donor

Once HLA-matching criteria have been used to select the best possible donor other criteria may be considered as follows:

CMV status:

- Choose same status as recipient, whenever possible. Refer to the CMV Management Guideline
    - All infant recipients will be considered CMV negative unless there is evidence of documented infection
    - For recipients with malignant conditions, ideally the serology which predates all therapy will be considered for evaluation (if available) unless there is documented CMV infection in which case the recipient is considered CMV positive
    - Similar consideration will be given to EBV status

Age:

- Younger donor preferred

Gender:

- Male preferred, especially for male recipients

Parity:

- Nulliparity or least number of pregnancies preferred

Blood group:

- ABO Compatibility preferred, especially for marrow CTPs

Order of priority

- After HLA-typing is the highest weighted factor. After HLA-typing, CMV status, and age of donor are the most important factors

Stem Cell Source Selection for Pediatric Allogeneic Transplants

**These criteria are not absolute and may vary based on physician choice/patient status.

Patients registered on a clinical trial will adhere to protocol rules preferentially unless following institutional standards is allowed. Published data for specific protocols can also be considered in unique circumstances.

In mismatched or haploidentical donors, donor specific HLA antibodies (DSA) may limit engraftment and lead to graft failure. DSA should be evaluated in all patients undergoing HSCT to inform appropriate donor selection.

1. Matched Sibling Donor

a) Acute Leukemia/Chronic Leukemia
   1) Peripheral blood stem cells (PBSC) from MSD - cap at 8 x 10^6 CD34 cells/kg recipient weight.
   2) Marrow – minimum dose 2.5 x 10^8 total nucleated cells (TNC)/kg recipient of wt. Once CD34 count is known, cap at 8 x 10^6 CD34 cells/kg recipient weight.
   3) Granulocyte – colony stimulating factor (G-CSF) primed marrow may be used if the donor requires a blood/albumin prime to collect PBSC.
      - In general, avoid exposing healthy sibling donors to a blood/albumin prime for PBSC collection. Instead, bone marrow harvesting is preferred if safe and feasible. If PBSCs are preferred, albumin prime can be discussed with the family and the donor physician. Plerixafor should be considered in these circumstances to facilitate safe collection and minimizing exposure to blood products.
      - When collecting GCSF primed bone marrow, consider the possibility of an artificially elevated TNC due to the growth factor. As such, a determination of cell dose collected might need to be made on the basis of volume collected intraoperatively.
   4) Matched cord blood unit from sibling donor with adequate cell dose may be used alone or in conjunction to another stem cell source (typically bone marrow).

2. Matched/Mismatched Related or Unrelated Donor (including Cord Blood Units)

a. Acute Leukemia and difficult to treat or relapsed Chronic Myeloid Leukemia

1) PBSC from 9-10/10 matched related family donor – cap at 8 x 10^6 CD34 cells/kg recipient weight. Serious consideration should be given to choosing marrow in case of 9/10 family (non-sibling) donors, or the use of abatacept for children >2 years of age.
2) PBSC from 9-10/10 matched unrelated donor – cap at 8 x 10^6 CD34 cells/kg recipient weight.
3) Bone Marrow from 9-10/10 matched unrelated donor – minimum cell dose of 2.5 x 10^8 TNC cells/kg recipient weight.
4) Cord blood units as follows: (all cord blood units will be from accredited/certified cord blood banks).
    a. 6/6 single unit graft > 3.5 x 10^7 TNC/kg recipient weight
    b. 5/6 single unit graft > 4.5 x 10^7 TNC/kg recipient weight
    c. 4/6 single unit graft > 5.5 x 10^7 TNC/kg recipient weight

    Ideally the CD34 dose will be ≥ 2 x 10^5 CD34 cells/kg for all cord blood units.

    HLA typing at the C locus should be considered if available. After considering A, B, C, DR matching, the most permissive DP matching should also be considered.

    ** Cord selection at the discretion of the transplant physician depending on available donor products/recipient condition. Whenever possible, cord units which are red cell deplete should be selected.

5) Haploidentical family donor using PTCy as GVHD Prophylaxis.
    a. With new data becoming available for enhanced efficacy and safety of haploidentical transplantation, this source may take priority over MUDs depending on situation and urgency of transplantation
    b. Peripheral blood stem cells would be the preferred choice for FluBuP based regimens
    c. Dose of stem cells will typically be capped at 8-10x10^6 CD34/kg of recipient weight

b) Non-Malignant Indications

1) Marrow – minimum dose 2.5 x 10^8 nucleated cells/kg recipient wt.
2) PBSCs may be preferable for certain indications if reduced intensity conditioning is being used. Dosing would depend on the indication but would generally be ≥ 8 x 10^6 CD34 cells/kg recipient of wt for ATG based regimens. For alemtuzumab based regimens, dosing would be 10-15 x 10^8 CD34 cells/kg.
3) G-CSF primed bone marrow – See collection considerations above.
4) Cord units as described above. Often higher cell doses are preferred due to higher rates of graft rejection.

5) Haploidentical family donor.
    a. With new data becoming available for enhanced efficacy and safety of haploidentical transplantation, this source may take priority over MUDs depending on situation and urgency of transplantation
    b. Peripheral blood stem cells would be the preferred choice for alemtuzumab based regimens
    c. Marrow (including G-CSF primed):
        i. For TCR a/b depleted HSCT, there will be no CD34 cap, as long as TCR a/b content is below desired levels.
        ii. For PT-Cy based regiments, dose of stem cells will be capped at $8x10^6$ CD34/kg of recipient weight

Fertility Preservation for the Cellular Therapy Patient

Presented by: Tony Truong, Greg Guilcher, and Sarah McQuillan

The risk of infertility and choice of conditioning regimen should be clearly discussed and documented within the patient's medical record.

All patients of reproductive age should be offered fertility preservation options prior to cellular therapy conditioning; refer to *Fertility Preservation Referral Process* (HOTS10024). Parents of a pre-pubertal child may benefit from referral to the Regional Fertility Program (RFP) and Diagnostic Semen Laboratory (DSL) to have a consultation to ensure that all current standard of care options for fertility preservation have been considered. Regardless of age, if as patient/family wishes to seek consultation with the fertility clinic, all resources should be made available for timely access.

Every attempt should be made to ensure a fertility consult is completed and documented in the medical record. Fertility preservation should be revisited and discussed for patients who have undergone prior chemotherapy where previously fertility preservation has not been performed even though the patient may have had a high likelihood of infertility. Documentation of reasons for declining a fertility referral should be in the chart.

The social worker and/or primary nurse should be included in the consult to:

- Assist in the coordination of appointments and services related to sample procurement and storage, including testing required by the RFP to assist with banking and/or storage (all attempts to batch blood work will be made).
- Social workers can assist with family awareness regarding the cost of fertility preservation processes and discuss resources available to families that allow for offsetting such costs. **The costs of services of the RFP are incurred by patients/families and are NOT covered by Alberta Health**.

Infectious disease testing required for banking or storage should be completed in advance of the patient starting conditioning therapy.

Outcome of consults should be documented within the medical record.

Sperm banking

- Regular history and physical exam should be conducted to determine whether a sample can be collected (e.g. nighttime ejaculation, erection etc.).
- Testing should be reviewed after sperm banking and parents/patients advised as to the viability of sample and the need to continue banking.

Oocyte harvesting and cryopreservation

Prior to cellular therapy:

- **All female pediatric and adolescent patients** should be referred to gynecology regardless of fertility preservation goals to ensure menstrual suppression if required, need for contraception and discussion of genitourinary graft vs host disease are discussed and **all females** should be concurrently referred to the Regional Fertility Center as per clinical guideline *Fertility Preservation Referral Process* (HOTS10024) and *Referral of Pediatric Cellular Therapy Recipients to Gynecology (including fertility preservation)* to discuss fertility preservation goals. Following treatment, gynecology will follow these patients for return of menses, and revisit contraception and fertility goals.
- Oocyte preservation (egg freezing) requires medications to stimulate ovulation and needs to be timed to coincide with the patient's regular ovulatory cycle. Therefore, 2 weeks of time prior to conditioning may be required, if feasible.

RFP and DSL are a laboratory accredited by the College of Physicians and Surgeons of Alberta for the diagnosis and treatment of infertility. Additional information and contact details can be found at http://regionalfertilityprogram.ca/.

Ovarian Tissue Cryopreservation

Prior to cellular therapy:

- **All pubertal and pre-pubertal females** should be referred to gynecology and concurrently referred to the Regional Fertility Center as per *Fertility Preservation Referral Process* (HOTS10024) and clinical guideline *Referral of Pediatric Cellular Therapy Recipients to Gynecology (including fertility preservation)* to discuss fertility preservation goals. Documentation of reasons for declining a fertility referral should be in the chart.
- Ovarian tissue cryopreservation (either a complete ovary or 1/3 of the ovarian cortex) can be coordinated urgently for female patients not candidates for oocyte preservation or declining oocyte preservation or choosing ovarian tissue preservation. Ideally this procedure would be booked as first case of the day to allow for the transportation and processing of the tissue at the RFP.

Other Considerations:

- For prepubertal females, the tissue would be transplanted back when the patient is ready to conceive. These patients may still require pubertal induction or ongoing hormonal support.
- RFP and DSL are a laboratory accredited by the College of Physicians and Surgeons of Alberta for the diagnosis and treatment of infertility. Additional information and contact details can be found at http://regionalfertilityprogram.ca/.

Use of G-CSF For Mobilization and Post-Cellular Therapy Neutropenia

Presented by: Greg Guilcher

Purpose

To provide guidance on the use of granulocyte-colony stimulating factor (G-CSF) for hematopoietic stem cell mobilization and in the post-transplant period for neutropenia.

Background

G-CSF (Filgrastim), is a hematopoietic growth factor which regulates the production and function of neutrophils. G-CSF also stimulates the release of neutrophils from bone marrow storage pools and reduces their maturation time. In patients receiving chemotherapy and post cellular therapy product (CTP) infusion, G-CSF can accelerate neutrophil recovery, leading to a reduction in duration of the neutropenic phase.

G-CSF also acts to mobilize peripheral blood progenitor cells prior to Hematopoietic Progenitor Cell (HPC) collection in patients and healthy donors.

Points of Emphasis

- G-CSF shall be administered under the direct or indirect supervision of a physician experienced in its administration and side effects.
- G-CSF will be given to pediatric donors who are cleared and have agreed (consent obtained from parents, responsible guardian with consenting authority, or mature minor) to donate HPCs harvested by apheresis (HPC-Apheresis) or by bone marrow harvest (G-CSF-primed bone marrow).
- Sibling donors receiving G-CSF will be followed as per donor follow-up guidelines.
- G-CSF will be given to Pediatric oncology patients who will require HPC-Apheresis for their autologous CTP infusion.
- Consent for administration of G-CSF or mobilizing agent is part of the consent for cellular therapy treatment or consent to donate.
- Filgrastim must be administered subcutaneous (not intravenous) for mobilization for donors.
- Donors shall be evaluated for the risk of hemoglobinopathy prior to administration of the mobilization regimen. Risk will be determined by history, family history with HPLC testing performed if the treating physician determines laboratory testing is warranted.

Guidelines

1. **Use of G-CSF for mobilization:**
    - Doses shall be ordered according to patient/donor weight. The dose may be rounded to accommodate vial size and to minimize waste of medication. Typically, maximum dosing for adults is 600 micrograms per day.
    - For patients undergoing autologous collection, the dosing of G-CSF will be based on relevant protocols, the patient's white blood cell and CD34 counts.
    - For allogeneic donations, G-CSF will commence four (4) days prior to collection. Dosing will be adjusted to patient height and weight (however may be given according to the algorithm shown below to limit use without compromising mobilization). Collection shall be performed on the fifth day after a dose of G-CSF given on the morning of collection.
2. **For pediatric patients:** guidelines are individualized and included in the treatment protocol.
3. **Mobilization**
    i) **Mobilization following chemotherapy**
    - Start patients on G-CSF at 5 mcg/kg/day (IV or SC) as directed by the chemotherapy treatment regimen.
    - Increase G-CSF to 10 mcg/kg/day SC (QD or divided BID) when ANC≥1000.
        - Changes can be made at the discretion of the treating physician, as required.
    - Plan collection two days later, depending on peripheral blood CD34 count.
    - G-CSF should be discontinued once collection is complete and ensuring second collection is not needed on the following day.

    ii) **Mobilization in chemotherapy-naïve patients and sibling donors**
    - Start patients on G-CSF at 10 mcg/kg/day (SC) for four (4) days prior to the planned date of stem cell collection (no maximum dose).
    - A fifth (5th) dose of G-CSF at 10 mcg/kg should be given on the morning of collection.
    - G-CSF should be discontinued once stem cell collection is complete and ensuring second collection is not needed on the following day.
4. **Use of G-CSF post-cellular therapy**
    - G-CSF will be administered according to treatment protocol or based on individual need.
    - G-CSF should only be used as needed for patient's post-primary engraftment when the ANC is less than 500. This parameter does NOT apply to the use of G-CSF prior to primary engraftment.
    - In general, G-CSF use is not recommended in allogeneic transplant recipients receiving hematopoietic stem cells for transplantation for malignant conditions. Local data show that engraftment is not compromised in these patients by the avoidance of G-CSF. G-CSF can safely be used in patients undergoing autologous transplantation and allogeneic transplantation for non-malignant conditions using BM or PBSCs until the

ANC is >2000 for two consecutive days. Regimens vary according to stem cell source and underlying condition – reference the Protocol Detail Sheet for a given patient.

- For recipients of cord blood stem cell transplants, G-CSF will be started 24 hours after the stem cell infusion at 5 mcg/kg/day IV until the ANC > 2000 for two consecutive days or ANC > 5000 x 1 day.
- While usual dosing of G-CSF is 5 microgram/kg, the dose may be increased (e.g. Doubled) in a critically ill child or delayed engraftment as per physician discretion.
- Intravenous dosing is preferred for patients in hospital or in clinic to avoid needles.

3. **Administration of G-CSF**
    - Administration will be performed according to nursing policy & procedures.
4. **Administration of other mobilizing regimens/agents**
    - Plerixafor (AMD-3100) is an anti-CXCR4 agent that mobilizes stem cells and is indicated for patients who are at risk for poor mobilization, have failed a previous mobilization attempt, or for immediate salvage during a suboptimal mobilization attempt.
    - Plerixafor dosing is 0.24 mg/kg of body weight, administered by subcutaneous injection given on evening prior to apheresis morning (~12 hours prior to collection). It should be given in addition to G-CSF, with or without chemotherapy.
    - Approval for use of Plerixafor can be obtained through the Short-Term Exceptional Drug Therapy (STEDT) program (high cost drug) or the patient's private third party drug coverage plan (recently approved by Alberta Blue Cross).
    - Plerixafor may be used in small children to shorten the duration of time on the apheresis circuit in an effort to prevent hemodynamic instability.
    - Cyclophosphamide at 4 gm/m2 as a single dose or divided doses may be used to mobilize patients for autologous collection.

Patients may be mobilized using other drug regimens based on individualized or protocol-based treatment regimens. Most such regimens use G-CSF in addition to chemotherapy.

5. **Cell count criteria for collection**
    - If a patient is on a pre-determined study protocol, follow the peripheral blood cell counts (WBC, ANC, and CD34 count) criteria as dictated by protocol.
    - General count criteria on the day of apheresis are:
        - CD34 > 20 x 10^6/L (lower levels may be acceptable in poor mobilizing patients)
        - Platelet count > 75 x 10^9/L
        - Hemoglobin > 100 g/L

** Transfusion support may be given to reach these target levels. Hb 70g/L is acceptable if blood priming is planned as in children weighting less than 25 kg.

- See apheresis guidelines for more information
- For patients being treated on 'individualized protocols'
    - Autologous patients (Chemotherapy with GCSF)

- On the day of collection, peripheral blood CD34+ count should be ≥ 15 in order to proceed with collection.
- Proceeding at a lower CD34+ level is permissible with the approval of the transplant physician, if previous attempts to mobilize have been unsuccessful and other alternatives (postponing collection or use of plerixafor) have been considered. However, collection with CD34 counts ≤ 12 is generally unsuccessful.
- Higher CD34 counts are preferable for collection of larger products and collection may be delayed to achieve those counts.
- A 10 mcg/kg dose of GCSF may be given on the 'am' of collection.

- Allogeneic Donors (Family donors)
  - Collection will be done on the fifth day at a CD34 count ≥ 15.
  - Adult family donors will follow adult guidelines for mobilization and collection.

Infusion of Cellular Therapy Products Guideline

Presented by: Greg Guilcher, Victor Lewis, and Susan Berrigan

Purpose

To guide the procedure for the manipulation and infusion of cellular therapy products (CTP), both fresh and cryopreserved, ABO compatible and incompatible including:

- Bone marrow
- Peripheral blood stem cells (PBSC)
- Umbilical cord blood
- Immune Effector Cells (IECs)

Point of Emphasis

- Fresh products must be infused within 96 hours of collection (ideally within 72 hours).
- Deviations need to be documented and information provided to the recipient/family.
- Cryopreserved products contain dimethyl sulfoxide (DMSO). DMSO may induce anaphylactic reactions and emergency equipment must be in place.
- For administration of cryopreserved products ensure platelet counts on day of infusion are above 30K given the risk of hypertension.
- Washed products (including those CD34 selected boosts) contain minimal plasma, red cells and DMSO and do not require premedication or hydration precautions for DMSO or ABO incompatibility.
- Prior to infusion, the most responsible health professional (MRHP) or delegate will complete the cellular therapy infusion order set, which includes the prepare and infusion orders.
    - For IEC infusions, the MRHP or delegate will complete the CAR T cell Product Release order on day of infusion before CTL will release the product.
- Filters SHOULD NOT be used during administration unless specifically indicated when clots or fragments are suspected.
    - Minor clots or small fragments DO NOT require filtration and can pass through into the body.
    - The size of the filter to be used will be clearly indicated on the infusion documents when necessary.
- Fresh CTP (marrow or PBSC) SHOULD NOT be irradiated.
- Volume depletion is not performed in case of minor incompatibility, however, can be performed at discretion of physician and in consultation with CTL staff if there are concerns of volume overload.

Infusion of Fresh ABO Compatible CTP

1) No specific hydration is required.
2) Filters SHOULD NOT be used during administration unless specifically indicated.
3) Specific pre-medication is NOT required for fresh ABO compatible CTP. However, the following may be ordered prior to infusion of CTP:
    a. Tylenol 15 mg/kg PO
    b. Benadryl 1 mg/kg IV
    c. Hydrocortisone 1-2 mg/kg IV or equivalent
4) Infusion time depends on the CTP volume to be infused:
    a. The CTP does NOT need to be infused rapidly
    b. The CTP is NOT considered expired if infusion times exceed 3-4 hours
    c. The entire CTP shall be infused as directed by the responsible physician or delegate
5) During infusion:
    a. Monitor BP and pulse as per nursing guidelines
    b. Watch for transfusion reactions
    c. If patient is volume overloaded or has urine output < 1 ml/kg/hr
        i. Lasix 0.50 mg/kg IV prior to infusion
        ii. Lasix 0.50 mg/kg IV at the end of infusion.
            1. Check electrolytes (Na, K, Ca, Mg, PO4 prior to second dose of Lasix.

Infusion of Fresh ABO Incompatible Bone Marrow

(See below for fresh ABO incompatible PBSC)

Major Incompatibility

- Major Incompatibility is when the recipient's plasma has antibodies to the red blood cells (ABO blood group) of the donor. (Example: Recipient is O and the Donor is A, B or AB).
- If the recipient is alloimmunized (eg sickle cell disease with significant blood product exposure) and the donor red blood cells express the antigen to which the recipient has antibodies, treat as major ABO incompatibility.
- In all cases of major incompatibility the attending transplant physician will be notified.

Recommended action:

- Red blood cell depletion of the marrow product is performed by the CTL/Transfusion medicine as needed or per their recommendation as this process may lead to stem cell loss.
    1) Final CTP volume may be lower than originally obtained from donor center.
    2) RBC removal is performed by CTL using validated methods.
    3) CTL/Transfusion medicine notifies the transplant physician of 'estimated' residual RBC volume remaining in CTP.

4) Transplant physician determines number of aliquots necessary to allow for safe administration of incompatible CTP to be administered with minimal complications of hemolysis and renal compromise.
    a. Minimum number of aliquots = 1, Maximum number = 4.
    b. Maximum incompatible RBC volume/aliquot = 1 cc/kg of recipient weight.
5) Each aliquot will be administered as described below.

Procedure for infusion of each Fresh ABO incompatible aliquot:

1) Hydration:
    a. Initiate Ringers Lactate or appropriate hydration fluid for 4-6 hours at 125 ml/m2/h 2 hours prior to the infusion of CTP.
    b. Hold IV hydration during CTP.
    c. Resume IV hydration post CTP infusion and continue for a minimum of 4-6 hours OR until the start of a subsequent aliquot infusion.
2) Filters **SHOULD NOT** be used during administration unless specifically indicated.
3) Pre-medicate patient prior to each aliquot with:
    a. Tylenol 15 mg/kg PO
    b. Benadryl 0.5-1 mg/kg IV
    c. Hydrocortisone 1-2 mg/kg IV (or methylprednisolone equivalent) given 25-30 minutes prior to 'aliquot infusion'
4) Infuse aliquot over 2-4 hours
    a. Monitor BP and pulse as per nursing guidelines. Use Lasix (preferred) and/or calcium channel blockers as needed.
    b. Watch for transfusion reactions.
    c. Check CBC, lytes, BUN, Creat, HCO3, and urinalysis 1 hour after end of each aliquot.
    d. Patient's urine may change to dark red/brown. Ensure urine output (UOP) is > 1 cc/kg/h.
    e. If patient is volume over-loaded or has < 1 cc/kg/hr of UOP give.
        i. Lasix 0.5 mg/kg IV prior to transfusion; increase if 'no' response.
        ii. Lasix 0.5 mg/kg IV at the end of infusion.
5) Check electrolytes prior to second dose of Lasix.
6) Recommend 2-3 hour interval between infusions of each aliquot. If complications arise with any aliquot delivery, involve transplant physician in discussion on delivery of remaining aliquots.
7) Check labs (CBC, lytes, creat, urea, urinalysis) 1 hour after each aliquot.

Minor Incompatibility

- Minor incompatibility is when the donor's plasma has antibodies to the red blood cells (ABO blood group) of recipient. (Example: Recipient is A, B, or AB and the donor is O).

- The attending transplant physician is aware of incompatible infusions as noted in the cellular therapy infusion orderset.

Note:

1) It is not routine to check antibody titres in case of minor incompatibility of product. This is based on substantial local data showing non-utility of this procedure.
2) Titers MAY be checked based on a substantial 'reaction' history in the recipient.
3) Checking titers will be the responsibility of the 'recipients' primary physician.
    a. The attending physician on call may be different from the primary physician on day '0'.
    b. The recipient's primary physician is responsible to convey all relevant information regarding product manipulation to the attending physician on service.
    c. The attending physician on Day '0' may make relevant changes to fluid management based on the overall status of the recipient.
4) Based on the processing techniques, the final product volume might be considerably lower than that obtained at the donor center

Procedure for infusion of each aliquot of bone marrow product:

1) Hydration:
    a. Initiate Ringers Lactate or appropriate hydration fluid for 5-6 hours at 125 ml/m2/h within 1 hours prior to the infusion of CTP.
    b. HOLD IV hydration during Stem Cell infusion.
    c. Resume IV hydration post CTP infusion and continue for a minimum of 4-5 hours OR until the start of a subsequent aliquot infusion in case there are more than one.
2) Filters SHOULD NOT be used during administration unless specifically indicated. When used the size of the filter will be clearly indicated on the infusion documents.
3) Pre-medicate patient with:
    a. Tylenol 15 mg/kg PO
    b. Benadryl 1 mg/kg IV
    c. Hydrocortisone 1-2 mg/kg IV (or methylprednisolone equivalent) given 25-30 minutes prior to stem cell infusion
4) Monitoring guidelines:
    a. Monitor BP and pulse as per nursing guidelines
    b. Watch for transfusion reactions
    c. Patient's urine may change to dark brown. Ensure UOP is > 1 cc/kg/h
    d. If patient is volume over-loaded or has < 1 cc/kg/h of UOP give
        i. Lasix 0.50 mg/kg IV prior to transfusion
        ii. Lasix 0.50 mg/kg IV at the end of infusion.
5) Check electrolytes prior to second dose of Lasix.

***** For all patients who have had previous reaction to any plasma based products (platelet reactions) or substantial RBC infusion based reactions, one should consider prophylactic medications when giving stem cell infusions even if the methodology described above may not require that as per standard protocol.**

Bi-directional Incompatibility:

- Bi-directional Incompatibility is when both the donor and recipient have antibodies to the other's red blood cells (ABO blood group) (recipient is A and donor is B or vice versa).

Recommended action:

- Red blood cell depletion of the marrow product is performed by Apheresis.

Follow MAJOR incompatibility product infusion guidelines.

Infusion of Fresh ABO Incompatible PBSCs

1) The volume of RBC's in PBSC collection tends to be minimal. If however the volume of RBCs in the final collection is > 1 cc/kg of recipient weight, the product may be red cell depleted and/or aliquoted to contain < 1 cc/kg of RBC per aliquot.
2) Plasma depletion of the product will be performed by CTL at their discretion or that of the attending/primary physician, through mutual consultation, based on volume tolerance for the recipient and consideration of possible cell loss with such manipulations.
3) Cell product manipulation will be the responsibility of the primary physician assigned to the 'recipient'.
    a. The attending physician on call may be different from the primary physician on Day '0'.
    b. It will be the responsibility of the primary physician to convey all relevant information regarding product manipulation to the attending physician on service.
    c. The attending physician on day '0' may make relevant changes to fluid management based on the overall status of the recipient.
    d. In case of a major incompatibility, premedication and specific hydration are recommended but not required for PBSCs.
    e. As the volume of product is generally small, the contamination with PRBCs is low, hydration can be similar to that fresh matched or minor mismatched product.

Note:

1) For PBSC with a major ABO incompatibility, the volume of donor RBC in the product does not usually exceed the threshold to require a red cell depletion. The above process of infusion may be utilized or modified depending on the amount of RBCs within the product.
2) For minor incompatible PBSC fresh products, guidelines similar to infusion of fresh compatible marrow can be followed safely in most cases. Excessive hydration may not be required.

Patients can be given prophylactic Tylenol, Benadryl and hydrocortisone as deemed necessary by the responsible physician. Post infusion mannitol is not necessary with PBSCs that are minor-incompatible.

Infusion of Cryopreserved (Frozen) CTP

All CYROPRESERVED products contain DMSO (Di-methlysulfoxide). DMSO is toxic to stem cells once the cells are thawed. As such any thawed product needs to be transfused immediately and as fast as possible into the patient, unless it has been 'washed' to remove DMSO or diluted as per standard 'CTL guidelines'. Washing/dilution of any product may be requested at physician discretion. This is usually not necessary in 'autologous storage' products but may be requested (and is recommended) if:

a) If there is 5 ml/kg (recipient weight on Day 0) or greater of 20% DMSO in solution the infusion product (equivalent to 1g/kg maximum).
   For example: A 10 kg patient should not be infused more than 50 mL of 20% DMSO solution.
b) If (a) applies and washing or dilution are not performed the infusion WILL be slowed down to 500 mls/hour.

Unless the product is 'washed', it will contain DMSO in the final infusate. For all products that contain DMSO the above protocol needs to be followed. Mannitol may be omitted if a cord has been washed to eliminate DMSO, and is not required for cryopreserved PBSC products. DMSO is incompatible with polyurethane. Product with DMSO in it must be infused through a silicone line.

DMSO is known to cause allergic and anaphylactic reactions and hence pre-medications and hydration are required in all patients receiving cryopreserved stem cells.

1) Hydrate patient using Ringers Lactate or other relevant hydration fluids at 125 ml/m2 /hr for 6 hours. Start hydration at least 1 hour prior to stem cell infusion.
2) Filters **SHOULD NOT** be used during administration unless specifically indicated when clots or fragments are suspected. Minor clots or small fragments DO NOT require filtration and can pass through into the body. When used, the size of the filter will be clearly indicated on the infusion documents under such circumstances.
3) Gravol 0.5-1 mg/kg IV, given 1 hour prior to infusion.
4) Hydrocortisone 4 mg/kg IV (or methylprednisolone equivalent) 45 minutes prior to infusion (may be omitted if recipient is already receiving an equivalent or greater dose of steroids).
5) Benadryl 0.5-1 mg/kg IV 30 minutes prior to infusion.
6) Lorazepam is optional and can be used as an additional anti-emetic agent, 15 minutes prior to infusion.
7) Infuse frozen PBSC/marrow product after thawing as per CTL guidelines into patient with a wide open line (or equivalent).

8) If more than one bag of product available, flushes between bags are not necessary unless the subsequent bag(s) are not immediately available.
    a. It is appropriate, but required to wait between multiple bag infusions to ensure any side effects have subsided before the subsequent cryopreserved bad is infused.
    b. Thawing of additional bags should be done once such side effects are resolved and the risk of incurring additional side effects is decreased or negated.
9) **For cord blood only**: Upon completion of thawed product infusion, give mannitol 20% solution for a total of 0.5 grams/kg over 15minutes (max 12.5 grams).
    - ABO (in) compatibility does not remain an issue with frozen product as RBCs and plasma are depleted prior to freezing product. The precautions taken to prevent DMSO reactions can also prevent reactions that might occur with ABO incompatibility.
    - Also follow 'cord blood infusion' techniques as directed in 'cord blood infusion policy' for umbilical cord blood products.

****Cord blood** will be processed and infused as per standard operating procedures. Processing requirements are determined by the attending BMT physician prior to planned infusions. The following considerations are taken into account when determining processing requirements:

1) Volume of Unit(s)
2) Volume of product relative to recipient weight
3) Red Cell Content: Buffy coat and Red Cell Deplete units may be washed and/or diluted, or thawed at beside, at the discretion of the physician. Red Cell Replete units must be thawed, and diluted and/or washed.
4) History of previous reactions to blood products (transfusion reactions, APTR etc).
5) Discretion of attending BMT physician.

Notes for Cord Blood:

For cord blood products with a major ABO incompatibility, the volume of donor RBC in the product does not usually exceed the threshold to require a red cell depletion.Furthermore, red blood cell depletion is not recommended due to the loss of stem cells. ABO incompatible cord blood does not need to be in aliquots. However, infusion protocol should be followed as for 'frozen product infusion orders. As red blood cells in a cord product are a hemolysed product and generally a very small volume, it is not usually necessary to prepare aliquots based on RBC/kg. Such calculations are not known for the infant age group (patients under 10 kg) and therefore cautious monitoring of urine output and renal dysfunction/failure needs to be considered in this population. Washing rather than diluting product might be preferable in these circumstances, but comes at the risk of stem cell loss.

The pediatric program at the ACH will preferably use RBC depleted product in selecting the optimum cord unit. RBC replete products should undergo washing or dilution prior to infusion.

Infusion Immune Effector Cells

Immune Effector Cells (IEC) are delivered fresh or are cryopreserved. Chimeric antigen receptor (CAR) T-cells are a type of IEC. Currently, only Tisgenlecleucel is the sole CAR-T cell product commercially available in Canada for children. Note that other CAR-T cell products may require different management. This guideline will be amended as additional therapies become available.

Note: recommendations that differ from below and are specific in a research protocol supersede these guidelines.

Cryopreserved IECs contain varying amount of DMSO and silicone lines must be used.

IECs must be infused within 30 minutes of end thaw time if cryopreserved, or removal from dry shipper if fresh.

Anit-IL-6 therapies, such as tocilizumab, are required on site to be available for administration prior to starting infusion. Each IEC patient must have 4 doses secured, with 2 doses at ACH prior to administration. A filter should not be used.

IVIG Use in Cellular Therapy Recipients

Presented by: Greg Guilcher, Ravi Shah, and Luis Murguia

Purpose

To provide guidance on the use of intravenous immunoglobulin (IVIG) in cellular therapy product (CTP) recipients.

Points of Emphasis

Use of IVIG replacement in patients with hypogammaglobulinemia (IgG < 4-6g/L) post-allogenic stem cell transplant or CAR-T cell therapy should be considered. The normal IgG reference level in serum at AHS laboratory is 4-15g/L.

Background

The use of prophylactic intravenous gammaglobulin in CTP patients is controversial. However despite the controversy of the benefit of IVIG in CTP recipients, it has been used extensively in transplant protocols for many years. The early IVIG trials were performed when there were fewer effective agents for infectious complications and led to the original use of IVIG for prophylaxis against CMV and acute graft vs. host disease (aGVHD). While CMV prophylaxis/treatment and GVHD prophylaxis have been the two most common indications, few prospective, randomized and controlled trials have been reported. There are now several effective agents available to prevent and treat many of the infections that led to the initial use of IVIG.

The routine use of IVIG for many indications has come under scrutiny due to the high cost, limited supply and unclear benefit for many possible indications. There is also concern that IVIG may have long-term effects on immune reconstitution. A multi-centered, randomized, double- blind, dose effect placebo-controlled study (*Ann Intern Med*. 2003; 139: 8-18) showed that prophylactic IVIG in allogeneic sibling stem cell transplants had no benefit over placebo. Similarly a meta-analysis (J Clin Oncol 2009; 27:770-781) of thirty randomized controlled trials comparing IVIG prophylaxis versus control, showed no survival benefit and no difference in clinically documented infections. A Cochrane review of IVIG use in hematologic malignancies and post-hematopoietic stem cell transplant (HSCT) did not support the use of IVIG prophylaxis post-HSCT (*Cochrane Database Syst Rev* 2008; 8: CD006501). A landmark review was undertaken by leading international consortia in HSCT and infectious diseases, which recommended IVIG for bacterial prophylaxis in allogeneic HSCT recipients of 400 mg/kg/month in children if IgG < 4 g/L, or 500 mg/kg/week for adolescents with the same threshold (Biol Blood Marrow Transplant; 2009; 15: 1143-238). New American Society of Transplantation and Cellular Therapy guidelines are forthcoming, with a threshold of 4 g/L for replacement (*Guilcher*, personal communication).

Local data indicate delayed immune recovery in patients receiving regular IVIG post- transplantation. Data describing use in umbilical cord blood (UCB) transplantation suggests that these patients may derive more benefit. These findings are likely due to higher incidence and risk of infections after UCB transplantation.

It should be noted that aGVHD continues to be a significant complication post-HSCT despite various different regimens of immunosuppressive therapy. The trend for allogeneic transplantation to expand its use of HLA non-identical or unrelated donors also increases the incidence of aGVHD. Novel prophylactic approaches such as the use of post-HSCT cyclophosphamide may mitigate this risk of aGVHD. The increased number of alternative donor HSCT procedures may shift the indication for IVIG to patients at high risk of GVHD rather than for infectious prophylaxis, although some haploidentical regimens deplete B-cells with rituximab to prevent post-transplant lymphoproliferative disease. Rituximab use requires IVIG replacements and is sometimes associated with the need for prolonged replacement (e.g. years).

Chronic GVHD is associated with defects in the cellular and humoral immune responses, in addition to hyposplenism. A study comparing the effects of monthly IVIG infusion on chronic GVHD and associated infections showed no substantial benefits (*Biol Blood Marrow Transplant* 1996; 2: 44-53). Another study (*Bone Marrow Transplantation* 2001; 28: 187-196) showed that the incidence of GVHD after day 100 was similar in 3 different dosing groups. A significant decrease in serum IgG levels was observed when the dosing schedule was changed from weekly to monthly. Some authors suggest that a weekly administration schedule may be beneficial in patients with chronic GVHD and severe hypogammaglobulinemia.

Studies comparing IVIG dosing (100mg/kg, 250 mg/kg, and 500 mg/kg) have produced variable results. An increase in the risk of VOD has been reported in patients receiving IVIG 500 mg/kg/week (*Transplantation* 1996; 60: 1225-1230). This was not seen in the *Bone Marrow Transplantation* 2001 study mentioned above, but the use of polyvalent IVIG prophylaxis was associated with higher rates of VOD in the Cochrane Review. This study showed that the 3 different dosing schedules were associated with similar incidences of GVHD, infection, interstitial pneumonia, relapse and survival. Howel et al. retrospectively compared clinical outcomes after HSCT between patients who received routine IVIG (200 mg/kg weekly) and those who received IVIG when serum IgG level became below 400 mg/dL. While the incidences of GVHD, VOD, or documented infections were comparable between the two groups, total IVIG dosage and the cost were 6940 g vs. 1896 g and $924,408 vs. $252, 547 retrospectively. The suggested that IVIG application according to the individual IgG level was a cost-effective approach.

According to the 2023 long term follow-up (LTFU) manual by Fred Hutch, IVIG replacement is recommended at monthly intervals to maintain serum IgG levels above 400 mg/dL for 10 months after transplant before the start of vaccinations. Interestingly, it is considered for specific situations only but

isn't easy to create separate guidelines for each situation. According to 2009 ASBMT guidelines for preventing infectious complications, routine IVIG for bacterial infection prophylaxis is not recommended, and high-risk recipients who undergo unrelated HSCT with IgG < 400 mg/dL may be a candidate for Immunoglobulin replacement therapy. Systematic reviews and meta-analyses have identified no evidence that IVIG offers any advantage for infection prevention and overall survival and therefore do not support the routine use of prophylactic IVIG in BMT recipients, regardless of immunoglobulin levels. However, children specific data and indication specific data are lacking.

Allogeneic HSCT (Peripheral Blood Stem Cell/ Marrow /Cord Blood)

- Weekly serum IgG levels to be drawn for the **first three months** post-CTP (note that this does not apply to autologous CTP recipients).
- Patients may receive IVIG if serum IgG level <4g/L. IVIG dose to be 500 mg/kg (round to the nearest 2.5 grams). Conditional order to be entered on admission.
- Beyond the first month, IgG levels will be drawn monthly and above criteria followed should the risk of infection be perceived to be high. IVIG may be omitted at the discretion and medical judgment of the treating physician.
- **Patients with severe combined immunodeficiency will receive IVIG if the serum IgG level is <6 g/L. This does not apply to other patients with inborn error of immunity.**

Patients receiving Alemtuzumab or Rituximab

- This patient cohort will receive IVIG as directed above.
- In addition they will continue to receive IVIG on a monthly basis after completing their upfront IVIG dosing as directed above, if they enter the winter season in the first year post CTP (except sickle cell disease patients).
- Such administration will continue until the end of April of the following year at a minimum.

Post-CAR-T Therapy patients

- This cohort of patients will receive IVIG depending on IgG levels < 4.0 g/L.
- For patients on study protocols as registered patients, please follow study directions for IVIG supplementation.
- For patients on 'Commercial Products' IVIG dose is 500 mg/kg, rounded to the nearest 2.5 grams.
- IgG levels should be checked every 2 weeks till 3 months post CAR-T and then every month thereafter, until there is evidence of adequate IgG levels without support (with continued B-cell aplasia as is desirable with this treatment, this recovery might be unlikely).
- If IgG levels are low at interim checks, follow above dosing guidelines at such time points.

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Referral of Pediatric Cellular Therapy Recipients to Gynecology (including Fertility Preservation)

Presented by: Greg Guilcher and Sarah McQuillan

Purpose

To provide guidance for referrals to Pediatric and Adolescent Gynecology (PAG) for pediatric and adolescent patients undergoing cellular therapy infusion.

The literature has demonstrated that cellular therapy is associated with several possible gynecological complications. These include heavy menstrual bleeding secondary to thrombocytopenia, genital symptoms, or sexual dysfunction in the setting of chronic graft versus host disease (GVHD), secondary solid tumours due to immunosuppression, and premature ovarian insufficiency (POI) manifested as delayed puberty, amenorrhea, osteoporosis, and/or infertility. With the increasing survival rates following cellular therapy, it is important that the future reproductive health of female patients is taken into consideration when undergoing cellular therapy, particularly given the known gonadotoxic effects of some of the treatments. It is also imperative that adolescents who are sexually active use effective contraception and practice safe sex while undergoing their treatment.

Fertility preservation in females undergoing cellular therapy should represent a major concern for the clinician taking care of these patients. The risk of POI is increased with increasing age, post-pubertal status, high-dose total body irradiation, or the use of alkylating agents such as busulfan and cyclophosphamide. Studies have shown that females have a > 80 % risk of premature ovarian insufficiency after cellular therapy with cyclophosphamide/total body irradiation (TBI) or cyclophosphamide/busulfan. With the advent of new fertility preservation technologies over the last 10 years, patients now have the option to preserve their fertility prior to undergoing these treatments if referral is made in a timely fashion.

Female genital chronic GVHD (cGVHD) has been markedly underreported in the past but also has a significant impact on the patients' health and quality of life. Data on prevention and treatment of this complication are still limited. Both adult and pediatric patients should undergo regular gynecological care and cervical cancer screening (when appropriate) after cellular therapy. For example, women with Fanconi anemia have a several thousand-fold higher risk for vulvar cancer and at least a 100-fold higher risk for cervical cancer compared with the general population. Current recommendations include a visual examination of the external genitalia at age 13 years followed by annual comprehensive gynecologic examinations and the introduction of Pap smears when appropriate (prior to transitioning to adult care). A team-based approach, with communication between Pediatric Hematology/Oncology/Cellular Therapy, and Gynecology allows for anticipatory guidance, management of acute gynecological concerns, and ongoing health surveillance.

Given the significant risk of menstrual irregularities, impaired fertility, POI, higher than age matched control unplanned pregnancy rates, and development of chronic GVHD, **all assigned female at birth** patients undergoing HSCT should be referred to Gynecology prior to undergoing treatment. The Alberta Children's Hospital (ACH) has a PAG clinic within the hospital as well as a Fellow & Attending Physician providing call coverage during weekdays (8am-5pm). During the evening, weekends and holidays, there is always a gynecologist on call to ACH at either the Foothills Medical Center (FMC) or the South Health Campus (SHC) who can provide advice as well, the Regional Fertility Program (RFP)e always has a Reproductive Endocrinologist available for urgent Fertility Preservation Consultations. The PAG group is happy to provide longitudinal care to this population who is at high risk for life long gynecological concerns. In addition, the PAG Attending Staff also has an adult practice which ensures ongoing gynecologic care when these patients transition out of the pediatric system.

Of note, the document is only meant for guidance purposes and the actual referral is at the discretion of the treating team.

Referral Guidelines

- **All female pediatric** patients should be referred to the PAG clinic prior to cellular therapy. Please indicate the reason for referral (along with anticipated date of the cellular therapy) so these patients are triaged appropriately. Refer to *Fertility Preservation Referral SOP* (HOTS10024).
    - Please document if the family wishes to proceed with concurrent referral to the RFP and when the appointment is scheduled.
- **All females** should be currently referred to **Dr. Shu Foong** at the RRP by the PAG team on an urgent basis for discussion of fertility preservation prior to HSCT as per *Fertility Preservation Referral SOP* (HOTS10024).
- The goals of the pre-HSCT PAG consultation include:
    - Review of potential gynecological complications of HSCT
    - Discussion of options for menstrual suppression (if patient is menstruating), with goal to have plan in place prior to admission for HSCT
    - Discussion about potential impact on future fertility & ensure referral to RFP has been made if desired by patient and family
    - Discussion of contraception & safe sex practices if patient is sexually active
    - Review plans for long-term gynecological follow-up
- During transplantation, referrals may be made for assessment and management of:
    - Lesions involving the vaginal area
    - Assessment of dysfunctional uterine bleeding
    - Excessive bleeding from vaginal area.

- Hemorrhagic cystitis evaluation and separation from vaginal processes.

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Skin Care Guideline in Cellular Therapy Product Therapy Patients

Presented by: Greg Guilcher and Marsha Bucsis

Purpose

To provide guidance regarding skin care for cellular therapy product (CTP) recipients.

Points of Emphasis

- Skin toxicities are commonly observed in over 50% of patients receiving thiotepa, busulfan and/or treosulfan in conditioning regimens
- Cutaneous manifestations can vary from mild erythematous patches to erosions, desquamation or blister formation
- Common sites of involvement are intertriginous areas and during thiotepa and busulfan conditioning, previously occluded skin is involved.
- These can be mitigated by certain precautions but there is paucity of high-quality evidence regarding prevention of skin toxicity
- Breakdown of skin barrier can be a portal of entry for infectious organisms.

Guidelines for All CTP Recipients

- Daily baths or showers are required with warm water and mild soap if the patient is clinically stable.
- Bed linens to be changed daily.
- Skin to be moisturized with Hospital Formulary skin cream (Glaxal or Atlas base).
- Prevex or barrier cream may be applied to the perianal region after each bowel movement to prevent irritation or breakdown. Refer to Diaper Rash Management ACH (RES 036) https://insite.albertahealthservices.ca/main/assets/tms/achip/tms-achip-diaper-rash-resource.pdf
- Secaris to be applied to the lips as necessary.
- Areas of skin breakdown should be treated with Polysporin, excluding the central line site.
- Encourage patient mobility and ambulation when possible to minimize risk of pressure sores. Refer to Safest Together, Alberta Children's Hospital (ACH) Pressure Injuries at ACH | Insite (albertahealthservices.ca)
- For care of Central Venous Access Devices (CVAD) refer to Clinical Care Topic: Vascular Access Device Infusion Therapy: Adult & Pediatric at Vascular Access Device InfusionTherapy | Insite (albertahealthservices.ca)
    - Note: ACH is part of Safest Together Network. Refer to Central Line-Associated Bloodstream Infection (CLABSI) guidance at ACH | Insite (albertahealthservices.ca)
- Positioning and Mobility:
    - Encourage patient to regularly change position to avoid creating pressure points that can lead to sores.

- Regular position changes for infants is recommended
- Older children should be encouraged to get out of bed and mobilize
- Should sores develop, consult plastics, wound care, and other services as needed to establish the most ideal path of management.
- Refer to Safest Together, ACH, Pressure Injuries at ACH | Insite (albertahealthservices.ca)

Thiotepa Skin Precautions

Patients receiving thiotepa as part of conditioning regimen are at high risk of skin breakdown. There is an occlusive like phenomena which occurs with prolonged sitting or lying in bed which can lead to increase in dermal toxicity. Encourage ambulation as much as possible.

- Please refer to *Nursing Guidelines for Care of Patients Receiving Thiotepa.*
- Refer to the ACH Bed Surface Algorithm for choice of bed.
- NG tubes may be removed during thiotepa infusion days and re-inserted 24 hours after the last dose of thiotepa as per physician discretion.

Treosulfan Skin Precautions

Patients receiving treosulfan are at risk of skin burns if the drug resides on the skin for prolonged periods. Unlike thiotepa, this is a direct skin effect in excreted product rather than sweat excretion of product.

- Daily multiple baths are NOT required, but most centres in UK recommend frequent bathing and avoidance of barrier cream on days that treosulfan is given.
- It might be appropriate to place a foley catheter for infants and children in diapers for the duration of treosulfan treatment and 24 hours after the treatment is completed. Routine use of catheters is not recommended due to the risk of urinary tract infection
- Avoid placement of Foley catheters if the area can be kept clean with diaper changes
- Continue diaper changes every 2 hours for 24 hours after the treatment is completed. This frequency of diaper changes should also be adjusted if a Foley Catheter must be in place and is leaking.
- Refer to Diaper Rash Management ACH (RES 036) https://insite.albertahealthservices.ca/main/assets/tms/achip/tms-achip-diaper-rash-resource.pdf

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Outpatient Delivery of Subcutaneous Alemtuzumab for Conditioning

Presented by: Geoffrey Cuvelier, Victor Lewis, and Greg Guilcher

Purpose

To provide guidance on the outpatient delivery of subcutaneous alemtuzumab for conditioning in the pediatric Alberta Blood and Marrow Transplant Program (ABMTP).

This guideline is applicable to pediatric ABMTP patients receiving subcutaneous alemtuzumab for conditioning in the Trican Hematology, Oncology, Blood & Marrow Transplant and Immunology (HOT) Dayroom at the Alberta Children's Hospital (ACH).

Background

Alemtuzumab (Campath-1H) is often used before traditional cytotoxic chemotherapy as part of the conditioning regimen to immunosuppress the recipient and prevent graft rejection. If alemtuzumab is also present in vivo at the time of hematopoietic cell infusion, the monoclonal antibody will also further T-cell deplete the graft, preventing graft-versus-host disease.

Traditionally, alemtuzumab required admission to an inpatient unit where the drug was administered intravenously as an infusion (along with pre- and post-supportive care medications such as antihistamines, corticosteroids, and anti-pyretics). This mode of delivery results in high rates of infusion-related reactions including fevers, chills/rigors, urticaria, pruritis, bronchospasm, and potentially anaphylaxis. Data from studies in sickle cell anemia, aplastic anemia, and in unrelated donor transplant for malignant conditions in adults have shown that subcutaneous administration of alemtuzumab (including in the outpatient setting) compared to IV administration is associated with significantly fewer infusion-related adverse reactions, is safe, and has no deleterious impact on engraftment, neutrophil and platelet recovery, infectious complications, immune reconstitution, acute GVHD and survival. In a recent study published in sickle cell anemia (Plavsa et al, 2025), 54% of patients receiving subcutaneous alemtuzumab experienced no drug-related reactions (compared to only 16.7% of patients who received IV alemtuzumab), and most of the reactions seen with subcutaneous alemtuzumab were minor (grade 1). The most common adverse reaction with subcutaneous alemtuzumab were minor local reactions at the site of injection.

The pediatric ABMTP therefore has decided to offer conditioning with subcutaneous alemtuzumab as an outpatient in the HOT clinic in certain situations. This approach will reduce the amount of time in the inpatient unit and allow patients and families to spend more time at home before being admitted to hospital to start their intravenous conditioning regimen. This document reviews the protocol for outpatient subcutaneous alemtuzumab.

Indications for Outpatient Subcutaneous Alemtuzumab

1. Any conditioning regimen where alemtuzumab is used as the only drug being given that day as part of the conditioning regimen and where alemtuzumab is administered before traditional cytotoxic chemotherapy (with traditional cytotoxic chemotherapy still requiring inpatient admission for IV administration). An example includes HLH conditioning (Alemtuzumab-Flu-Mel +/- thiotepa), where alemtuzumab is given in either a distal or intermediary dosing schedule before fludarabine / melphalan.

Exclusion Criteria for Outpatient Administration

1. Patients with sickle cell anemia receiving conditioning with subcutaneous alemtuzumab and 300 cGY TBI (e.g., SUN study), where there are reports of higher rates of systemic inflammatory response syndrome have been reported (Chok et al, 2025). These patients should continue to receive subcutaneous alemtuzumab in the inpatient setting.

Place of Administration

Outpatient subcutaneous alemtuzumab shall only be administered in the outpatient HOT clinic at the ACH. Since it is part of the conditioning regimen, administration at other hospitals before the patient arrives in Calgary (e.g., Stollery Children's Hospital) is not allowed.

Required Pre-medications Before Each Subcutaneous Alemtuzumab

All patients receiving outpatient subcutaneous alemtuzumab should receive as pre-medication acetaminophen 15 mg/kg/dose PO x 1 dose (15-30 minutes before), oral cetirizine (15-30 minutes before) at appropriate doses for age/weight, and IV methylprednisilone1 mg/kg/dose (15 minutes before).

Outpatient Monitoring Before and After Subcutaneous Alemtuzumab

Vital signs shall be performed before subcutaneous administration. Vital signs after subcutaneous alemtuzumab administration shall be taken every 15 minutes for 1-hour after, in the HOT clinic, before the patient is allowed to be discharged from the clinic to return home.

Ongoing Management of Fevers and other Non-Serious Adverse Effects once Patients are Discharged from Clinic

Patients and parents are allowed and encouraged to administer oral acetaminophen and oral cetirizine at home (a second dose of cetirizine can be given approximately 12-hours after the first dose that day if needed) as needed for fevers (≥38 degrees Celsius) and urticaria / pruritis, respectively, that may occur following discharge and that are likely due to alemtuzumab. Parents are still required to phone the BMT physician on-call with any adverse reactions (including all new fevers) for phone advice and for the physician on-call to assess if there is any possibility for a more serious adverse event. Patients do not need to be seen routinely in the Children's ER, HOT after-hours clinic, or unit 1 following outpatient clinic discharge (e.g., for blood cultures). Routine administration of IV or oral antibiotics is not mandatory for fevers when the patient is not neutropenic. If the patient is known

to be neutropenic, then follow routine febrile neutropenia guidelines including an emergent assessment, blood cultures, and admission for IV antibiotics.

If the BMT physician on-call assesses by phone that the patient may be having a more serious adverse reaction (e.g., bronchospasm, anaphylaxis, sepsis), the patient may be guided into the Children's ER, HOT clinic, or unit 1 (or have an ambulance called) as appropriate. Given the almost non-existent risk of anaphylaxis, routine prescription of an EpiPen for home is not generally required.

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Related Donor for Cellular Therapy with Laboratory Variants – Safety Guidance Document

Presented by: Greg Guilcher

Purpose

To provide guidance for the safety of related donors (<18 years of age) undergoing apheresis or bone marrow collections.

Points of Emphasis

- Any test or physical exam results that deviate from normal values must be communicated to the donor (or guardian as appropriate) and with necessary documentation completed in the patient record; follow-up review should be conducted as relevant.
- For pediatric patients - normal values based on age and sex will be used as the reference range.
- If the indication for transplant is an inherited genetic condition, the disease in question should be excluded through appropriate testing/subspecialty referral for both donor and recipient safety, as indicated.
- Donor clearance must follow the process and requirements outlined in the Donor Eligibility and Suitability SOP (BMTS10212) and Related Donor (<18 years of age) Eligibility and Suitability Evaluation SOP (BMTS20005). For donor follow-up refer to Related Donor (<18 years of age) Follow-Up Procedure (BMTS20010).
- This document serves as a guide for the management of abnormal results in the donor prior to the start of the recipient's conditioning regimen and/or on the day of collection.Black 12 pt 1.15 spacing.

Guidelines

1) Prior to the start of the recipient's conditioning regimen:
    a. The donor physician should ensure the donor's blood counts and chemistries are within age, sex, and ethnicity (if applicable) based normal values or acceptable ranges if slightly deviating from normal values.
        i. Minor deviations do not need to be worked up unless there are clinical concerns regarding donor health. Donation can continue as previously planned, however follow-up review of laboratory findings should be a strong consideration depending on the degree of deviation from normal values. Deviations can be considered to be minor at physician discretion and acknowledgment of these results should be documented.

ii. Deviations outside normal ranges that are not determined to be minor will require the donor physician to assess whether the donation poses risk to the donor or recipient.
iii. If deviations may impact the timing of transplant or requested stem cell product the recipient's physician should be notified as appropriate and necessary documentation placed on both the recipient and donor health records.
iv. The donor (or guardian as appropriate) should be informed of results and potential risks, as well as the proposed plan of care with referrals made as necessary. Complete follow up of such results and plans is not necessarily the responsibility of the donor physician. However the donor physician, needs to ensure that results are within acceptable limits and that any medical issues have been addressed appropriately prior to reconsidering the donor donation.

2) On day of collection:
   a. The donor physician should:
      i. Ensure the donor's pre-collection results are within age and sex based normal values or within acceptable ranges safe for collection. If deviations are identified the donor physician should: ensure the values in question are accurate and that donor health is not compromised in any way.
      ii. Review/update donor history to reassess if evidence is available to explain the deviation from normal results.
      iii. Complete a donor exam as necessary to establish safety of the donor prior to allowing collection to proceed.
      iv. If a physician delegate (who might be different from the donor physician) is the first to come across deviations in results on day of collection, (s)he should review such results with the donor physician or delegate before continuing with the collection procedure.
   b. Donation may continue at the discretion of the donor physician even if supportive care is required, such as the use of blood products in healthy related donors if risks and benefits have been clearly explained to the donor (and guardian as appropriate) and documented.
   c. At no point should donor health be at risk.
3) Post collection:
   a. Minor issues such as pain at femoral line site or bone marrow harvest site and mild deviations in lab values such as electrolyte disturbance must be addressed by donor physician or physician delegate as applicable.
   b. Although no studies are available to recommend iron supplementation for one time donations, consideration must be given to iron replacement after bone marrow stem cell harvest.

Appendices

Abbreviations

ABMTP, Alberta Blood and Marrow Transplant Program; ACH, Alberta Children's Hospital; AG, aminoglycoside; AHS, Alberta Health Services; AIDS, acquired immunodeficiency syndrome; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; AML, acute myeloid leukemia; ANC, absolute neutrophil count; APC, antigen presenting cells; APL, Alberta precision laboratory; APS, acute pain service; ARO, antibiotic resistant organism; AST, aspartate aminotransferase; ATG, antithymocyte globulin; AYA, adolescent and young adult; BAL, bronchoalveolar lavage; BID, twice a day; BMM, bone marrow media; BMT, bone marrow transplant; BP, blood pressure; BSI, bloodstream infections; BUN, blood urea nitrogen; CAPD, Cornell Assessment of Pediatric Delirium; CAR-T, chimeric antigen receptor T-cell therapy; CBC, complete blood count; CBT, cord blood transplants; CIBMTR, Center of International Blood and Marrow Transplant Research; CLABSI, central line associated blood stream infections; CrCl, creatinine clearance; CMV, cytomegalovirus; CNS, central nervous system; CRP, c-reactive protein; CSA, cyclosporine A; CSF, cerebrospinal fluid; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTP, cellular therapy product; CVAD, central venous access device; CVC, central venous catheter; CXR, chest x-ray; DHFR, dihydrofolate reductase; DHPS, dihydropteroate synthase; DLCO, diffusing capacity of the lungs for carbon monoxide; DLI, donor lymphocyte infusion; DMSO, dimethyl sulfoxide; DNA, deoxyribonucleic acid; DSA, donor specific HLA antibodies; DSL, diagnostic semen laboratory; EBMT, European society for blood and marrow transplantation; EBV, Epstein-barr virus; ECOG, eastern cooperative oncology group performance status scale; EORTC, European Organisation for Research and Treatment of Cancer; FEV, forced expiratory volume; FMC, Foothills Medical Center; FN, febrile neutropenia; FO, fluid overload; FQ, fluoroquinolone; FVC, forced vital capacity; G-CSF, granulocyte colony-stimulating factor; GERD, gastroesophageal reflux disease; GFR, glomerular filtration rate; GI, gastrointestinal; GLDH, glutamate dehydrogenase; GM-CSF; granulocyte-macrophage colony-stimulating factor; GNB, gram negative bacteria; GP, gram positive; GVHD, graft-versus-host disease; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; GVL, graft versus leukemia; h, hour; HBOT, hyperbaric oxygen therapy; HC, hemorrhagic cystitis; HCT, hematopoietic cell transplantation; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HLH, hemophagocytic lymphohistiocytosis; hMPV, human metapneumovirus; HPC, hematopoietic progenitor cell; HPLC, high-performance liquid chromatography; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; HVPG, hepatic venous pressure gradient; HZ, herpes zoster; ICU, intensive care unit; ID, infectious disease; IDSA, Infectious Disease Society of America; IECs, immune effector cells; IFI, invasive fungal infections; Ig, immunoglobulin; IMV, invasive mechanical ventilation; INR, international normalized ratio; IP&C, infection prevention and control; ISOO, International Society for Oral Oncology; IV, intravenous; IVC, inferior vena cava; IVIg, intravenous immunoglobulin; JPJ, *Pneumocystis jiroveci* pneumonia; KDIGO, Kidney Disease: Improving Global Outcomes score; LDH, lactate dehydrogenase; LFTs, liver function tests; LRTI, lower respiratory tract infection; LTFU, long term follow-up; LVEF, left ventricular ejection fraction; MASSC, Multinational Association of Supportive Care in Cancer; MDS, myelodysplastic syndromes; MFD, matched family donor; MMP, matrix metalloproteinases; MOF, multi-organ failure; MRD, matched-related donor; MRHP, most responsible health professional; MRI, magnetic resonance imaging; MRSA, Methicillin resistant Staphylococcus aureus; MSD, matched sibling donor; MSS, mucositis study section; MTX, methotrexate; MUD, matcher-unrelated donor; NF-κB, nuclear factor-κB; NIV, non-invasive ventilation; NK, natural killer; NO, nitric oxide; NPA, nasopharyngeal aspirate; NS, normal saline; NSAIDS, nonsteroidal anti-inflammatory drugs; PAG, pediatric and adolescent gynecology; PALISI, pediatric acute lung injury and sepsis investigators; PBM, Photobiomodulation; PBSC, peripheral blood stem cells; PCA, patient-controlled analgesia; PCR, polymerase chain reaction; PK, pharmacokinetics; PO, per os (by mouth); POI, premature ovarian insufficiency; PPE, personal protective equipment; PRSP, penicillin resistant Streptococcus pneumonia; PTCy, post-transplant cyclophosphamide; PV, portal vein; q, every; QD, once a day; RFP, regional fertility program; RBC, red blood cell; RIC, reduced intensity conditioning; ROCA, regional on call application; ROS, reactive oxygen species; RSV, respiratory syncytial virus; RT, refractory thrombocytopenia; RUQ, right upper quadrant; SC, subcutaneous; SCT, stem cell transplant; SECs, sinusoidal endothelial cells; SF, shortening fraction; SHC, South Health Campus; SMX, sulfamethoxazole; SOP, standard operating procedures; SOS, sinusoidal obstructive syndrome; STEDT, short term exceptional drug therapy; STR, short tandem repeats; TA-TMA, transplant-associated thrombotic microangiopathy; TBI, total body irradiation; TCR, T-cell receptor; TID, three times a day; TIPS, intrahepatic portosystemic shunt insertion; TMA, transplantation-associated microangiopathy; TMP, trimethoprim; TNC, total nucleated cells; TNF, tumor necrosis factor; UCB, umbilical blood; UOP, urine output; URTI, upper respiratory tract infection; VEGF, vascular endothelial growth factor; VNTR, variable number of tandem repeats; VOD, veno-occlusive disease; VRE, vancomycin resistant Enterococcus; VSTs, virus-specific T cells; VZV, varicella zoster virus; WBC, white blood cell.

Disclaimer

The recommendations contained in this guideline are a consensus of the Pediatric Alberta Bone Marrow and Blood Cell Transplant Program and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements
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Revision History

Date	Topic Title	Action
May 1, 2018	Central Line Associated Blood Stream Infections	New
Mar 21, 2018	Skin Care	New
Mar 21, 2018	Hepatic Sinusoidal Obstructive Syndrome	New
Feb. 3, 2020	Autologous	New
Feb 3, 2020	CMV	New
Feb 3, 2020	Indications For Allogeneic BMT	New
Feb 3, 2020	Donor Chimerism	New
Feb 3, 2020	Fungal Infections	New
Feb 3, 2020	Hemorrhagic Cystitis	New
Feb 3, 2020	Mucositis	New
Feb 3, 2020	PJP	New
Feb 3, 2020	Respiratory Viruses	New
Feb 3, 2020	Criteria for Eligibility-Allogeneic CTR	New
Feb 3, 2020	Criteria of Allogeneic Donor Selection	New
Feb 3, 2020	Fertility Preservation	New
Feb 3, 2020	G-CSF for Mobilization and Post-Cellular Therapy Neutropenia	New
Feb 3, 2020	IVIG Use	New
Feb 3, 2020	Physician Roles	New
Jun 10, 2020	Graft Versus Host Disease	New
Nov 26, 2020	Donor Chimerism	Updated
Nov 26, 2020	Febrile Neutropenia	New
Apr 6, 2021	Central Line Associated Blood Stream Infections	Updated
Apr 22, 2021	Hemorrhagic Cystitis	Updated
Jun 3, 2021	IVIG Use	Updated
Jun 25, 2021	Hepatic Sinusoidal Obstructive Syndrome	Updated
Jun 25, 2021	Skin Care	Updated
Jun 30, 2021	PJP	Updated
Jul 26, 2021	Graft Versus Host Disease	Updated
Nov 8, 2021	Respiratory Viruses	Updated
Nov 16, 2021	Mucositis	Updated
Nov 16, 2021	Antibiotic Treatment in Cases of Compromised Product	New
Nov 19, 2021	Fertility Preservation	Updated
Nov 19, 2021	Gynecology Referral	New
Nov 23, 2021	Graft Versus Host Disease	Updated
Apr 1, 2022	G-CSF for Mobilization and Post-Cellular Therapy Neutropenia	Updated
Jun 28, 2022	Physician Roles	Updated
Jul 8, 2022	Indications For Allogeneic BMT	Updated
Jul 8, 2022	Autologous	Updated
Jul 8, 2022	Criteria for Eligibility-Allogeneic CTR	Updated
Aug 10, 2022	CMV	Updated
Aug 12, 2022	Criteria of Allogeneic Donor Selection	Updated

Sep 28, 2022	Fungal Infections	Updated
Oct 13, 2022	Donor Chimerism	Updated
Jan 4, 2023	Febrile Neutropenia	Updated
Mar 3, 2023	Hemorrhagic Cystitis	Updated
Mar 3, 2023	Central Line Associated Blood Stream Infections	Updated
Mar 3, 2023	Related Donor for Cellular Therapy with Laboratory Variants - Safety	New
April 6, 2023	PJP	Updated
April 6, 2023	Hepatic Sinusoidal Obstructive Syndrome	Updated
Apr 27, 2023	IVIG Use	Updated
Apr 26, 2023	Skin Care	Updated
May 3, 2023	Inpatient Activity	Updated
Sep 22, 2023	Mucositis	Updated
Sep 25, 2023	Respiratory Viruses	Updated
Nov 16, 2023	G-CSF for Mobilization and Post-Cellular Therapy Neutropenia	Updated
Nov 7, 2023	Graft Versus Host Disease	Updated
Nov 22, 2023	Antibiotic Treatment in Cases of Compromised Product	Updated
Feb 3, 2024	PK management in patients receiving Busulfan	Updated
Jun 25, 2024	Donor Chimerism	Updated
Jun 28, 2024	Physician Roles	Updated
Sept 18, 2024	CMV	Updated
Oct 10, 2024	Infusion of Cellular Therapy Products	Updated
Nov 5, 2024	Fungal Infections	Updated
Dec 5, 2024	HSV, VZV	New
Dec 14, 2024	Criteria for Eligibility-Allogeneic CTR	Updated
Dec14, 2024	Criteria of Allogeneic Donor Selection	Updated
Mar 13, 2025	Gynecology Referral	Updated
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Jun 2, 2025	Outpatient Delivery of Subcutaneous Alemtuzumab for Conditioning	New
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Jul 16, 2025	Autologous	Updated
Jul 21, 2025	Related Donor for Cellular Therapy with Laboratory Variants - Safety	Updated
Sept 16, 2025	G-CSF for Mobilization and Post-Cellular Therapy Neutropenia	Updated
Nov 10, 2025	PJP	Updated