LEUKEMIA/BMT MANUAL

E-Edition

LEUKEMIA/BMT MANUAL E-EDITION

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Preface

The field of malignant hematology and stem cell transplantation continually evolves with advances in therapeutics and supportive care. The electronic version of the BMT manual is intended to allow timely revision and updating as these changes occur. Although every effort is made to keep the Manual up-to-date this may not always be the case. In addition, this Manual is intended to provide guidance for frequently encountered routine issues for which reference is not easily accessible through other sources and is therefore not intended to be comprehensive. Please forward suggestions for improvement of the manual to any one of us. The purpose of this Manual is to serve as a guide, but should not replace reasoning and basic knowledge. All decisions should be well thought out and clinically justified. Also, many of these guidelines are new or changing. If you notice any items that do not appear correct, always check with the pharmacist and attending physicians. If there are doubts or questions concerning any of the guidelines, please discuss these concerns with the BMT team prior to making a decision. In doing so, hopefully the best decisions can be made for the patients to whom this Manual is dedicated.

Sincerely,

Kevin Song, MD, FRCPC, Program Director, Leukemia/BMT Program
Judith Rodrigo, MD, FRCPC, Quality Director, Leukemia/BMT Program

Important Phone Numbers

	Phone Number	Pager
BC Cancer Agency		
Note: BCCA E-Telephone Directory is available on all PHSA computers.		
Direct from VGH	81 + local	
Main Switchboard	81-6000	
Chimerism results	81-2094	
Cytogenetics Lab	81-2094	
Molecular Genetics Lab	81-2094	
Terry Fox Lab – Clinical Cell Therapy	604-675-8000 ext. 7745	
Terry Fox Lab – Stem Cell Assay	604-675-8000 ext. 7746	
Abbotsford CA Centre	1-604-851-4710	
Kelowna CA Centre	1-250-712-3900	
Victoria CA Centre	1-250-519-5500	
Canadian Cancer Society Jean C. Barber Lodge	604-879-9131	
Lancaster Pharmacy	604-873-8585	
Fax (CSA/FK-506 prescriptions)	604-873-2381	
MacDonalds' Prescriptions & Medical Supplies	604-872-2662	
Fax (G-CSF prescriptions)	604-876-0242	
PharmaCare: Special Authority Requests	1-877-657-1188	
St. Paul's Hospital		
Main Switchboard	604-682-2344	
Virology Lab	604-806-8420	
Vancouver General Hospital		
Note: VCH E-Directory is available @ www.vcha.ca/directory		
Admitting		
JP	54300	
Emergency – *Call when admitting pts. from Emerg.*	62238	
Bone Marrow Biopsy	54381 / 63599	
Apheresis Unit/Hematology Daycare		
Reception/Nursing Station	54626	
Fax	55053	
Chemical Dependency Resource Team	54788	604-871-5056
Consults		
Call Main Switchboard 55000 for pager number *except for the following consult requests:*		
Infectious Diseases	54588	
Palliative Care	54715	
Emergency – Reception	54995	
Dietician	62998	604-205-2302
Health Records	54070	
Interpreter Service	604-297-8400	

Laboratories

Results Hotline 1-800-992-8801
Bone Marrow Room 54381
Cytogenetics 54129

Leukemia/BMT Program

Administration Office 54863
Fax 54763

BMT Case Navigators
Brace, Laura/McGuinness, Anne-Marie…….. 68549……...604-707-1447
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Macleod, Kristy……. ..... 63432……..606-707-1459

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Katie Lacaria..... 68099 604-328-9252
Outpatient Pharmacist (Carmen Mountford) 68099 604-290-4581
Rotating Pharmacist T14L..... 604-707-1436
Rotating Pharmacist T15..... 604-872-9789

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Janet Nitta, Senior Data Coordinator..... 63167

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Fax 55248

Outpatient Daycare – Krall Centre, BP6..... 54073
Fax 55419

Patient Services Manager, Mandy Lowery 55297

Research Program
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Hogge, Donna, Director, Cell Therapy Laboratory 54662 604-877-3831
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Li, Charles..... 63858 604-877-2874
Nantel, Stephen, Head, Division of Hematology..... 66268 87-05095
Narayanan, Sujaatha..... 63079 604-877-5985
Nevill, Thomas..... 63073 87-03396
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Power, Maryse 69557 604-877-5815
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Sreenivasan, Gayatri, Director, Apheresis Unit..... 63066 604-707-3077
Sutherland, Heather..... 68286 604-877-5633
Toze, Cynthia..... 63168 604-707-1457
Tsang, Peter..... 62874 604-450-8290
White, Jennifer……. 22923……...604-871-5011
Yenson, Paul, Director, General Hematology 61409 604-877-5939
Zypchen, Leslie..... 67281 604-707-1493

Social Workers
- T15 office 54941 604-871-0728
- BP6 office 54697 604-675-6066
- Pre-Transplant office 604-875-5285

Occupational Therapist 54343 87-03673

Physiotherapist 63573 604-872-9875

Pharmacy (VGH)
- T15 Satellite (services T15 & BP6) ..... 63587 / 55717
- BP Dispensary 62481
- BP IV Admixture 63589

PICC Line Insertion – Team Pager 604-872-9847

Radiology
- Switchboard 54533
- CT Scan 63444
- GI – Reception/Booking 68158
- Portable X-Ray 63743

Respiratory Therapy
Therapists (RT Wards) 54896 87-04526

Spiritual Care & Multi-faith Services
- Reception 54151
- On-Call Chaplain 604-877-5918

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CHAPTER 1. SCORING SYSTEMS

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1-1. Prognostic Score for Initial Treatment of Advanced Hodgkin's Disease

Risk Factors Considered in the Model

Score 1 for each of the factors present below:

1. Serum Albumin < 40 g/L
2. Hemoglobin < 105 g/L
3. Male sex
4. Stage IV disease
5. Age ≥ 45 yr
6. White cell count ≥ 15 x 10^9/L
7. Lymphocyte count < 0.6 x 10^9/L or < 8% of WCC

Table 1. Rate of freedom from progression of disease and overall survival at 5 years according to grouped prognostic scores

Prognostic Score	Freedom from Progression %	Rate of Overall Survival %
0 or 1	79	90
> 2	60	74
0–2	74	86
> 3	55	70
0–3	70	83
> 4	47	59

Reference:
Hasenclever et al, NEJM, Vol 339, pp. 1506–1514, 1998.

1-2. International Prognostic Index (IPI) for NHL

Factors Independently Prognostic of Overall Survival

1. Age > 60
2. Serum LDH > 1 x normal
3. Performance status 2–4
4. Stage III or IV
5. Extranodal involvement > 1 site

Table 1. Outcome according to risk group (all patients)

Risk Group	No. of Risk Factors	CR Rate %	Relapse Free Survival		Overall Survival	
			2 yr	5 yr	2 yr	5 yr
Low	0 or 1	87	79	70	84	73
Low/Intermediate	2	67	66	50	66	51
High/Intermediate	3	55	59	49	54	43
High	4 or 5	44	58	40	34	26

Factors for Age-Adjusted (≤ 60) IPI

1. Serum LDH < 1 x normal
2. Performance status 2–4
3. Stage III or IV

Table 2. Outcome according to risk group (all patients)

Risk Group	No. of Risk Factors	CR Rate %	Relapse Free Survival		Overall Survival	
			2 yr	5 yr	2 yr	5 yr
Low	0	92	88	86	90	83
Low/Intermediate	1	78	74	66	79	69
High/Intermediate	2	57	62	53	59	46
High	3	46	61	58	37	32

Reference:
Shipp et al. NEJM 329: 987–994, 1993.

1-3. Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndrome (2012)

Table 1. MDS Cytogenetic Scoring System

Prognostic subgroups, % of patients	Cytogenetic abnormalities	Median survival*, y	Median AML evolution, 25%,* y
Very Good (4%*/3%†)	-Y, del(11q)	5.4	NR
Good (72%*/66%†)	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8	9.4
Intermediate (13%*/19%†)	Del(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5
Poor (4%*/5%†)	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities	1.5	1.7
Very Poor (7%*/7%†)	Complex: >3 abnormalities	0.7	0.7

OS indicates overall survival; and NR, not reached.

Table 2. IPSS-R prognostic score values

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very Poor
BM blast, %	≤2%	—	>2%-<5%	—	5%-10%	>10%	—
Hemoglobin	≥10	—	8-<10	<8	—	—	—
Platelets	≥100	50-<100	<50	—	—	—	—
ANC	≥0.8	<0.8	—	—	—	—	—

— indicates not applicable.

Table 3. IPSS-R prognostic risk categories/scores

Risk category	Risk Score
Very Low	≤1.5
Low	>1.5-3
Intermediate	>3-4.5
High	>4.5-6
Very High	>6

Adjustment for age:
(years – 70) x [0.05 – (IPSS-R risk score x 0.005)]
Example: 45-year-old patient with an IPSS-R risk score of 3.5 (Intermediate risk): (45-70) x (0.5 – (3.5 x 0.0050)] = -0.81. Thus, 3.5-0.8=2.7 [age-adjusted IPSS-R score, IPSS-RA: Low Risk].

Table 4. IPSS-R prognostic risk category clinical outcomes

	No. of patients	Very Low	Low	Intermediate	High	Very High
Patients, %	7012	19	38	20	13	10
Median survival (yrs)*		8.8	5.3	3.0	1.6	0.8

Table 5: Differentiating Variables for Survival: Score Values*

Variables	Variables	Prognostic power	Raw Score Points**
ECOG Score	0 vs 1 vs 2-4	0.02	-0.8/0.2/1.0
Serum Ferritin	≤ vs >350ng/ml	0.01	-.04/0.5
Serum LDH	Normal vs High	0.01	-0.2/0.5
β-2 Microglobulin	≤ vs >2g/ml	0.03	-1.0/.5

**To include the impact of only one of the above listed features on survival risk, the appropriate raw score/decimal should be added to the IPSS-R score and the resulting score should be categorized according to the limits given in Table 3.

Reference:
Greenberg, PL et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood 120:2454, 2012.

1-4. Myeloma Staging System

Durie/Salmon system

Stage	Criteria
I	All of the following: 1. Hb > 100g/L 2. Serum Calcium ≤ 2.6 mmol/L 3. X-rays – Normal bone structure (scale 0) or solitary bone plasmacytoma only 4. Low M component production rates • IgG value < 50g/L • IgA value < 30g/L • Urinary light chain M band < 4g/24hrs
II	Fitting neither Stage I or III
III	One or more of the following: 1. Hb < 85g/L 2. Serum Calcium > 2.6 mmol/L 3. X-Rays – Advanced lytic bone lesions (scale 3) 4. High M component production rates 8. IgG value > 70g/L 9. IgA value > 50g/L 10. Urinary light chain M band > 12g/24hrs

Subclassification

1. Relatively normal renal function (serum creatinine < 175mmol/L)
2. Abnormal renal function (serum creatinine > 175mmol/L)

Bone Lesions Scale

1. Normal bones – 0
2. Osteoporosis – 1
3. Lytic bone lesions – 2
4. **Extensive** skeletal destruction and major fractures – 3

Myeloma Staging System (cont.)

International Staging System (ISS)

Stage	Criteria	Median Survival (months)
I	serum β_2M < 3.5 mg/L serum albumin ≥ 35 g/L	62
II	serum β_2M < 3.5 mg/L serum albumin < 35 g/L or serum β_2M 3.5 to < 5.5 mg/L	44
III	serum β_2M ≥ 5.5 mg/L	29

Revised International Staging System (R-ISS)

Stage	Criteria	5-year Overall Survival
I	ISS stage I And No high risk CA* And Normal LDH level	82%
II	Not R-ISS stage I or III	62%
III	ISS stage III And high risk CA* or high LDH level	40%

* High risk CA (Chromosomal Abnormalities) are del17p and/or t4;14) and/or t(14;16)

References:

- Durie B, Salmon S. Clinical staging system for myeloma: Correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. Cancer 36: 842, 1975.
- Alexanian R, Balcerzak S, Bonnet JD, Gehan EA, Haut A, Hewlett JS, Monto RW. Prognostic factors in multiple myeloma. Cancer 36: 1192, 1975.
- Greipp P, San Miguel J, Durie B et al. International staging system for multiple myeloma. JCO 23: 3412, 2005.
- Palumbo A, Avet-Loiseau H, Olivia S et al. Revised international staging system for multiple myeloma: A report from International Myeloma Working Group. JCO 33: 2863, 2015.

1-5. Chronic Lymphocytic Leukemia Staging System

International Prognostic Index (CLL-IPI)

Table 1. CLL-IPI prognostic score values

Prognostic Variable	Score
Age > 65	1
Advanced Clinical Stage (Binet B-C or Rai I-IV)	1
IGHV unmutated	2
11. B2-microglobulin > 3.5g/L	2
12. Presence of del[17p] or *TP53* mutation or both	4

Table 2. CLL-IPI prognostic risk categories/scores

Risk category	Risk Score	Median OS (months)	5-year OS
Low	0-1	NR	93.2%
Intermediate	2-3	105	79.3%
High	4-6	75	63.3%
Very High	7-10	29	23.3%

References:
The International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Onc 2016:17:779-790.

1-6. Dynamic International Prognostic Scoring System (DIPSS) for Myelofibrosis

	Value		
Prognostic variable	0	1	2
Age, y	≤65	> 65	
White blood cell count $X10^9$/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Y/N	N	Y	

The **DIPSS** risk category is obtained adding up the values of each prognostic variable: low, 0; Intermediate-1, 1 or 2; Intermediate-2, 3 or 4; High, 5 or 6.

DIPSS plus scoring assigns a point each to unfavorable karyotype (complex karyotype or 1 or 2 abnormalities involving +8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3) or 11q23 rearrangement), platelets lower than $100X10^9$/L and need for red cell transfusion. Intermediate-1 by DIPSS (see table above) receives 1 point, Intermediate-2 and High risk receive 2 and 3 points, respectively. The 4 risk groups by DIPSS plus are low (0 points, median survival 180 mos), intermediate-1 (1 point, median survival 80 mos), intermediate-2 (2 or 3 points, median survival 35 mos) and high risk (4 to 6 points, median survival 16 mos).

References:

Passamonti F et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood 2010:115:1703-1708.

Gangat N et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from kayotype, platelet count, and transfusion status. J Clin Oncol. 2011: 29:392-397.

1-7. Prognostic Scores for CML in Chronic Phase

Sokal Score

See www.medalreg.com for automatic calculators for Sokal and Hasford scores.

Prognostic score for survival of CML patients treated with busulfan or hydroxyurea

Hazard Ratio
EXP (0.0116 (Age – 43.4) + 0.0345 (Spleen – 7.51) + 0.188 [(Platelet/700)2 – 0.563] + 0.0887(Blasts – 2.10)

Age _____years
Spleen _____cm below costal margin
Platelet _____x 10^9/L
Blasts _____% blasts in peripheral blood

Relative Risk	2-year Survival	Median Survival (months)
< 0.8	90%	60
0.8–1.2	80%	42
> 1.2	65%	32

Reference:
Sokal et al. Blood 63: 789–799, 1984.

Hasford Score (HS)

See www.medalreg.com for automatic calculators for Sokal and Hasford scores.

Prognostic score for survival of CML patients treated with Interferon Alfa.

HS = (0.6666 x age [0 when age < 50 years; 1, otherwise] + 0.0420 x spleen size [cm below costal margin] + 0.0584 x blasts [%] + 0.0413 x eosinophils [%] + 0.0239 x basophils [0 when basophils < 3%; 1, otherwise] + 1.0956 x platelet count [0 when platelet < 1500 x 10^9/L; 1, otherwise]) x 1000

Risk	Score	5-year Survival	Median Survival (months)
Low	< 780	76%	98
Intermediate	780–1,480	55%	65
High	> 1,480	25%	42

Reference:
Hasford et al. J Nat Cancer Institute 90(11): 850–858, 1998.

1-8. ECOG and Karnofsky Performance Status Scores

ECOG PERFORMANCE STATUS*	KARNOFSKY PERFORMANCE STATUS**
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any self-care; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.
**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960:11:7-33.
Available at http://ecog-acrin.org/resources/ecog-performance-status. Accessed May 2, 2016.

1-9. Regiment Related Toxicity: Bearman Toxicity Criteria

	Grade I	Grade II	Grade III
Bladder Toxicity	• Macroscopic hematuria after two days from last chemotherapy dose – no subjective symptoms of cystitis – no infection	• Macroscopic hematuria after 7 days from last chemotherapy dose – no infection • Hematuria after 2 days with subjective symptoms of cystitis – no infection	• Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with instillation of sclerosing agents, nephrostomy or other surgical procedure
Cardiac Toxicity	• Dysrhythmias: recurrent or persistent, no therapy required • Ejection Fraction – asymptomatic decline or resting ejection fraction by more than 20% of baseline value • Ischemia – asymptomatic ST and T wave changes suggesting ischemia • Pericardial – pericarditis • Rub, chest pain, ECG changes	• Dysrhythmias: requires monitoring or treatment • Mild CHF – responsive to therapy • Ischemia – angina without evidence for infarction • Pericardial – symptomatic effusion – drainage required	• Dysrhythmias with hypotension or ventricular tachycardia or fibrillation • Severe or refractory CHF • Ischemia – acute myocardial infarction • Pericardial – tamponade – drainage urgently required
Stomatitis Toxicity	• Pain and/or ulceration not requiring a continuous IV narcotic drug	• Pain and/or ulceration requiring a continuous IV narcotic drug (morphine drip)	• Severe ulceration and/or mucositis requiring preventative intubation • Severe ulceration – resulting in documented aspiration pneumonia with or without intubation

Regimen Related Toxicity: Bearman Toxicity Criteria (cont.)

	Grade I	Grade II	Grade III
CNS Toxicity	• Somnolence patient is easily arousable and oriented after arousal	• Somnolence with confusion after arousal • Other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding or CNS infection	• Seizures or coma not explained (documented) by other medication, CNS, infection or bleeding
GI Toxicity	• Watery stools > 500 ml, but < 2000 ml every day not related to infection	• Watery stools > 2000 ml every day not related to infection • Macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection • Subileus not related to infection	• Ileus requiring nasogastric suction and/or surgery and not related to infection • Hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion
Renal Toxicity	• Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)	• Increase in creatinine above twice baseline – no dialysis	• Requirements of dialysis

Regimen Related Toxicity: Bearman Toxicity Criteria (cont.)

	Grade I	Grade II	Grade III
Hepatic Toxicity	• Mild hepatic dysfunction with bilirubin > 34.2 µmol/L and bilirubin < 102.6 µmol/L • Weight gain > 2.5% and < 5% from baseline, of noncardiac origin • AST increase more than 2-fold, but less than 5-fold from lowest pre-conditioning	• Moderate hepatic dysfunction with bilirubin > 102.6 µmol/L and < 342 µmol/L • AST increase > 5 fold from pre-conditioning • Clinical ascites or image documented ascites	• Severe hepatic dysfunction with bilirubin > 342 µmol/L • Hepatic encephalopathy • Ascites compromising respiratory function
Pulmonary Toxicity	• Dyspnea – no CXR changes – no infection – no congestive heart failure • CXR showing isolated infiltrate or mild interstitial changes – no infection – no congestive heart failure – asymptomatic	• CXR with extensive localised infiltrate or moderate interstitial change combined with dyspnea and not caused by infection or CHF • Decrease of PO_2 (> 10% from baseline), but not requiring mechanical ventilation or > 50% O_2 on mask and not caused by infection or CHF	• Interstitial changes requiring mechanical ventilatory support or > 50% O_2 on mask and not caused by infection or CHF

- Grade IV toxicity is defined as fatal.
- All toxicity scores should be graded up to day +100.

1-10. Amyloidosis

Mayo Staging System (2004)

Factors

1. *NT-ProBNP > 332ng/L
2. Cardiac troponin-T(cTnT)>0.035mcg/L or Cardiac troponin-I (cTnI) > 0.1mcg/L

Mayo Stage	No of Factors	Median Overall Survival months (Based on cTnI)
1	0	27.2
2	1	11.1
3	2	4.1

Data based on treatment of patient before the novel agent era

*NT-ProBNP can be tested upon special request to the biochemist

Reference: Dispenzieri et al JCO 22(18); 3751-3757; 2004.

Mayo Staging System (2012)

Factors

1. *NT-ProBNP > 1800ng/L
2. Cardiac troponin-T(cTnT)>0.025mcg/L
3. dFLC > 180mg/L

Mayo Stage	No of Factors	Median Overall Survival (months)
1	0	94.1
2	1	40.3
3	2	14
4	3	5.8

Reference: Kumar et al JCO 30(9); 989-995; 2012.

European Collaborative Study of Cardiac Mayo stage 3 patients

Factors

1. NT-ProBNP > 8500ng/L
2. SBP <100mm hg

No of Factors	Median Overall Survival months (Based on cTnI)
0	25
1	6
2	3

Reference: Wechalekar et al Blood 121(17); 3420-3427; 2013.

CHAPTER 2. HSCT CRITERIA & WORK-UP

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2-1. Patient Stem Cell Transplant Work-Up

Patient Work-Up

PATIENT NAME:
Blood Work: CBC, diff, plts, lytes, BUN, Cr (eGFR)*, AST, ALT, LDH, alk phos, GGT, Bili – total and direct, total protein, albumin, INR, PTT
HIV Ag/Ab, Anti HTLV 1&2, HBsAg†, Anti-HBc (total)†, Anti-HBs, Anti HCV‡, Anti CMV, Anti HSV, Anti VZV, EBV Ab and syphilis screen
Detailed pulmonary function tests
Chest x-ray PA and lateral
12 lead electrocardiogram
RVG (MUGA) heart scan/echocardiogram
Bone marrow biopsy and aspirate [with cytogenetics/molecular analysis if known to have a disease marker]

If you have any questions, please contact the BMT Navigator at 604-875-4863.

* Formal 24 hour creatinine clearance is required if estimated GFR < 65 ml/min.

† HBsAg or HBcAb positive patients (even if also HBsAb positive) who proceed to SCT *(see Organ Function Guidelines)* should receive LAMIVUDINE (or suitable alternative) until off all immunosuppression or for at least 12 months post-SCT and should be reviewed by a hepatologist.

‡ HCV antibody positive patients require HCV RNA testing. If also RNA positive, patients have "chronic" hepatitis C should be reviewed by a hepatologist and have at minimum a FibroScan before proceeding to SCT (*see Organ Function Guidelines*). A formal liver biopsy may also be helpful.

Patient Stem Cell Transplant Work-Up (cont.)

Organ Function Guidelines

	Normal organ function myeloablative Allo/Auto*	Compromised organ function values acceptable for RICT
Cardiac Function	• Left ventricular fraction > 40% • Absence of significant coronary disease i.e., critical (> 90%) stenosis of any vessel, or ongoing need for anti-angina medications	• Left ventricular ejection fraction > 35% • Absence of significant coronary disease i.e., critical (> 90%) stenosis of any vessel • Moderate coronary disease; optimal symptomatic control with anti-angina medication (stress test clinically and electrically negative at 60% of maximal effort)
Pulmonary Function	• FEV1/FVC > 60% and DLCOc > 50% of predicted	• FEV1/FVC > 50% and DLCOc > 40% of predicted
Renal Function	Creatinine clearance: • > 65 ml/min (Allogeneic) • > 20 ml/min (Auto)*	Creatinine clearance: • > 60 ml/min
Hepatic Function	• AST < 4 times upper normal (unless due to underlying disease) • No histologic evidence of cirrhosis • Absence of piecemeal necrosis and/or bridging/portal fibrosis • F0/F1 FibroScan (*see p.4*) • F2 FibroScan (Auto only)	• AST < 4 times upper normal (unless due to underlying disease) • Bilirubin < 50 • Histologic evidence of severe fibrosis or cirrhosis without: ascites, portal hypertension, metabolic encephalopathy, INR > 1.5, albumin < 25 g/L • F2 FibroScan (*see p.4*)

* For high-dose Melphalan autografts for myeloma patients, cardiac and pulmonary function guidelines will also be more liberal (i.e., as per RICT organ function criteria)

What is a FibroScan?

A FibroScan is a test that measures the amount of fibrosis (thickening or scarring of tissues) in your liver.

It can be used alone or with other tests (such as biopsy, blood tests, ultrasounds) to see how much scarring there is on your liver.

What is my FibroScan result and what does it mean?

Results are measured using kiloPascal's (or kPa) and range from 2 to 75.

The normal range for a FibroScan is between 2 to 7 kPa. The average normal result is 5.3 kPa.

Your liver doctor will explain these results to find out how much scarring you have. Your result will vary based on what liver disease you have.

Scarring has 4 stages:

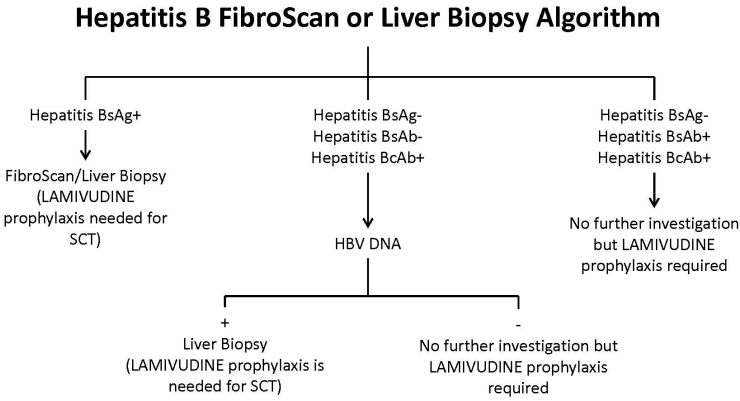
- ***F0 means no scarring***
- ***F1 is mild fibrosis***
- ***F2 is moderate fibrosis***
- ***F3 is severe fibrosis***
- ***F4 is cirrhosis or advanced fibrosis***

Disease	*Fibrosis stage and approximate cutoff value*			
	F0 to F1	*F2*	*F3*	*F4*
Hepatitis B	*2 to 7*	*8 to 9*	*8 to 11*	*18 or higher*
Hepatitis C	*2 to 7*	*8 to 9*	*9 to 14*	*14 or higher*
HIV/HCV co-infection	*none*	*7 to 11*	*11 to 14*	*14 or higher*
Cholestatic liver	*2 to 7*	*7 to 9*	*9 to 17*	*17 or higher*
NASH or NAFLD	*2 to 7*	*7.5 to 10*	*10 to 14*	*14 or higher*
Alcohol	*2 to 7*	*7 to 11*	*11 to 19*	*19 or higher*

Patient Stem Cell Transplant Work-Up (cont.)
Organ Function Guidelines (cont.)

Pre-transplant FibroScan and/or liver biopsy is mandatory in patients with:

- Hepatitis B surface Ag positivity or HBcAb+/HBV DNA+ at any time
- Hepatitis C RNA positivity at any time
- Suspected iron overload
- History of idiopathic, drug, alcohol, autoimmune or viral-induced hepatitis within past 2 years
- Unexplained direct bilirubin or AST > 1.5 times normal



References:
Bearman et al. Bone Marrow Transplant 5: 173, 1990.
Ghalie et al. Bone Marrow Transplant 10: 359, 1992.
Nash et al. Blood 80: 1838, 1992.
MacDonald et al. Ann Intern Med 118: 255, 1993.
Shuhart and McDonald. In: Forman, Blume, Thomas, eds. Bone Marrow Transplantation, Blackwell Scientific Publications: 454, 1994.
Ganem et al. Int J Radiat Oncology Biol Phys 14: 879, 1988.

Patient Stem Cell Transplant Work-Up (cont.)

Renal Function Guidelines

For those patients with impaired renal function undergoing autografts:

a. The safest conditioning regimens which can be given without modification in patients with moderate to severe renal dysfunction (20–40 ml/minute) are BuCy-2 (for AML) or Cy/TBI (for lymphoma). In discussing the treatment-related complications, patients should be informed that toxicities (such as mucositis) are likely to be more severe and duration of hospitalisation will be prolonged, although TRM is not dramatically different.

b. For Multiple Myeloma†, MEL(200) will be used for conditioning with the following dose adjustments for renal function:

Creatinine Clearance (ml/min)	Dose
≥ 50	200 mg/m^2
< 50*	140 mg/m^2

c. Supportive care should also be modified and individualised. Changes should include reduction in the allopurinol dose, uroepithelial prophylaxis may need to be changed to a more moderate hydration regimen and/or mesna as per Shepherd et al, J Clin Oncol 9: 2016, 1991. Antimicrobial agents: aminoglycosides/vancomycin avoided if at all possible.

d. Avoid amphotericin use for anti-fungal prophylaxis and treatment of suspected or proven invasive fungal infection.

† Patients with AL Amyloidosis should receive high-dose Melphalan according to dosing guidelines in Blood 99: 4276–4282, 2002.

* A melphalan dose of 100 mg/m^2 should not be used to treat plasma cell dyscrasias and novel therapies (Bortezomib and Lenalidomide) should be considered for individuals who are felt to be inappropriate for MEL(140) or who are dialysis-dependent.

TB Screening for HSCT and Leukemia Patients

Policy on Pre-Transplant TB Screening for L/BMT Patients – In Patient

All new acute leukemia patients must undergo the following TB screening. The purpose of this screening is to identify patients with or at risk for TB infection, and initiate treatment to prevent active TB disease. Assess whether the patient has any of the four possible TB risk factors:

1. Birth in high incidence country for TB*
2. Lived in or travelled to a high incidence country for ≥3 more months
3. Prior history of exposure, diagnosis OR treatment for TB (active or latent) OR previous positive TB skin test or IGRA
4. CT or CXR changes suggestive of prior TB (e.g. granulomas, apical scarring)

If the answer to all four questions is NO, then no further screening related to TB is required. Specifically, TST/IGRA testing is not recommended.

If the answer to any one question is YES, ensure that the patient has not had treatment for latent TB infection or active TB in the past. If they have, consult Transplant ID to determine whether treatment

was adequate. If they have not been treated for TB, check CareConnect to ensure that they have not had an IGRA in the past. If they have, do NOT repeat the IGRA. Use that result. If they have not, then look at the lymphocyte count.
If the lymphocyte count is ≥ 0.5, then perform an IGRA. If the IGRA is positive, assess whether the patient can initiate LTBI therapy based on drug interactions and liver function tests. If yes, consult Transplant ID to initiate LTBI treatment as an inpatient. If no, monitor for signs and symptoms of TB reactivation while waiting for a safe time to initiate LTBI therapy. Before initiating LTBI, repeat CXR and make sure patient does not have symptoms of active TB disease.

If the lymphocyte count is too low for an IGRA OR the IGRA is negative, assess whether the patient was born in a high incidence country AND has abnormal imaging. If both risk factors are present, assess whether the patient can initiate LTBI therapy based on drug interactions and liver function tests. If yes, consult Transplant ID to initiate medication as an inpatient. If no, monitor for signs and symptoms of TB reactivation while waiting for a safe time to initiate LTBI therapy. If patients are not foreign borne but have a history of exposure to TB or previous positive TB skin testing, consult Transplant ID to determine whether the patient needs treatment. For any other patient with only ONE risk factor, monitor for signs or symptoms of active TB.

At discharge from the inpatient unit, complete the TB Transplant Physician Referral form (attached) and fax to Provincial TB Services to coordinate medication and follow-up 604-707-2690. A referral form should be completed and faxed for any IGRA+ patient or patient on LTBI.

Policy on Pre-Transplant TB Screening for L/BMT Patients – Out Patient

All BMT candidates should undergo TB screening. However, you should keep in mind that patients may have already been screened as an inpatient or in another context.
First, assess whether the patient has any of the four possible TB risk factors:

1. Birth in high incidence country for TB
2. Lived in or travelled to a high incidence country for >3 more months
3. Prior history of exposure, diagnosis OR treatment for TB (active or latent) OR previous positive TB skin test or IGRA
4. CT or CXR changes suggestive of prior TB (e.g. granulomas, apical scarring)

If the answer to all four questions is NO, then no further screening related to TB is required. Specifically, TST/IGRA testing is not recommended.

If the answer to any one question is YES, ensure that the patient has not had treatment for latent TB infection or active TB in the past. If they have, consult Transplant ID to determine whether treatment was adequate. In addition, check CareConnect for prior IGRA results. If they have had a prior IGRA, do NOT repeat the IGRA - if there is a result on file use that result. If they have not had prior IGRA, then look at the lymphocyte count.
If the lymphocyte count is ≥ 0.5 and there is no prior IGRA result, then perform an IGRA. If the IGRA is positive, determine the type of transplant the patient is getting. If it is an autologous transplant, complete the TB Transplant Physician Referral form (attached) and fax to Provincial TB Services to coordinate LTBI medication and follow-up 604-707-2690 post-transplant. If it is an allogeneic stem cell transplant, assess whether the patient can initiate LTBI therapy. If they can as an inpatient (based on liver function tests and drug interactions) consult Transplant ID to initiate LTBI medication as an inpatient. If LTBI treatment is not currently an option, monitor for signs and symptoms of TB reactivation while waiting for a safe time to initiate LTBI therapy. Before initiating LTBI, repeat CXR and make sure patient does not have symptoms of active TB disease.

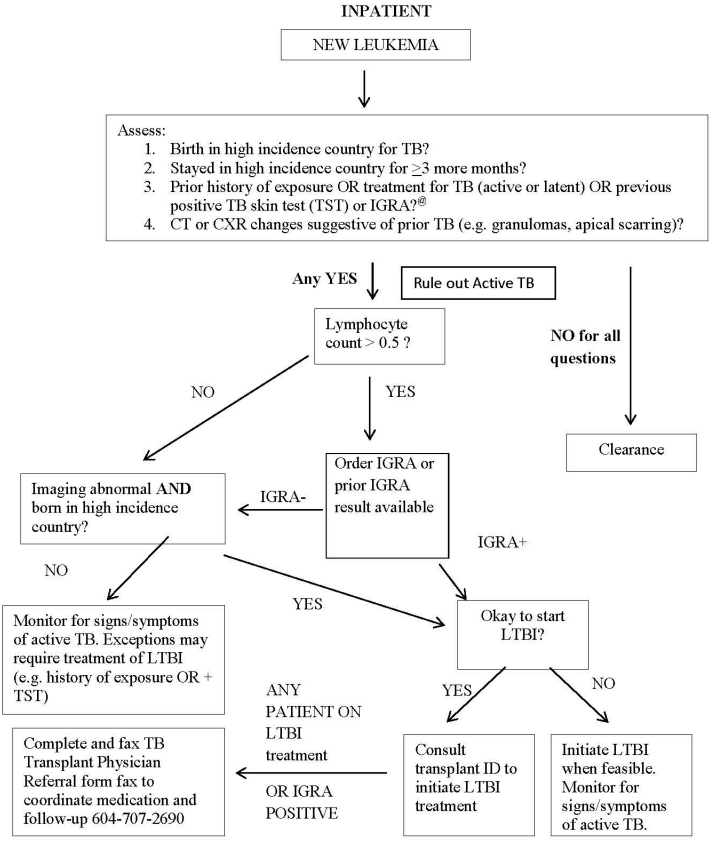
If the lymphocyte count is too low for an IGRA OR the IGRA is negative, assess whether the patient was born in a high-incidence country AND has abnormal imaging. If both risk factors are present, determine the type of transplant the patient is getting. If it is an autologous transplant, complete the TB Transplant Physician Referral form (attached) and fax to Provincial TB Services to initiate LTBI medication and follow-up 604-707-2690 post-transplant. If it is an allogeneic stem cell transplant, assess whether the patient can initiate LTBI therapy. If they can as an inpatient (based on drug interactions and liver function tests), consult Transplant ID to initiate LTBI medication as an inpatient. If LTBI treatment is not currently an option, monitor for signs and symptoms of TB reactivation while waiting for a safe time to initiate LTBI therapy. Before initiating LTBI, repeat CXR and make sure patient does not have symptoms of active disease. If patients are not foreign borne but have a history of exposure to TB or previous positive TB skin testing, consult Transplant ID to determine whether the patient needs treatment. For any other patient with only ONE risk factor, monitor for signs or symptoms of active TB.
At discharge from the inpatient unit, complete the TB Transplant Physician Referral form (attached) and fax to Provincial TB Services to coordinate medication and follow-up 604-707-2690. A referral form should be completed and faxed for any IGRA+ patient or patient on LTBI.

LTBI Treatment in L/BMT Patients

L/BMT patients with evidence of latent TB infection (LTBI) should be started on therapy whenever feasible. Nine months of isoniazid (INH) and pyridoxine (vitamin B6) is the preferred regimen for treatment of LTBI in this patient population. Rifampin is often complicated by drug interactions in this patient population and is discouraged.
Some recipients will be unable to take LTBI therapy due to drug interactions or toxicity. Patients who have not initiated or completed LTBI treatment should begin or resume a full therapeutic course of treatment for LTBI whenever feasible. If these individuals develop symptoms in the setting of incomplete treatment, TB should be in the differential diagnosis.
Patients without evidence of LTBI (i.e. normal chest imaging and negative TST and/or IGRA pre-transplant) but with epidemiologic risk factors for TB (i.e. country of origin) should still be monitored for signs or symptoms of active TB. Fever, pulmonary infiltrates or cavitation, or other organ specific symptoms/signs are potentially signs of active disease.
Patients who have previously completed therapy for active TB or LTBI should still be clinically monitored. Retreatment for LTBI would not be routinely recommended. Treatment of LTBI is 90% effective; there remains a very small chance of reactivation after treatment.
Patients with LTBI who do not have documentation of adequate LTBI therapy should be re-offered therapy as outlined above.
Prior immunosuppression or transplantation is not considered in the decision to offer treatment for LTBI. Recipients who have evidence of LTBI and have not received therapy should be treated regardless of their previous immunosuppression exposure.

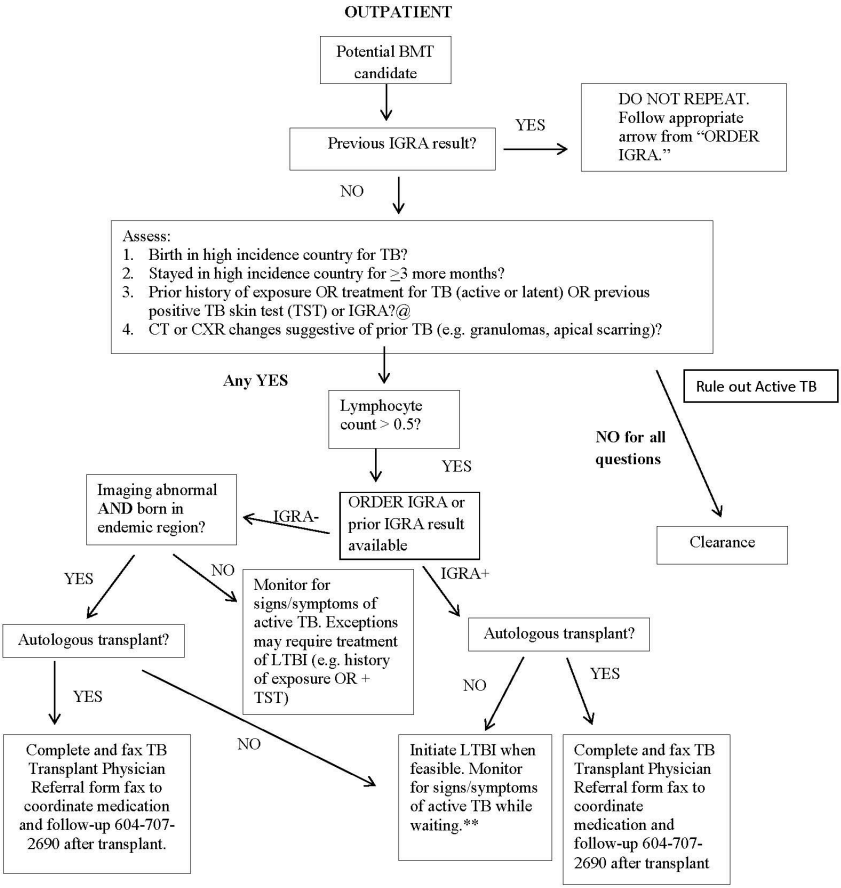
** High incidence is defined by TB Services as >40/100,000. https://www.who.int/tb/country/data/profiles/en/*

Flowchart for TB – Acute Leukemia at VGH and pre-allogeneic/autologous BMT (L/BMT)



**Consult transplant ID for inpatient medication initiation. Send to TB Services at discharge for medication initiation. TB Services defines high incidence country as > 40/100,000.
https://www.who.int/tb/country/data/profiles/en

Flowchart for TB – Acute Leukemia at VGH and pre-allogeneic/autologous BMT (L/BMT)



@Information about prior TB treatment may be available from TB Services. Contact at 604-707-5678.
**Consult transplant ID for inpatient medication initiation. Send to TB Services at discharge for medication initiation. TB Services defines high incidence country as > 40/100,000.
https://www.who.int/tb/country/data/profiles/en

2-2. Allogeneic Stem Cell Transplant

Suggested Recipient Criteria

Myeloablative

1. ECOG ≤2 (Karnofsky ≥60%)
2. Donor selection will be as follows:
   - A 10/10 HLA-antigen match (related/unrelated) is preferred; alternatives, in order of preference, are:
     - 9/10 match (related/unrelated) OR haploidentical related
     - Double cord SCT (if recipient <60 yrs); 1 cord must be ≥6/8 allele match
   - - 8/10 unrelated donor (mismatches cannot be at same locus except DQ)
3. In selecting HLA antigen mismatches, an allele mismatch is equal to an antigen mismatch (Exception is HLA-C 0303 and HLA-C 0304 which are considered equivalent); however, antigen mismatches are not permitted at HLA-DRB1, only allele mismatches
4. Disparity preference for HLA mismatches

B > DQB1 > C = A > DRB1

5. Donor Preference for Haploidentical SCT

Son > Brother† > Father > Daughter > Sister† > Mother

+NIMA mismatch is better than NIPA mismatch.

6. Adequate organ function*
7. HCT-CoI score ≤5 (*see Section 2.5*)
8. No active infection within 2 weeks of conditioning
9. Acceptance of standard blood product support
10. Informed consent

Reduced-intensity conditioning

As per "Myeloablative" criteria above except:

1. Recipient is of advanced age and/or has compromised organ function*
2. Double cord SCT is NOT an option for stem cell source

*see Organ Function Guidelines, pp 26-27

Donor Criteria

- Age <75 years.

Potential donors aged 65 to 70 years with no medical problems, as indicated by health screening questionnaires and work up test results, do not require a BMT or GPO physician assessment.

- Donors over the age of 70 years will be assessed by a GPO in person at a clinic visit; the donor physician will review this assessment as part of the final suitability determination.
- If there are cardio-respiratory concerns in any age group, additional work up (tests and consultations) will be arranged by the donor physician to determine suitability.

- HIV Ag/Ab, HBsAg*/HBcAb**, Hep C Ab†, HTLV I/II, WNV RNAγ and syphilis testing negative
- No HIV high-risk behavior within 1 year of harvest‡
- No active autoimmune disease that would pose a risk to the recipient[1]
- No active ischemic heart disease[1]
- AST and direct bilirubin < 1.5 x upper normal
- $FEV_{1.0}$, FVC, and DLCOc ≥ 60% of predicted[2]
- No malignancy within 5 years of harvest[3] and no prior chemotherapy
- No substance abuse within 2 months of harvest
- Informed consent or consent of legal guardian
- No significant medical conditions that would pose undue risk to the donor (or the recipient) as determined by an independent consultant

- Unless recipient is already HBsAg or HBsAb/cAb positive (see algorithm on next page)

** If donor is isolated HBcAb+(i.e. HBsAg and sAb negative), they must also be HBV DNA negative to be a suitable donor (see algorithm on next page).

† Unless recipient is already HCV Ab positive; if donor is the only available donor for a relative with a lethal condition, HCV Ab positivity does not exclude donor if HCV RNA is negative.

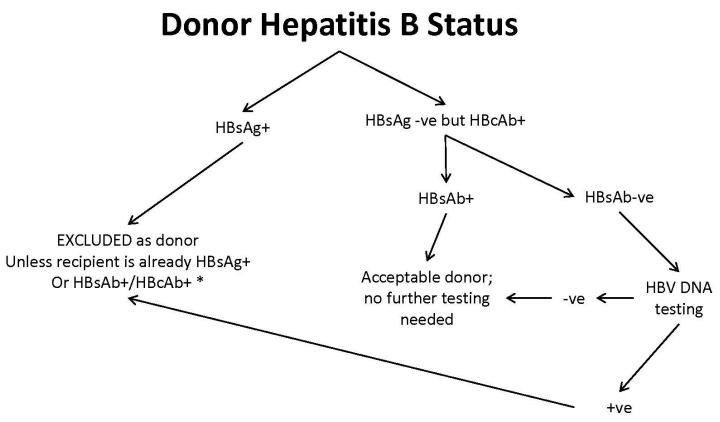
γ Testing is seasonal and country-dependent

‡ This criteria will be considered on a case-by-case basis.

[1] Clinical activity or requirement for medication

[2] PFTs to be done only if clinically indicated

[3] Except non-melanomatous skin cancer or cervical ca-in-situ



**** If used as a donor, donor should be treated with LAMIVUDINE (or alternative) for at least 6 – 8 weeks to ensure HBV DNA becomes negative. Recipient should also be treated with LAMIVUDINE and have negative HBV DNA at start of conditioning (ongoing HBV DNA monitoring of recipient may be appropriate after SCT).***

Allogeneic Stem Cell Transplant (cont.)

Donor Work-Up Pre Stem Cell Harvest

DONOR NAME:
History: Detailed history to include allergies, medications, prior malignancies, history of convulsions, hepatitis, prior transfusion, travel, HIV high-risk behaviour and pregnancies. Also to include details of previous surgeries including post-op bleeding. *Form available in BMT Coordinators' Office.*
Height & Weight
Bloodwork: CBC, diff, plts, lytes, BUN, Cr, AST, LDH, alk phos, GGT, Bili – total and direct, total protein, albumin, INR, PTT, random glucose
Anti HIV 1&2, HIV p24Ag, Anti HTLV 1 &2, HBsAg, Anti-HBc (total)†, Anti-HBs, Anti HCV‡, Anti CMV, Anti HSV, EBV Ab, WNV RNA ᵞ and syphilis screen
Routine urinalysis
Chest x-ray PA and lateral*
12 lead electrocardiogram*

If you have any questions, please contact the BMT Navigator at 604-875-4863.

† HBV DNA if anti-HBcAb positive and HBsAg/HbsAb both negative
ᵞ Testing is seasonal and country-dependent
‡ HCV RNA if HCV Ab positive
* Only required for donors ≥ 40 years or if clinical concern

2-3. Autologous Stem Cell Transplant

Suggested Patient Criteria

Patients ≥ 70 years are generally not considered appropriate for autologous or allogeneic SCT unless the age-adjusted Co-I score is 1. Exceptions to this for patients being referred for curative autologous SCT where the benefit is believed to outweigh potential risks maybe considered following group discussion at Transplant and Cellular Therapy LBMT rounds.

- If ≥ age 70 years, age-adjusted Co-I score of 1 (ie. no comorbidities) †
- ECOG ≤ 2 (Karnofsky ≥ 60%)
- Adequate organ function*
- No significant active infection within 2 weeks of conditioning
- Acceptance of standard blood product support
- Informed consent

† For age < 70 years, there is currently no maximum Co-I score for eligibility for auto SCT

* Refer to Pre-myeloablative Allogeneic SCT Organ Function Guidelines except (a) creatinine clearance ≥ 20 ml/min is considered acceptable for autologous SCT recipients and (b) multiple myeloma autograft recipients will only be expected to meet the organ function guidelines developed for RICT recipients

2-4. Autologous Stem Cell Transplant for Amyloidosis

Suggested Eligibility Criteria

Organ function as per the "Autologous Stem Cell Transplant" Criteria (Section 2-3)

In Addition:

- "Physiologic" age ≤ 70 years of age
- Performance status ≤ 2
- Systolic blood pressure ≥ 90 mmHg (Caution for SBP < 100 mmHg)
- Troponin T level < 0.06 ng/ml (or high-sensitivity troponin T level < 75ng/ml
- CrCl ≥ 30ml/min
- NYHA Class I/II

Melphalan doing should be based upon renal function guidelines.

AL amyloid Conversion:

Model	cTnT	cTnI	Hs-cTnT
Mayo ASCT troponin risk marker[d]	≥ 0.035 mcg/L	ND	≥ 75 ng/L[f]

Abbreviations: ASCT, Autologous stem cell transplantation; NA, not applicable; ND, no data.
[d]Simple binary troponin T threshold predicting for transplant-related mortality 25% versus 4%
[f]Extrapolated numbers are based on quartic formula applied to a dataset of 224 newly diagnosed AL amyloidosis patients.

Ref: Muchtar et al Mayo Clin Proc June 2021:96(6):1546-77. http:msmart.org

2-5. Hematopoietic Cell Transplantation (HCT) Comorbidity Index (Age-Adjusted) for Risk Assessment Before Allogeneic HCT (HCT-CoI)

Table 1. Definitions of comorbidities (Sorror et al. Blood 106: 2912, 2005)

Comorbidity	Definitions of comorbidities	HCI-CI weighted scores
Age	≥ 40	1
Arrhythmia [1]	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease [2], congestive heart failure, myocardial infarction, or EF ≥ 50%	1
Inflammatory bowel disease [1]	Crohn disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone [3]	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident [4]	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment [3]	1
Hepatic, mild	Chronic hepatitis [5], direct bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN [6]	1
Obesity	Patients with a body mass index > 35 kg/m^2	1
Infection	Started pre-conditioning and requiring continuation of antimicrobial treatment after day 0 [7]	1
Rheumatologic [1]	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatic or sarcoidosis	2
Peptic ulcer [8]	Requiring treatment	2
Moderate/severe renal	Serum creatinine > 2 mg/dL [9], on dialysis, or prior renal transplantation	2
Moderate pulmonary	DLCO [10] and/or FEV1 66%–80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point [11] in the patient's past history, excluding nonmelanoma skin cancer	3
≥ Moderate Heart valve disease [12]	Except asymptomatic mitral valve prolapse	3
Severe pulmonary	DLCO [10] and/or FEV1 ≤ 65% or dyspnea at rest or requiring oxygen within 4 weeks of conditioning	3
Moderate/severe hepatic	Liver cirrhosis, direct bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN	3

Hematopoietic Cell Transplantation (HCT) Comorbidity Index for (Age-Adjusted) Risk Assessment Before Allogeneic HCT (HCT-CoI) (cont.)

To convert creatinine from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 88.4.
EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythmatosis; RA, rheumatoid arthritis; CTD, connective tissue disease; DLCO, diffusion capacity of carbon monoxide.

1. ***Requiring medical treatment (or cardioversion) at anytime***
2. ***Angina requiring medical treatment or surgical intervention***
3. ***Within 4 weeks of first day of conditioning***
4. ***Includes subarachnoid hemorrhage***
5. ***History of having had Hepatitis B or Hepatitis C regardless of carrier status***
6. ***Liver function is assessed as close to first day of conditioning as possible***
7. ***Includes fever, documented infection, ongoing antifungals and TB prophylaxis***
8. ***At any time, but MUST be endoscopically or radiologically documented***
9. ***2 mg/dL = 177 umol/L***

10. ***DLCO must be corrected for hemoglobin (Hb) by the Dinkara Equation and used to calculate the % Reference (Ref) DLCO to calculate the co-morbidity index above.***

$$DLCO_{corr} = \frac{\text{DLCO}_{uncorr}}{\text{Hb (g/L) x 0.006965}}$$

Dinkara Equation:

11. ***Treatment may include surgery only***

12. ***Includes patients with prior valve replacement or TAVI procedure***

Table 2. The new HCT-CI scores and predictions for NRM and survival the training versus the validation set

Score	Training Set			Validation Set		
		NRM			NRM	
	Patients, %	HR* (95% CI)	2-year, %	Patients, %	HR* (95% CI)	2-year, %
0	38	1	9	38	1	14
1	17	1.66 (0.9-3.1)	14	18	1.57 (0.7-3.3)	22
2	17	3.48 (2.0-6.0)	27	17	1.26 (0.6-2.8)	19
3	17	6.09 (3.7-10.1)	41	15	3.95 (2.1-7.5)	41
4	11	6.93 (4.0-12.0)	43	13	3.05 (1.5-6.2)	40

For the training set, n = 708; for the validation set, n = 346.
* Adjusted for age, disease risk, and conditioning.

Reference:
Sorror et al. Blood 106: 2912, 2005.

LEUKEMIA/BMT MANUAL E-EDITION

CHAPTER 3. CYTOTOXIC AGENTS and CONDITIONING REGIMENS

TABLE OF CONTENTS

3-1. Directives

Reference Materials on BC Cancer Website

The B.C. Cancer web site, www.bccancer.bc.ca, under 'Health Professionals' contains extensive reference material on the following topics (and many others):

1. Chemotherapy protocols for different tumour sites: www.bccancer.bc.ca/ChemoProtocols

2. Chemotherapy guidelines for safe handling of cancer treatments, including extravasation management: http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual

Patient Consent

Refer to SOP CL-600 Ordering of Cytotoxic Agents

Drug Ordering & Checking

Refer to SOP CL-600 Ordering of Cytotoxic Agents

3-2. Process for Patient Discharge or Admission in the Middle of Chemotherapy Protocol

Patients are sometimes discharged or admitted before finishing their chemotherapy protocol. A standardized process should be followed to ensure treatment continuity and minimize risk of medication errors and transcription errors.

Patient Discharge from Inpatient to LB6

1. Inpatient MD to complete Leukemia/BMT Daycare Admissions Orders
2. Specify the chemotherapy medication, dose, route, frequency, days to be given
3. Specify the name and date of the original chemotherapy protocol orders
4. Inpatient to fax the LB6 Admission Orders and a copy of the original chemotherapy protocol orders to LB6 and pharmacy.
5. Outpatient MD to verify orders and co-sign.

Example:
"Vincristine 2 mg IV ONCE on Oct 20 and Oct 27 as per ALL 89-1 protocol orders dated Oct 5, 2007"

Patients Admitted from LB6 to Inpatient

1. Outpatient MD to complete Admissions Orders using VGH general physician order form
2. Specify the chemotherapy medication, dose, route, frequency, days to be given
3. Specify the name and date of the original chemotherapy protocol orders
4. LB6 to send the Admission Orders and a copy of the chemotherapy protocol orders to Inpatient and fax to pharmacy.
5. Inpatient MD to verify orders and co-sign.

3-3. Dose Modification & Monitoring During Asparaginase Therapy

Asparaginase is an enzyme that can be isolated from several bacteria including *Escherichia coli* and *Erwinia chrysanthemi.* Available asparaginase formulations include pegylated *E. coli*-derived asparaginase (pegaspargase, Oncaspar® and calaspargase pegol, Asparlas®) and *Erwinia*-derived asparaginase (crisantaspase recombinant, Rylaze®). Native *E. coli* asparaginase (Kidrolase®) and Asparaginase-erwinia (Erwinase®) have been discontinued from the market.

Asparaginase therapy is associated with several adverse effects including hypersensitivity or infusion reactions, hyperammonemia, thrombosis, hepatotoxicity, acute pancreatitis, hyperglycemia and abnormalities in lipid metabolism, predominantly hypercholesterolemia and hypertriglyceridemia.

Monitor coagulation profile, fibrinogen, LFTs, lipase and/or amylase, fasting triglycerides and blood glucose during asparaginase therapy. See guidelines for asparaginase toxicity monitoring and management in table below.

Exposure to asparaginase can lead to antibody development which may reduce asparaginase activity. Both antibody-mediated hypersensitivity and non-antibody-mediated infusion reactions can occur, and neutralizing antibodies can develop without overt hypersensitivity (“silent inactivation”). Monitoring serum asparaginase activity (SAA) can help distinguish infusion reactions from hypersensitivity and detect silent inactivation. A switch in asparaginase formulation should be considered in cases of hypersensitivity or silent inactivation. SAA monitoring is not available in BC but may be accessible through CHU Sainte-Justine in Montreal, QC.

Toxicity	≤ Grade 2	Grade 3	Grade 4
Hypersensitivity	Urticaria without bronchospasm, hypotension, angioedema, or need for parenteral intervention ➢ CONTINUE Mild erythema or injection site pain (IM) ➢ CONTINUE	Wheezing or other symptomatic bronchospasm ± urticaria, angioedema, hypotension or need for parenteral intervention ➢ DISCONTINUE ➢ Consider switching pegylated asparaginase product to Crisantaspase recombinant IM 3x/week (MWF)	Life-threatening consequences or urgent intervention indicated ➢ DISCONTINUE ➢ Consider switching pegylated asparaginase product to Cristantaspase recombinant IM 3x/week (MWF)
Pancreatitis	ASYMPTOMATIC amylase and/or lipase elevation > 3x ULN (chemical pancreatitis) or only radiological abnormalities ➢ HOLD ➢ Resume when laboratory values normalize	Hyperamylasemia syndrome – amylase and/or lipase elevation > 3x ULN and abdominal pain < 72 hours ➢ HOLD ➢ Resume when symptoms and laboratory values normalize ➢ DISCONTINUE if recurrent episode	Clinical pancreatitis – abdominal pain, nausea/vomiting and amylase and/or lipase elevation > 3x ULN for > 72 hours and/or development of pancreatic pseudocyst ➢ DISCONTINUE
Hypertriglyceridemia	If fasting triglycerides < 11.3 mmol/L ➢ CONTINUE ➢ Monitor closely for pancreatitis	If fasting triglycerides > 11.3 mmol/L but < 22.6 mmol/L ➢ CONTINUE and ➢ Initiate lipid-lowering agent, e.g. fenofibrate (Lipidil Supra) 160 mg daily ➢ Monitor closely for pancreatitis	If fasting triglycerides > 22.6 mmol/L ➢ HOLD and ➢ Initiate lipid-lowering agent, e.g. fenofibrate (Lipidil Supra) 160 mg daily ➢ Resume once fasting triglycerides return to < 11.3 mmol/L ➢ Monitor closely for pancreatitis
Hyperglycemia	Uncomplicated hyperglycemia ➢ CONTINUE	For hyperglycemia requiring insulin ➢ HOLD until BG regulated with insulin	For hyperglycemia with life-threatening consequences or requires urgent intervention ➢ HOLD until BG regulated with insulin ➢ Do not make up for missed doses
Hepatotoxicity (transaminitis)	If ALT or AST > 3 to 5x ULN ➢ CONTINUE	If ALT or AST > 5 to 20x ULN ➢ HOLD until transaminitis ≤ Grade 2	If ALT or AST > 20x ULN ➢ HOLD until transaminitis ≤ Grade 2 ➢ DISCONTINUE if transaminitis takes > 1 week to resolve to ≤ Grade 2
Hepatotoxicity (hyperbilirubinemia)	If direct bilirubin < 51.3 µmol/L ➢ CONTINUE	If direct bilirubin ≥ 51.3 to 85 µmol/L ➢ HOLD until < 34 µmol/L	If direct bilirubin > 85 µmol/L ➢ DISCONTINUE

Toxicity	≤ Grade 2	Grade 3	Grade 4
Hyperammonemia / Encephalopathy	Moderate symptoms limiting instrumental ADLs ➢ HOLD ➢ Resume when < Grade 2 DO NOT HOLD for abnormal laboratory findings WITHOUT clinical correlate	Severe symptoms limiting self-care ADLs ➢ HOLD and ➢ Institute therapy to lower ammonia levels (e.g. lactulose) ➢ Resume when < Grade 2 If recurrent ≥ Grade 2 encephalopathy ➢ PERMANENTLY DISCONTINUE	Life-threatening consequences, urgent intervention indicated ➢ PERMANENTLY DISCONTINUE
Hypofibrinogenemia *	If fibrinogen > 1 g/L ➢ CONTINUE	If fibrinogen ≤ 1 g/L but > 0.5 g/L ➢ CONTINUE - give cryoprecipitate/fibrinogen concentrate followed by asparaginase product	If fibrinogen < 0.5 g/L ➢ HOLD and ➢ Give cryoprecipitate/fibrinogen concentrate ➢ Resume once grade 3 or less
Non-CNS Hemorrhage *	For bleeding with hypofibrinogenemia ➢ HOLD until bleeding ≤ Grade 1 DO NOT HOLD for abnormal laboratory findings WITHOUT clinical correlate	➢ HOLD until bleeding ≤ Grade 1, acute toxicity and clinical signs resolved and coagulant replacement therapy stable or completed	
Non-CNS Thrombosis	For abnormal lab findings WITHOUT correlated clinical symptoms ➢ CONTINUE For SYMPTOMATIC thrombosis ➢ HOLD until stable on anticoagulation	➢ HOLD until acute toxicity & clinical signs resolve and anticoagulant therapy stable or completed DO NOT HOLD for abnormal laboratory findings WITHOUT clinical correlate	➢ HOLD until acute toxicity & clinical signs resolved and anticoagulant therapy stable or completed ➢ After resuming DISCONTINUE if recurrent thrombosis occurs while on anticoagulation
CNS Hemorrhage *	➢ DISCONTINUE until symptoms resolve ➢ For thrombosis institute anticoagulant therapy		➢ PERMANENTLY DISCONTINUE
CNS Thrombosis			

* Fresh frozen plasma NOT RECOMMENDED because it contains asparagine and could counteract benefit of asparaginase products.

3-4. QT Prolongation

QT interval prolongation is a recognized toxicity associated with several chemotherapeutic and supportive care medications used in the L/BMT Program. QT prolongation increases the risk of dangerous arrhythmias, notably Torsades de Pointes (TdP), which can lead to syncope, seizures or sudden death, making QT monitoring essential during treatment.

QT correction (QTc)

QT interval varies with heart rate and must be corrected for heart rate (QTc) to assess ventricular repolarization accurately. Several formulae are used in clinical practice; see below or online QTc calculators (e.g. https://www.mdcalc.com/calc/48/corrected-qt-interval-qtc).

Bazett	$QTc = QT / \sqrt{RR}$
Framingham	$QT_C = QT / RR^{1/3}$
Fridericia	$QT_C = QT + 0.154\ (1 - RR)$

RR (in seconds) = 60 / HR (bpm)

While Bazett is most commonly used, it is inaccurate at heart rate extremes, overestimating QTc at high heart rates and underestimating at low heart rates. Framingham and Fridericia provide more accurate estimates of QTc at heart rate extremes and were better predictors of 30-day and all-cause mortality. Clinical studies have shown discordance in QTc grading depending on the formula used, which may impact treatment decisions.

In patients with left or right bundle branch block (LBBB/RBBB), the widened QRS complex artificially prolongs the QT interval (QT_{BBB}), complicating accurate QTc assessment. There are several formulas for QT correction in the setting of BBB, but the Bogossian formula provides a practical method for calculating a modified QT (QTm) which can then be input into standard heart rate correction (QTc) formulas:

Bogossian	$QTm = QT_{BBB} - 0.5*QRS_{BBB}$

Although the definition of what constitutes of a normal, borderline, and prolonged QTc can vary, a QTc interval of 500 ms or greater is linked to a higher risk of ventricular arrhythmias.

Risk Factors for QT Prolongation

Medications can delay ventricular repolarization – either directly by interfering with potassium channels, or indirectly through electrolyte disturbances – resulting in QT prolongation. Medication-induced QT prolongation is dose or concentration-related, can be additive when multiple QT-prolonging medications are used, and may be exacerbated by drug interactions that alter the metabolism or excretion of these agents. QT-prolonging medications commonly used in L/BMT patients include:

Drug Class	Examples*
Chemotherapy	Arsenic Trioxide, Tyrosine Kinase Inhibitors
Antiemetics	Ondansetron, Olanzapine
Antifungals – azoles	Fluconazole, Voriconazole, Posaconazole
Antibiotics – fluoroquinolones, macrolides	Levofloxacin, Ciprofloxacin, Clarithromycin
Antipsychotics	Haloperidol, Quetiapine, Risperidone
Antidepressants	Citalopram, Escitalopram, Amitriptyline
Opioids	Methadone
Antiarrhythmics	Amiodarone, Sotalol
Diuretics	Furosemide

*Consult www.crediblemeds.org for a complete list

However, most cases of drug-induced TdP involve one or more other risk factors for QT prolongation, both non-modifiable and potentially modifiable:

Genetic Predisposition (e.g. congenital long QT syndrome)	Electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia)
Structural Heart Disease	Anorexia, Nausea/Vomiting, Diarrhea
Advanced Age (>65 years)	Renal dysfunction
Female gender	Hepatic dysfunction
Sepsis/Systemic Inflammation	Thyroid dysfunction
Autonomic dysfunction	Foods

Monitoring and Mitigation Strategies

Given the risk of serious arrhythmias with QT prolongation to result in serious arrhythmias, proactive monitoring and mitigation strategies are essential:

- Obtain baseline and serial ECGs in patients with major or multiple risk factors.
- Minimize QT-prolonging drugs and interactions; use lowest effective dose and duration.
- Reassess all QT-prolonging drugs* if QTc > 500ms or increases >30ms from baseline (*may require detailed medication history including OTCs/supplements/foods).
- Adjust dose or interrupt therapy if needed (refer to chemotherapy protocol if applicable).
- Monitor and correct electrolytes (keep K^+ >4 mmol/L, Mg^{++} ideally >1 mmol/L).
- Address contributing factors such as nausea, vomiting, diarrhea or poor oral intake.
- Monitor for and promptly evaluate symptoms of syncope, dizziness or palpitations.

References:

1. Davies RA, Simpson CS, Tang ASL, et al. The 2023 Canadian Cardiovascular Society Clinical Practice Update on Management of the Patient with a Prolonged QT Interval. *Can J Cardiol.* 2023;39(10):1285-1301.
2. BC Cancer. Community Oncology Network Pharmacy Educators – Pharmacy FAQs: QT Prolongation in Oncology. March 2023. Accessed October 16, 2025. Available from: https://www.bccancer.bc.ca/pharmacy-site/Documents/Pharmacy%20FAQs/Pharmacy-FAQ-QT-Prolongation.pdf

3-5. Selection and Conditioning Regimens

ACUTE LEUKEMIA & MYELOID NEOPLASMS

	Myeloablative (MA)		Reduced-intensity (RIC)		Autologous
	Related	Unrelated	Related	Unrelated[1]	
AML/MDS/CML/MPN	BUCYATG	BUCYATG	BU2FLUPTCY	BU2FLUPTCY	IVBUCY
≥60y	BU4FLUATG	BU4FLUATG	BU2FLUPTCY	BU2FLUPTCY	IVBUCY
ALL/MPAL/CML BP(L)	CYTBIATG	CYTBIATG	BU2FLUPTCY	BU2FLUPTCY	--
≥60y	BU4FLUATG	BU4FLUATG	BU2FLUPTCY	BU2FLUPTCY	--

[1] If 9/10 VUD, may opt for BU2FLUATG
NB: If prior Busulfan-based SCT, RIC FLUTREOATG is an option

LYMPHOID MALIGNANCIES - 1

	Myeloablative (MA)		Reduced-intensity (RIC)		
	Related	**Unrelated**	**Related**	**Unrelated**[1]	**Autologous**
NHL (excl. CNS/HGL[2])	CYTBIATG	CYTBIATG	BU2FLUPTCY	BU2FLUPTCY	BEAM[2] Mel + Etoposide [If <60y and Lung Co-I]
≥60y	BU4FLUATG	BU4FLUATG	BU2FLUPTCY	BU2FLUPTCY	BEAM[2]
1° CNS lymphoma	--	--	--	--	Thiotepa and IV Busulfan
2° CNS lymphoma/HGL[2]	CYTBIATG	CYTBIATG	--	--	TBuMel
≥60y	BU4FLUATG	BU4FLUATG	--	--	Thiotepa and IV Busulfan
LBL/Burkitt/HGL[2]	CYTBI (1200)[4]	CyTBI (1200)[4]	--	--	VP-16+CY+TBI **BMT** [BEAM if advanced age or comorbidities]

[1] If 9/10 VUD, may opt for BU2FLUATG
[2] HGL includes high-risk double/triple-hit NHL and high-grade lymphoma, NOS
[3] MCL receives post-SCT Rituxan q3mos x 2y
[4] AlloSCT is preferred if documented marrow involvement of in histologically aggressive LBL such as B-LBL or ETP-LBL

LYMPHOID MALIGNANCIES - 2

	Myeloablative (MA)		Reduced-intensity (RIC)		
	Related	**Unrelated**	**Related**	**Unrelated**[1]	**Autologous**
Hodgkin lymphoma	--	--	BU2FLUPTCY (**BMT**)	BU2FLUPTCY (**BMT**)	BEAM[2] Mel + Etoposide [If <60y and Lung Co-I]
CLL	--	--	BU2FLUPTCY	BU2FLUPTCY	--
Multiple myeloma	--	--	--	--	BMTMM0301[3] If GFR >50 ml/min: Melphalan 200 mg/m^2 If GFR 20-50 ml/min: Melphalan 140 mg/m^2

[1] If 9/10 VUD, may opt for Bu2FluATG
[2] Post-SCT RT/Brentuximab guided by day +60 PET scan
[3] Lenalidomide maintenance (10 mg daily) starting 3 months post-ASCT until progression; del(17p) and t(4;14) patients may alternatively receive Bortezomib maintenance (1.3 mg/m^2) q2wks x 2 years

OTHER INDICATIONS & STEM CELL SOURCES

	Myeloablative (MA)		Reduced-intensity (RIC)		Autologous
	Related	Unrelated	Related	Unrelated	
Aplastic anemia	CY+ATG	CY+ATG+TBI(200)	FLUCYATGAM[1]	FLUCYATGAM[1]	--
Graft failure- Stable	CY+ATG	CY+ATG	BU2FLUPTCY[2]	Bu2FLUPTCY[2]	--
- Unstable[5]	FLUCYTBI HAPLO	FLUCYTBI HAPLO	FLUCYTBI HAPLO	FLUCYTBI HAPLO	--
Cord blood transplant	BMT 09-01[3]	BMT 09-01[3]	--	--	
Haploidentical SCT	BU4FLU HAPLO	--	BU2FLU HAPLO	--	
Germ cell tumour	--	--	--	--	Tandem BMT 00-04[4]

[1] Reduced-intensity is appropriate for: elderly AA (≥60y), Fanconi anemia & Dyskeratosis congenita
[2] If prior Busulfan-based SCT, Treosulfan 12 g/m^2 x 3 days should replace Busulfan x 2 days
[3] BMT 09-01 contains Fludarabine 40 mg/m^2 x 4 and TBI 150 cGy x 9 (1350 cGy total)
[4] BMT 00-04 contains Etoposide 2250 mg/m^2 x 1 and Carboplatin 550 mg/m^2 x 3; 2 cycles are given with stem cell support, ideally 30 days apart
[5] The management of all graft failure patients should be individualized and discussed amongst the Attending Staff

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CHAPTER 4. BODY SURFACE AREA AND WEIGHT CALCULATIONS

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4-1. Body Surface Area and Weight Calculations

1) Patients being treated with chemotherapy for acute leukemia, lymphoma, myeloma, etc have their chemotherapy drug doses calculated based on their actual body weight and using the Body Surface Area (BSA) calculation below.

Height: _____cm	Actual Weight: _____kg
▪ Document height and weight on Nursing Assessment Form and must be co-signed by 2 nurses	
$BSA(m^2) = \sqrt{\frac{Height(cm) \times Weight(kg)}{3600}}$ Round all BSA calculation to 2 decimal places	BSA = _____ m^2

2) Vincristine is capped at 2 milligrams in all regimens.

3) Patients undergoing stem cell transplant, autologous or allogeneic, regardless of intensity, have their Ideal Body Weight (IBW) calculated using the formula below. Patients whose actual body weight is greater than their IBW have an Adjusted Body Weight (ABW) calculated. The ABW is used to calculate the BSA for chemotherapy dosing using the formula above. Patients whose actual body weight is less than their IBW will have the BSA calculated using their actual body weight.

Ideal Body Weight (IBW):
Male = 50 + 0.91 (height in cm – 152.4) Female = 45.5 + 0.91 (height in cm – 152.4)
Adjusted Body Weight (ABW):
ABW = Ideal Body Weight (IBW) + 0.4 (Actual Body Weight – IBW)

4) Because there is generally little change in weight in patients undergoing chemotherapy for myeloma or MDS, it is not necessary to repeat height and weight measurements and calculation of BSA before each cycle of chemotherapy. The treating prescriber will ensure that a new height and weight is done if the patient's weight changes significantly (e.g. 10% or more) during these treatments to ensure safe dosing.

5) The Body Mass Index (BMI) is calculated for all patients and recorded on the chemotherapy orders.

$$\text{BMI (kg / m}^2\text{)} = \frac{\text{Weight (kg)}}{[\text{Height(m)}]^2}$$

OR

https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm

CHAPTER 5. SUGGESTED GUIDELINES FOR ROUNDING MEDICATIONS

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5-1. Chemotherapy

Arsenic Trioxide ..... 1 mg
ATRA ..... 10 mg cap (cannot split)
Azacitidine……..1 mg
Bortezomib..... 0.1 mg
Busulfan IV (60 mg amp) ..... 5 mg
Carboplatin..... 10 mg
Carfilzomib (10 mg, 30 mg vials)…….1 mg
Carmustine (100 mg vial)..... 10 mg
Cisplatin..... 5 mg
Cyclophosphamide
IV ..... 100 mg
PO……..25 mg
Cytarabine
IV standard dose (100–200 mg/m^2/day)..... 5 mg
IV high dose..... 100 mg
Intrathecal ..... 5 mg
Daratumumab (100 mg, 400 mg vials)…….20 mg
Daunorubicin ..... 5 mg
Doxorubicin ..... 5 mg
Etoposide
IV low dose..... 5 mg
IV high dose..... 100 mg
PO……...50 mg cap (cannot split)
Fludarabine ..... 5 mg
Gemcitabine..... 100 mg
Gemtuzumab..... .0.1 mg
Ifosfamide ..... 100 mg
Inotuzumab……..0.1 mg
Melphalan
IV (50 mg vial)..... 5 mg
PO……..2 mg tab (cannot split)
Methotrexate
Intrathecal……....1 mg
IV low dose..... .1 mg
IV high dose..... 25 mg
PO……2.5 mg
Mercaptopurine (6-MP) …….25 mg (half of 50 mg tab)
Mitoxantrone……...…1 mg
Pegaspargase……75 units
Thioguanine…….20 mg (half of 40 mg tab)
Thiotepa (15 mg, 100 mg vials)…….. 10 mg
Treosulfan…….. 100 mg
Vincristine..... 0.1 mg

5-2. Supportive Care

Acyclovir IV .....25 mg
Alemtuzumab ……0.1 mg
Allopurinol…….100 mg
Amphotericin .....5 mg
Cyclosporine
IV .....5 mg
PO .....25 mg, 50 mg, 100 mg caps
Dexamethasone
IV……..1 mg
PO……. ……..2 mg (half of 4 mg tab)
Foscarnet……24 mg
Ganciclovir.....25 mg
Heparin .....100 units
Leucovorin
IV……1 mg
PO……...5 mg
Methylprednisolone IV……5 mg
Phenytoin .....30 mg, 100 mg caps
Posaconazole……...100 mg tab
Rituximab (100 mg + 500 mg vial).....100 mg (if possible) or 50 mg
Thymoglobulin
rabbit ATG (25 mg vial) .....1 mg
horse ATG (250 mg amp) .....5 mg
Tacrolimus
IV .....0.1 mg
PO .....0.5 mg, 1 mg, 5 mg caps
Valacyclovir.....500 mg
Valganciclovir ……...450 mg tab
Vancomycin
IV……250 mg
PO……...125 mg cap
Voriconazole
IV ……..10 mg
PO ……50 mg, 200 mg tabs

As per BCCA Policy 111-10, a maximum of 5% variance in dosage calculation is permitted.

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CHAPTER 6. CENTRAL NERVOUS SYSTEM

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6-1. Prophylaxis & Treatment of CNS Malignancy

CNS PROPHYLAXIS

1.1 Acute lymphoblastic leukemia (ALL)

a. Patients being treated with curative intent:

- The diagnostic lumbar puncture (LP) for cytological evaluation of CSF and first injection of intrathecal (IT) chemotherapy is performed during induction when the blast cells have been cleared from the peripheral blood, unless otherwise directed. The platelet count should be 50 x 10^9/L or above (if necessary, under the coverage of platelet transfusion).
- If positive for blasts, the patient is treated as per CNS Treatment on page 4.
- If the LP is negative, patients should continue with CNS prophylaxis according to the chemotherapy protocol with which they are being treated.
- Patients treated on the ALL 89-1 protocol will receive four IT injections of methotrexate 12 mg given during induction phase II (i.e., a total of 5 IT therapies). Patients aged 40 - 50 years will also receive prophylactic cranial irradiation during induction phase II. The cranial irradiation and IT chemotherapy should not be given concurrently (i.e., delay IT therapies until irradiation is completed because of concerns regarding increased CNS toxicity).
- Patients treated on the ALL 13-01 protocol will receive a total of 13 IT therapies beginning on day 1 of induction therapy. Patients will also receive cranial irradiation concurrently with CNS phase chemotherapy.
- Patients receiving blinatumomab consolidation integrated into the ALL 89-1 or ALL 13-01 protocols will receive additional LPs with methotrexate 12 mg IT between cycles of blinatumomab (i.e., 2 additional IT therapies).
- Patients with Ph+ ALL treated on the ALL 20-01 protocol will receive a total of 12 IT therapies.
- Patients with relapsed/refractory ALL receiving immunotherapy with blinatumomab or inotuzumab should receive methotrexate 12 mg IT before starting therapy and in between cycles.
- Patients with ALL (other than L3 and T-cell subtypes) and MPAL with B cell component undergoing allogeneic SCT (TBI-based regimen) in first remission should receive a total of 5 IT therapies pre-BMT, but no cranial irradiation.

b. Patients treated palliatively with modified ALL 89-01 protocol should receive one LP with methotrexate 12 mg IT on count recovery from induction chemotherapy. If negative, and are receiving consolidation blinatumomab, they still should be considered for IT chemotherapy before and in-between blinatumomab cycles. No cranial irradiation will be given.

1.2 L3 and T-Cell ALL, MPAL with T cell component, Lymphoblastic lymphoma (LbL) and Burkitt's lymphoma (BkL)

The diagnostic LP and first IT injection of methotrexate 12 mg is performed during induction when the platelet count is 50 x 10^9/L or above and leukemia/lymphoma cells have been cleared from the blood, unless otherwise directed. Patients in first remission proceeding to allogeneic or autologous BMT (TBI-based regimen) as consolidation receive another 3 IT therapies of methotrexate 12 mg pre-BMT and 4 IT therapies of methotrexate 12 mg alternating with cytarabine 50 mg every 1–2 weeks post-BMT (i.e., a total of 8 IT therapies). For patients who are treated with chemotherapy alone with curative intent, a total of 8 LPs with IT chemotherapy (methotrexate or cytarabine) instillation should be performed during and after completion of chemotherapy.

1.3 Acute myeloid leukemia (AML)

Patients being treated with curative intent.

1. AML responding to induction and in CR1
a. If symptomatic at any time during treatment (e.g. unexplained cognitive changes, seizures, focal neurological deficit): LP with CSF exam is warranted after appropriate imaging. If CNS disease is identified, patients should receive appropriate treatment as per existing guidelines (see page 4).
b. If patients are being treated with curative intent but not planned to receive at least 1 cycle of INDAC/HIDAC: 1 LP with CSF exam and IT chemotherapy with cytarabine 50 mg should be done.
c. Consideration can be given for screening LP with IT chemotherapy if patients present with WCC above 100, have numerous sites of extra-medullary disease at presentation (especially if CNS adjacent) or present with "myelo-monocytic or monocytic" AML. Where possible, perform the LP with IT chemotherapy on a different day from other parenteral route chemotherapy. Select an IT chemotherapy agent that is different than what is being given systemically.
d. If CSF positive when LP done, treat as per existing CNS treatment guidelines (page 4).

Routine screening LPs with IT chemotherapy are not otherwise mandated.

2. Relapsed/Refractory AML in CR2 and beyond.
a. If symptomatic at any time during treatment (e.g. unexplained cognitive changes, seizures, focal neurological deficit): LP with CSF exam is warranted after appropriate imaging. If CNS disease is identified patients should receive appropriate treatment as per existing guidelines (see page 4).
b. If patients are being treated with curative intent but not planned to receive MEC salvage (e.g. receiving cyclophosphamide/etoposide (CY/VP16), gilteritinib or azacitidine/venetoclax as salvage): 1 screening LP with CSF exam and IT chemotherapy with cytarabine 50 mg should be done.
c. Consideration can be given for screening LP with IT chemotherapy if patients present with WCC above 100, have numerous sites of extra-medullary disease at presentation (especially if CNS adjacent) or present with "myelo-monocytic or

monocytic" AML. Where possible, perform the LP with IT chemotherapy on a different day from other parenteral route chemotherapy. Select an IT chemotherapy agent that is different than what is being given systemically.
d. If CSF positive, treat as per existing CNS treatment guidelines (page 4).

Routine screening LP with IT chemotherapy is not otherwise mandated.

Patients being treated with Non-Curative intent (e.g. azacitidine/venetoclax)

a. If symptomatic at any time during the course of treatment (e.g. unexplained cognitive changes, seizures, focal neurological deficit): LP with CSF exam is warranted after appropriate imaging. If CNS disease is identified patients should receive appropriate treatment as per existing guidelines (page 4).

Routine screening LP with IT chemotherapy is not otherwise mandated.

1.4 Pre-SCT

Patients with the following diagnoses should, as a routine practice, have a lumbar puncture performed with administration of intrathecal chemotherapy prior to SCT:

Lymphoid malignancy:

- Acute lymphoblastic leukemia
- Richter's transformation of Chronic lymphocytic leukemia
- Non-Hodgkin's lymphoma, excluding Mantle Cell Lymphoma and follicular NHL with no evidence of transformation

Myeloid Malignancy:

Patients with AML (including secondary) or MDS/AML or CML-BP/AP should undergo 1 screening LP with CSF exam and IT cytarabine 50 mg if they meet the following criteria;
a. If prior history of CNS disease.
b. If patients have not received at least 1 cycle of intermediate dose cytarabine prior to proceeding with allo-SCT (e.g. INDAC/HIDAC/MEC)*
c. Consideration can be given for screening LP with IT chemotherapy if patients present with WCC above 100, have numerous sites of extra-medullary disease at presentation (especially if CNS adjacent) or present with "myelo-monocytic or monocytic" AML.*
d. If CSF positive, treat as per existing CNS treatment guidelines (page 4).

Routine screening LP with IT chemotherapy is not otherwise mandated in MDS, MPN, MDS/MPN or CP-CML

*If patients have already had 1 screening LP with IT chemotherapy during their course of treatment (immediately prior to SCT) and this is negative, then LP does not have to be repeated pre-SCT

CNS TREATMENT

If the leukemia or lymphoma involves the CSF, IT or intraventricular (via an Ommaya reservoir) methotrexate 12 mg or cytarabine 50 mg is given every 2–3 days until clearing is achieved. Thereafter, IT therapy is administered every 7 days until 5 doses have been given after the last cytologically negative CSF sample. Depending on circumstances, additional therapy may include cranial irradiation and/or maintenance IT therapy every 4 weeks.

6-2. Guidelines for Elective Lumbar Punctures

Elective lumbar punctures (LPs) should be performed when the patient is hemostatically normal. Therefore, LPs in patients with acute leukemia should be deferred until their counts have recovered from chemotherapy, whenever possible, unless otherwise specified in the protocol. In other circumstances the following guidelines will apply:

1. Platelet count should be documented to be 20 x 10^9/L or above at the time of the lumbar puncture.
2. The PTT should be normal and the INR less than 1.5 within 48 hours of the lumbar puncture.
3. Ensure medications were held prior to the lumbar puncture as per local guidelines for anticoagulation and antiplatelet therapy management in the L/BMT Manual (Chapter 23).
4. For patients with a platelet count of 50 x 10^9/L or above, the physician performing the LP should make no more than four attempts to perform the procedure at one/or two intervertebral spaces. Repositioning the needle without removing it is still considered one attempt.
5. For patients with a platelet count of 20 to 49 x 10^9/L, there should only be a maximum of two attempts at the bedside.
6. If unsuccessful at the bedside, the procedure should be abandoned and rescheduled for image-guided lumbar puncture in Radiology at a future date, unless exceptional clinical circumstances necessitate same-day escalation.
7. There will be occasions in which LPs are required urgently for clear clinical indications and the senior hematology staff should be consulted if the above guidelines cannot be adhered to under these circumstances.
8. Patients who are systemically unwell at the time of a scheduled elective LP should have the LP deferred until the issue resolves. These issues include but are not limited to:

    - Disabling headache, neck stiffness, nausea, vomiting etc. from a prior LP
    - Intercurrent active viral, bacterial or fungal infection whether proven or suspected
    - Active, uncontrolled acute GVHD

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Chapter 7. Treatment of Febrile Neutropenia

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Chapter 7. Treatment of Febrile Neutropenia

7-1. Outpatient Management of High Risk Neutropenia

A. Criteria of Outpatient Management[$$]

Introduction of appropriate antimicrobial prophylactic regimen[#]

Hemodynamic stability

Absence of serious or multiple comorbidity including, but not limited to: uncontrolled arrhythmias, heart failure, angina; chronic lung disease; renal insufficiency (CrCl < 30 ml/min); hepatic insufficiency (AST or ALT > 5 x ULN) or active viral hepatitis; HIV; uncontrolled DM; severe mucositis (grade 3-4); active autoimmune diseases (e.g. rheumatoid arthritis)

Absence or resolution of coagulopathy

Absence of complex infection – CNS infection, pneumonia, severe skin and soft tissue infection, acute intra-abdominal sepsis, or uncontrolled catheter related infection with persistent bacteremia or secondary complications like thrombosis

Has a confirmed reliable English-speaking caregiver with a telephone. The Lodge or Easter Seal House is acceptable without a caregiver.

Lives within identified acceptable boundaries (see map, Appendix A)

B. Criteria for Admission

Absolute

Hemodynamic instability

Hypotension unresponsive to fluid challenge

Marked tachycardia

Syncope

Hypoxia (sat < 92% RA) or chronic lung disease

Altered mental status or seizures

Any evidence of severe sepsis (HR > 90, SBP < 90 or SBP decrease > 40, RR > 20, altered LOC, plus evidence of end-organ damage)

Lactate > 4

Uncontrolled arrhythmias, heart failure, angina

Renal insufficiency (CrCl < 30 ml/min)

Hepatic insufficiency (AST or ALT > 5 x ULN)

WHO grade 3 bleeding not responding to platelet transfusions

Evidence of complex infection – CNS infection, pneumonia, severe skin and soft tissue infection, acute intra-abdominal sepsis, or uncontrolled catheter related infection with persistent bacteremia or secondary complications like thrombosis

Progressive or uncontrolled infection not responding to antibiotics

Development of medical complications during course of illness (e.g. pneumothorax, pericardial effusion)

Allergy to all outpatient IV antibiotics used or requires IV antibiotics dosed greater than once daily

Caregiver overwhelmed

Relative

T > 39°C

Fever > 3 days; rigors

Failure to thrive

Age > 65 years

Mild autoimmune disorders (e.g. rheumatoid arthritis); well-controlled HIV; DM; mucositis

[$$] These guidelines do not apply to patients in palliative care. It is up to the discretion of the attending physician if and when these patients are admitted.

[#] Patients who have a history of MDR organism that will not be covered by the current antimicrobial prophylaxis should be admitted as soon as they have fever & neutropenia for appropriate antibiotic therapy (e.g. MDR gram negative organisms R to ciprofloxacin, VRE)

C. Primary Outpatient Regimen

Febrile neutropenia is considered an oncologic and medical emergency with high mortality if untreated, and empiric broad-spectrum antibiotics must be administered immediately. Allergies, prior antibiotic history, clinical picture, and local flora should be considered as guides for initial antibiotic therapy.[1-3]

The initial antibiotic therapy (outpatients) should be one of the following broad spectrum regimens:[1-6]

1. The preferred initial antibiotic therapy is combination intravenous ceftriaxone and once-daily aminoglycoside plus IV fluids (refer to BMT AMB Febrile Neutropenia Initial Management Plan). This regimen is appropriate for penicillin-allergic or anaphylactic patients.

   a. Metronidazole (oral) should be added to the above regimen if a patient is known or suspected to have an intra-abdominal source. The first dose should be ordered to be given in Daycare, followed by a prescription with instructions for the patient to take at home.

2. Ertapenem in combination with once-daily aminoglycoside is an alternative to the above regimen. It should be reserved for known or suspected infection with ESBL/AmpC cephalosporinase-producing organisms. Note: ertapenem does NOT cover Pseudomonas and lacks activity against Acinetobactor and Enterococci compared to other carbapenems.

3. Empiric vancomycin:
   - Empiric vancomycin should not be routinely used, but should be considered in the following situations:
     - Clinically obvious, serious catheter-related infection
     - Known colonization with penicillin/cephalosporin-resistant pneumococci or MRSA
     - Positive blood cultures for gram-positive bacteria before final identification and susceptibility testing
     - Hemodynamic instability
     - Pneumonia documented radiographically
     - In some centres, other indications include intensive chemo resulting in substantial mucosal damage or quinolone prophylaxis
   - Discontinue vancomycin after 2–3 days if cultures are negative for beta-lactam resistant Gram positive organism

4. If atypical pneumonia bacteria (Legionella/Mycoplasma/Chlamydophila) expected (e.g. severe presentation of community acquired pneumonia), antibiotic coverage may be extended by adding a macrolide (e.g. azithromycin) or doxycycline.

5. Investigate for invasive fungal infection in patients with persistent or recurrent fever after 4 – 7 days of treatment with broad spectrum antibiotics. Refer to Chapter 10. Antifungal Therapy.

6. In the absence of serious infection, filgrastim (G-CSF) is not indicated to improve clinical outcomes, but may reduce hospitalization by 1 day.[2,6]

References:

1. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2011 Feb 15;52(4):427-431 PubMed ID 21205990.

2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections. Version 3.2022. Available at: www.nccn.org. Accessed 03/22, 2023.

3. Sepkowitz KA. Treatment of patients with hematologic neoplasm, fever, and neutropenia. Clin Infect Dis 2005 Apr 1;40 Suppl 4:S253-6.

4. Blondel-Hill E FS. Bugs and Drugs. Edmonton: Capital Health; 2012.

5. Klastersky J, de Naurois J, Rolstron B, et al. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Ann Oncol 2016, 27 Suppl 5:v111-118.

6. British Columbia Cancer Agency (BCCA). BC Cancer Agency Cancer Management Guidelines. Febrile Neutropenia. 2023; Available at: http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-manual/supportive-care/febrile-neutropenia Accessed 03/22, 2023.

D. Criteria for Early Discharge (ED) of Neutropenic Patients to Daycare

** Patients receiving induction or salvage chemotherapy are not candidates for early discharge and should remain in hospital until neutrophils are above 0.5.

Medical Criteria

ECOG performance status of 0 to 1. Patients who are ECOG performance status 2 can be evaluated on a case-by-case basis.

Total bilirubin ≤ 2.5 x upper limit of normal (ULN) (unless elevation is thought to be due to Gilbert's syndrome or hemolysis)

AST or ALT ≤ 1.5 x ULN

SCr ≤ 1.5 x ULN

No clinical evidence of heart failure (LVEF > 40%)

No active bleeding

Not receiving IV antibiotics x 48 hours

Afebrile x 24 hours

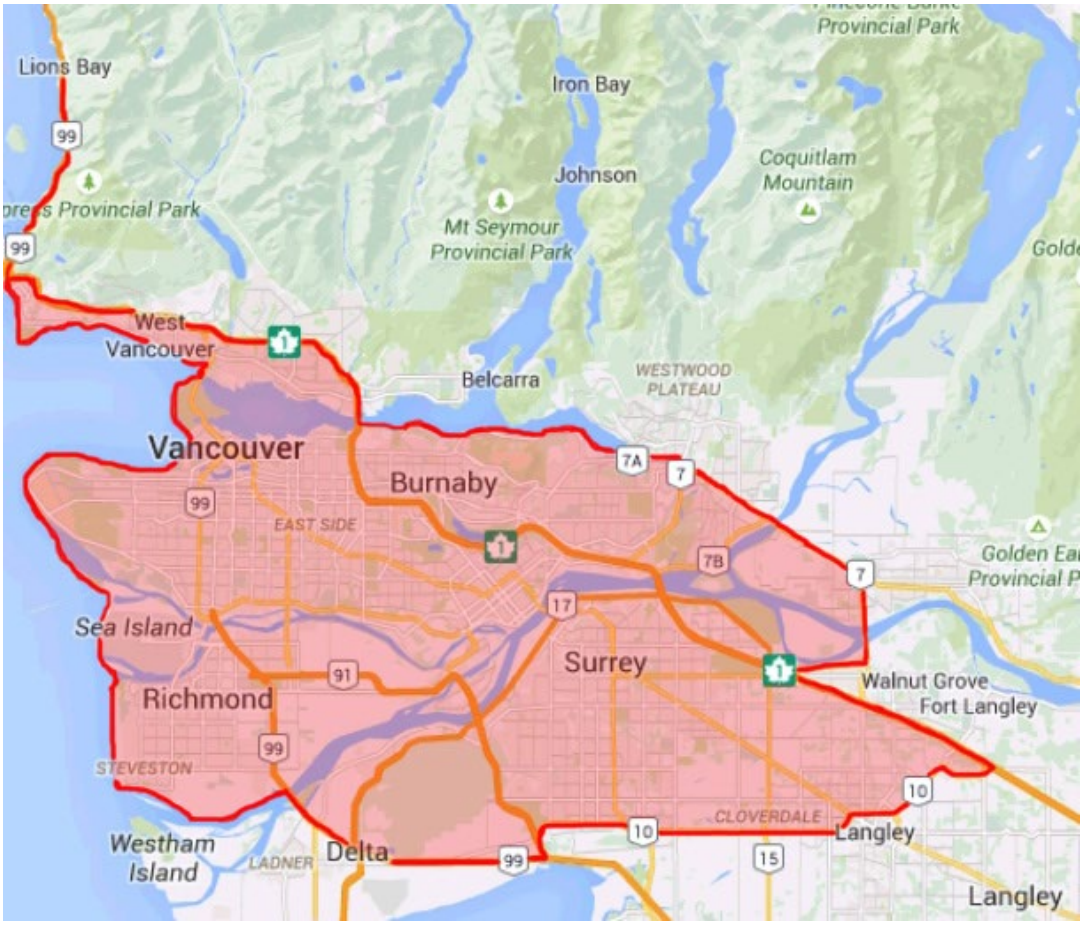
No allergies to antimicrobial prophylaxis

Logistic criteria

Has a confirmed reliable English-speaking caregiver with a telephone. The Cancer Lodge or Easter Seal House is acceptable without a caregiver.

Lives within identified acceptable boundaries (see map, Appendix A).

Appendix A



7-2. Primary Inpatient Regimen

Febrile neutropenia is considered an oncologic and medical emergency with high mortality if untreated, and empiric broad-spectrum antibiotics must be administered immediately. Allergies, prior antibiotic history, clinical picture, and local flora should be considered as guides for initial antibiotic therapy.[1-3]

The initial antibiotic therapy (inpatients) should be one of the following broad spectrum regimens:[1-6]

1. The preferred initial antibiotic therapy is intravenous piperacillin/tazobactam plus IV fluids (refer to BMT Febrile Neutropenia Initial Management Plan).

2. Ceftazidime with or without metronidazole is an alternative to piperacillin-tazobactam for penicillin-allergic or anaphylactic patients.

3. Carbapenem monotherapy is an alternative to piperacillin-tazobactam. In order to prevent the selection of carbapenem resistance, carbapenems should not be used as first line unless there is known or suspected infection with ESBL/AmpC cephalosporinase-producing organisms.

4. Empiric vancomycin:
   - Empiric vancomycin should not be used for persistent fever, but should be considered in the following situations:
     - Clinically obvious, serious catheter-related infection
     - Known colonization with penicillin/cephalosporin-resistant pneumococci or MRSA
     - Positive blood cultures for gram-positive bacteria before final identification and susceptibility testing
     - Hemodynamic instability
     - Pneumonia documented radiographically
     - In some centres, other indications include intensive chemo resulting in substantial mucosal damage or quinolone prophylaxis
   - Discontinue vancomycin after 2–3 days if cultures are negative for beta-lactam resistant Gram positive organisms

5. If atypical pneumonia bacteria (Legionella/Mycoplasma/Chlamydophila) expected (e.g. severe presentation of community acquired pneumonia), antibiotic coverage may be extended by adding a macrolide (e.g. azithromycin) or doxycycline.

6. Investigate for invasive fungal infection in patients with persistent or recurrent fever after 72 hours of treatment with broad spectrum antibiotics. Refer to Chapter 10. Antifungal Therapy.

7. In the absence of serious infection, filgrastim (G-CSF) is not indicated to improve clinical outcomes, but may reduce hospitalization by 1 day.[2,6]

References:

1. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2011 Feb 15;52(4):427-431 PubMed ID 21205990.

2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections. Version 3.2022. Available at: www.nccn.org. Accessed 03/22, 2023.

3. Sepkowitz KA. Treatment of patients with hematologic neoplasm, fever, and neutropenia. Clin Infect Dis 2005 Apr 1;40 Suppl 4:S253-6.

4. Blondel-Hill E FS. Bugs and Drugs. Edmonton: Capital Health; 2012.

5. Klastersky J, de Naurois J, Rolstron B, et al. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Ann Oncol 2016, 27 Suppl 5:v111-118.

6. British Columbia Cancer Agency (BCCA). BC Cancer Agency Cancer Management Guidelines. Febrile Neutropenia. 2023; Available at: http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-manual/supportive-care/febrile-neutropenia Accessed 03/22, 2023.

7-3. Treatment of Specific Infections

Stenotrophomonas maltophilia

Stenotrophomonas maltophilia has emerged as a serious pathogen in Leukemia/BMT patients. Based on our recent experiences with this infection we have developed the following guidelines:

All patients who have blood cultures positive for *Stenotrophomonas* should have their Hickman® line removed.

Patients who are growing gram-negative organisms while on gram-negative coverage should have TMP-SMX (co-trimoxazole) added to their antibiotic regimen.

Patients with a history of *Stenotrophomonas* infections with one cycle of chemotherapy should be covered with TMP-SMX (co-trimoxazole) during subsequent neutropenic periods if they do not promptly defervesce on routine antibiotic coverage.

Vancomycin Resistant Enterococci Infection (VRE)

- The **incidence of infections** due to vancomycin-resistant enterococci (VRE) has been rising in leukemia patients and HSCT recipients.[1] Reports indicate VRE colonization rates as high as 40.2% in SCT recipients with 34.2% of those colonized patients developing bacteremia[1]. The mortality rate associated with VRE for these bacteremic patients was 35.7%.
- Typically, E. faecium represents the majority of VRE strains that are cultured. In contrast, 100% of E. faecalis isolates at VGH are currently ampicillin (or piperacillin) susceptible.
- **Risk factors for VRE colonization** include the use of vancomycin, cephalosporins or anti-anaerobic antibiotics (e.g., metronidazole), increased length of hospital or ICU stay, and care by a nurse caring for other VRE colonized patients or location near other VRE colonized patients[2].
- No currently available antimicrobial agent can eradicate VRE colonization.
- Neutropenic patients colonized with VRE are at risk for VRE bacteremia as a result of gut translocation, CVC infections, or urinary tract infections.
- When to suspect VRE:
    - patient has previously had VRE infection or is known to be VRE colonized. In this case, Transplant ID should be notified if they are unstable or if they have gram-positive organisms suggestive of Streptococcus/Enterococcus even on their initial blood cultures.
- When not to suspect VRE:
    - initial blood cultures grow gram positive organisms suggestive of Streptococcus/Enterococcus as these are usually a viridans group streptococci (e.g. S. mitis, S. salivarus, S. mutans)
    - any blood cultures that have gram positive organisms suggestive of Staphylococcus species. Vancomycin will work in this setting.

Therapeutic options for the treatment of VRE infection in leukemia/HSCT recipients include daptomycin, linezolid, and tigecycline[3].

- There is limited human data for the use of tigecycline in the treatment of VRE and given its broad spectrum of activity, it is likely best reserved for poly-microbial infections with potentially multi-drug resistant organisms[4]. There is an FDA warning about tigecycline causing an increased risk of death compared to other agents. Healthcare providers should reserve tigecycline for use in situations when alternative treatments are not suitable.
- **Daptomycin** is a cyclic lipopeptide with activity against gram-positive organisms that exhibits concentration-dependent killing[5]. It is unlikely to cause adverse hematological effects and is bactericidal in vitro against VRE, posing a potential advantage over other agents. In comparative studies, elevated creatine phosphokinase (CPK), elevated liver enzymes and hypotension were the adverse effects that occurred more commonly with daptomycin. VRE can develop resistance to daptomycin. This has been occurring with increased frequency for LBMT patients, so it is important to preserve daptomycin for documented infections for cases where there are no other alternative agents.
    - Daptomycin is a restricted antibiotic that requires Infectious Disease approval. If the patient is critically ill and sent to ICU, ICU would be able to approve the daptomycin. Please consult Transplant Infectious Disease if a patient has a suspected VRE bacteremia, or if you need help selecting an agent for VRE infections presenting at other sites, such as cystitis or to give advice on empiric therapy for febrile neutropenia for patients with previous known VRE colonization/infection.
- Vancomycin Resistant Enterococci Infection (VRE) (cont.). Linezolid is an oxazolidinone with activity against gram-positive organisms, including bacteriostatic activity against VRE[6]. The main concern with using linezolid in patients with pre-existing cytopenias is its potential to cause reversible myelosuppression with extended durations of therapy, typically after two or more weeks of treatment[7].Another potential concern is the drug interaction between linezolid and concomitant medications such as serotonin re-uptake inhibitors (SSRIs)[8] or meperidine and the development of serotonin syndrome.[9]
    - Overnight, patients can be treated with one dose of linezolid if there is significant concern to cover for VRE.

Treatment of Specific Infections

	Linezolid (Zyvoxam®)	Daptomycin (Cubicin®)
Dosage	600 mg PO b.i.d. 600 mg IV q12h	10 mg/kg IV q24h
Renal Impairment	No adjustment required	CrCl < 30 ml/min: 10 mg/kg IV q48h
Hepatic Impairment	No adjustment required	No adjustment required
Adverse Effects	Thrombocytopenia (up to 10%, more common after > 2 weeks of therapy), myelosuppression, headache (up to 11%) nausea/vomiting (up to 10%), diarrhea (3–11%),	Increased CPK (3–9%) & musculoskeletal pain, elevated LF Ts (2–3%), nausea (6–10%), dyspepsia, diarrhea or constipation (5–12%)
Drug Interactions	Linezolid is a non-selective inhibitor of MAO – avoid/ caution with adrenergic drugs, sympathomimetics, SSRIs, meperidine, INH, MAOI inhibitors &	HMG Co – A reductase inhibitor can increase the risk of myopathy

Extended Spectrum β-Lactamase Producers (ESBL)

Extended Spectrum Beta Lactamases (ESBL) are enzymes that are produced by gram-negative bacteria which inactivate antibiotics belonging to the beta-lactam class – penicillins, cephalosporins, and monobactams (i.e. aztreonam). *Escherichia coli* and *Klebsiella spp.* are the most common bacteria that have these enzymes. However, with increasing use of extended spectrum beta-lactam antibiotics, many other gram-negative organisms have acquired ESBL enzymes. Resistance to beta-lactams may be detected in these bacteria with initial testing or may develop during therapy with beta-lactam antibiotics. Unfortunately, ESBL-producing organisms are also typically resistant to other classes of antibiotics such as aminoglycosides, fluoroquinolones, tetracyclines, chloramphenicol and sulfonamides. These organisms usually remain susceptible to carbapenems such as meropenem. Carbapenems are first line therapy for anyone with an ESBL infection in the setting of neutropenia regardless of the susceptibility results given by the laboratory.

AmpC β-Lactamase Producers

AmpC is another beta-lactamase enzyme produced by gram-negative bacteria which inactivate antibiotics belonging to the beta-lactam class – penicillins, most cephalosporins (except cefepime), and monobactams (i.e. aztreonam). These enzymes are found in the DNA of specific gram-negatives including *Enterobacter spp., Citrobacter freundii, Morganella morganii, Providencia spp., Hafnia alvei* and *Serratia spp.* The AmpC enzyme is usually turned off but can be activated by therapy with beta-lactam antibiotics. As with ESBL-producing organisms, carbapenems are first line therapy for anyone with an infection with an AmpC-producing organism in the setting of neutropenia regardless of the susceptibility results given by the laboratory.

References:

1 Weinstock DM, Conlon M, Iovino C, et al. Colonization, bloodstream infection, and mortality caused by vancomycin-resistant enteroccus early after allogeneic stem cell transplant. Biol Blood Marrow Transplant 2007; 13: 615–21.

2 Murray BE. Vancomycin-resistant enterococcal infections. N Engl J Med 2000; 342: 710–21.

3 Linden PK. Optimizing therapy for vancomycin-resistant enterococci (VRE). Sem Resp Crit Care Med 2007; 632–45.

4 Stein GE, Craig WA. Tigecycline: a critical analysis. Clin Infect Dis 2006; 43: 518–24.

5 Schriever CA, Fernandez C, Rodvold KA, Danziger LH. Daptomycin: a novel cyclic lipopeptide. Am J Health Syst Pharm 2005; 62: 1145–58.

6 Pankey GA, Sabath LD. Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of gram-positive bacterial infections. Clin Infect Dis 2004; 38: 864–70.

7 Kuter DJ, Tillotson GS. Hematologic effects of antimicrobials: focus on the oxazolidinone linezolid. Pharmacotherapy 2001; 21: 1010–3.

8 Debellis RJ, Schafer OP, Liquori M, et al. Linezolid-associated serotonin syndrome after concomitant treatment with citalopram and mirtazapine in a critically ill bone marrow transplant recipient. J Intensive Care Med 2005; 20: 303–5.

9 Das PK, Warkentin DI, Hewko R, Forrest DL. Serotonin syndrome after concomitant treatment with linezolid and meperidine. Clin Infect Dis 2008; 46: 264–5.

10 Paterson DL. Clinical experience with recently approved antibiotics. Curr Opin Pharmacol 2006; 6: 486–90.

7-4. Vancomycin Dosing Guidelines

KEY

1. Establish patient age, weight, and serum creatinine.
2. Consider loading doses only for critically ill patients
3. Using Table 1, identify initial loading dose and maintenance dose per interval according to patient weight.
4. Using Table 3, identify initial dosing interval by age and serum creatinine.
5. Using Table 4, determine dialysis dosing.

TABLE 1. INITIAL DOSE PER INTERVAL

TOTAL BODY WEIGHT (in kg)	LOADING DOSE [FOR CRITICALLY ILL][α] (maximum dose 3000 mg) Target pre-level 10-15 mg/L (20 mg/kg)	MAINTENANCE DOSE[β] (15 mg/kg)
40-50	1000 mg	750 mg
51-60	1250 mg	1000 mg
61-70	1250 mg	1000 mg
71-80	1500 mg	1250 mg
81-90	1750 mg	1250 mg
91-100	2000 mg	1500 mg

[α] Higher loading doses may be considered. Consult Pharmacy.
[β] Suggested maximum maintenance dose is 4.5 g per day.
If loading dose used, give maintenance dose at next dosing interval (See Table 3)

TABLE 3, FOR ALL INDICATIONS TARGET TROUGH 10-15 mg/L
INITIAL DOSING INTERVAL (hours)

SCr (µmol/L)	Age Group (years)					
	20-29	30-39	40-49	50-59	60-69^	70-79^
40-60	8	8	12	12	12	18
61-80	8	12	12	12	18	18
81-100	12	12	12	18	18	18
101-120	12	12	18	18	18	24
121-140	12	18	18	18	24	
141-160	18	24	24	24		
161-180	24	24				
181-200	24					
Above 200						
Dialysis	See TABLE 4 (back of card)					

^In elderly patients with low muscle mass, use clinical judgment as SCr may not reflect renal function accurately

Shaded boxes: These patients have unstable and/or reduced renal function, and the nomogram may not be as predictive.

- For those with no dosing interval stated, patients should receive a dose followed by 3 hour and 24 hour post-dose serum levels to determine subsequent dosing.
- A clinical pharmacist should be contacted for assistance with dosing and interpretation of levels.

TABLE 4 DIALYSIS DOSING

	Hemodialysis (HD)	Continuous Ambulatory Peritoneal Dialysis (CAPD)
Loading Dose	25 mg/kg	Intraperitoneal (IP): 30 mg/kg **OR** Intravenous (IV): 20 mg/kg
Maintenance Dose	**weight < 70 kg:** 500 mg QHD **weight ≥ 70 kg:** 750 mg QHD	IP: 30 mg/kg every 5-7 days **OR** IV: 20 mg/kg every 4-7 days
When To Draw Level	Pre-second maintenance dose	3-4 days after first dose
Target Vancomycin Level	Pre-HD level: 10-20 mg/L	Trough level: 10-20 mg/L

THERAPEUTIC DRUG MONITORING

Vancomycin serum levels should be ordered prior to the 3rd or 4th dose in the following situations:

1. Vancomycin treatment is anticipated for greater than 7 days and ongoing therapeutic drug monitoring is indicated (e.g. MRSA, bacteremia, infective endocarditis, osteomyelitis, septic arthritis)
2. Vancomycin treatment is greater than 72 hours WITH one or more of the following:
   - Receiving aggressive dosing (where target trough is 15 mg/L)
   - Renal function unstable, serum creatinine increase by 30 umol/L or 1.5 times baseline
   - On dialysis (hemodialysis or peritoneal – see Table 4)
   - Receiving concurrent nephrotoxic or ototoxic drug
   - Altered volume of distribution or clearance, including
     - Age 65 years or greater
     - Hypermetabolic (e.g. burn patient, cystic fibrosis)
     - Low body weight/muscle mass or frail
     - Obese (125% of ideal body weight or greater)
     - Patient not responding to treatment

Pre- and 3 hour post-vancomycin level (target post level of 20-40 mg/L) if calculation of precise kinetic parameters are necessary (e.g. in cases when target pre-vancomycin level of 10-15 mg/L cannot be achieved while on prolonged therapy, or in an obese, pregnant or pediatric patient, especially when aggressive dosing is required). Target AUC_{24} is 400-600 mg·h/L.

7-5. Antibiotic Discontinuation

ECIL recommendations and recent clinical data suggest antibiotic discontinuation or de-escalation is safe in selected patients.[1-3]

The following groups can be considered for discontinuation or de-escalation of antibiotics with the L/BMT attending's approval. All patients should be discussed with the pharmacy, Transplant Infectious Disease, and the L/BMT attending before discontinuation or de-escalation is carried out.

1. Autologous Stem-cell Transplant, ALL and AML patients who start empiric antibiotics and are neutropenic (ANC < 0.5):

   If all the following criteria are met, discuss stopping antibiotics with Transplant ID:

   a. Clinically stable for 72 hours (blood pressure at baseline, heart rate < 100 bpm, stable oxygen requirements)
   b. Afebrile for 72 hours
   c. Cultures negative for at least 72 hours (when taken associated with fever)
   d. No cultures positive during this neutropenic episode
   e. No mucositis (oral or GI)
   f. No sign of or identifiable source of infection
   g. Discussed with L/BMT attending

2. Autologous Stem-cell Transplant, ALL and AML patients who have received > 14 days of antimicrobial therapy for a documented infection and are neutropenic (ANC < 0.5):

   If all the following criteria are met, discuss stopping antibiotics with Transplant ID:

   a. Clinically stable for 72 hours (blood pressure at baseline, heart rate < 100 bpm, stable oxygen requirements)
   b. Afebrile for 72 hours
   c. Documented negative cultures after initial positive cultures
   d. No sign of infection
   e. No mucositis (oral or GI)
   f. Patient has completed a full course of therapy for their infection (2 weeks from negative cultures for uncomplicated bacteremia, 4 or 6 weeks in complicated cases - e.g. endocarditis or osteomyelitis – with Transplant ID input
   g. Discussed with the L/BMT attending

3. Candidates for de-escalation of meropenem to alternative antibiotics (e.g. piperacillin-tazobactam) regardless of ANC:
   a. If all the following criteria are met, discuss stopping antibiotics with Transplant ID:
   b. No organism identified (past or current) that requires the spectrum of a carbapenem
   c. Clinically stable for 72 hours (blood pressure at baseline, heart rate < 100 bpm, stable oxygen requirements)
   d. Afebrile for 72 hours
   e. Discussed with the L/BMT attending

References

1. Aguilar-Guisado et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomized, controlled phase 4 trial. Lancet Haematol. 2017 Dec;4(12):e573-e583.
2. Averbuch et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica. 2013 Dec;98(12):1826-35.
3. Le Clech et al. Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study. Infect Dis (Lond). 2018 Jul;50(7):539-549.

8-1. Outpatient Antibiotic Prophylaxis for Chemotherapy Patients

SUMMARY OF RECOMMENDED ANTIMICROBIAL PROPHYLAXIS DURING CHEMOTHERAPY‡

Indication		HSV+[1]	VZV+[2]	Antibiotic[3]	Fungal[4]	PJP[5]	HBV[6] Risk of HBV reactivation: HbsAg+	HBV[6] Risk of HBV reactivation: HbsAg- and HbcAb+
AML	Induction							
	7 + 3 +/- midostaurin or gemtuzumab; Vyxeos Induction 1	Y	N	N	Y	N	High	Moderate
	Consolidation							
	HIDAC or INDAC +/- midostaurin or gemtuzumab; Vyxeos	Y	N	Y[3a]	Y	N	High	Moderate
	Azacitidine + Venetoclax	Y	Y	Y[3e]	Y[4a]	N	Moderate	Moderate
AL	Salvage VP16/CY or MEC; Vyxeos Induction 2	Y	N	N	Y[4b]	Y	High	Moderate
	Salvage Azacitidine + Venetoclax	Y	Y	Y[3e]	Y[4b]	N	Moderate	Moderate
APL	Induction							
	ATO/ATRA/Dauno	Y	Y	N	N	N	High	Moderate
	ATO/ATRA	Y	Y	N	N	N	High	Moderate
	Consolidation ATO/ATRA	N	Y	N	N	N	High	Moderate
	Relapsed ATO	N	Y	N	N	N	Low	Low
ALL	Induction							
	ALL 89-1 Induction Phase I; ALL 13-01 Induction; ALL 20-01 Induction Phase I	Y	N	N	Y	Y	High	Moderate
	Beyond Induction							
	ALL 89-1 Induction Phase II; ALL 89-1 Consolidation Cycle 3; ALL 20-01 Consolidation + TKI	Y	N	Y	Y	Y	High	Moderate
	ALL 89-1 Consolidation Cycle 1, 2, 4 & 5 ALL 20-01 Maintenance + TKI	N	N	Y[3b]	N	Y	High	Moderate
	ALL 13-01 Consolidation 1A	Y	N	Y	Y	Y	High	Moderate
	ALL 13-01 Consolidation 1B	Y	N	Y[3a]	Y	Y	High	Moderate
	Blinatumomab	Y	N[2a]	N	N[4c]	Y	Very High	Very High
	Inotuzumab	Y	N[2a]	N	N[4c]	Y	Very High	Very High
MPAL / LL	MPAL Induction / NHL 98-1 Induction	Y	N	N	Y	Y	High	Moderate
BL	Magrath A & B	Y	N	Y	Y[4a]	N[5a]	Very High	Very High
MDS/AML	Azacitidine	N[1a]	N[2a]	N[3d]	N[4d]	N	Low	Low
SAA	CsA-ATG	Y	N[2a]	N[3c]	N[4c]	Y[5b]	Moderate	Moderate

1. Valacyclovir 500 mg PO BID to start when ANC ≤ 0.5 **OR** day 1 of steroid and continue until ANC ≥ 0.5 **OR** off steroid (refer to protocol).
   a. Routine prophylaxis not recommended. Risk of infection following therapy with intensive chemotherapy or HSCT may warrant prophylaxis at the discretion of the attending MD.
2. Valacyclovir 500 mg PO BID to start on day 1 of chemotherapy and to continue until 4 weeks after last chemotherapy dose.
   a. Routine prophylaxis not recommended. Prophylaxis may be warranted in very severe AA (ANC < 0.2) with additional risks for infection (e.g. prior history, age above 50) or in blinatumomab / inotuzumab / azacitidine treated patients with additional risks for infection (e.g. prior history, age above 50) and/or following HSCT at the discretion of the attending MD,.

3. No routine prophylaxis for inpatient protocols. For outpatient protocols or if discharged with ANC ≤ 0.5 or expecting ANC ≤ 0.5, ciprofloxacin 500 mg PO BID to start when ANC ≤ 0.5 and continue until ANC ≥ 0.5. Modify based on prior infections. Dose adjust for renal dysfunction.
   a. Combination ciprofloxacin **AND** penicillin V 300mg PO QID or Clavulin 875 PO BID when ANC ≤ 0.5 and continue until ANC ≥ 0.5 for outpatient protocols. Modify for penicillin allergy per protocol.
   b. Ciprofloxacin for Cycle 1 only and consider for subsequent cycles only if prolonged neutropenia (> 7 days) documented in Cycle 1.
   c. Routine prophylaxis not recommended. Consider prophylaxis in very severe AA (ANC < 0.2) with additional risks for infection (e.g. prior infections) at the discretion of the attending MD.
   d. Routine prophylaxis not recommended. Risk of infection following therapy with intensive chemotherapy or HSCT may warrant prophylaxis at the discretion of the attending MD.
   e. Refer to ULKAMLAVEN protocol on BC Cancer website for antibiotic prophylaxis, if needed.
4. Refer to the BMT Manual for current management. Modification may be required based on prior infections. If on treatment for invasive fungal infection, continue treatment until complete resolution of infection.
   a. Fluconazole 400 mg PO daily to start when ANC ≤ 0.5 and continue until ANC ≥ 0.5. Dose adjust for renal dysfunction.
   b. Posaconazole tabs 300 mg PO BID x 1 day, then 300 mg PO daily if prolonged neutropenia. Continue until ANC ≥ 0.5. Check trough level after 5-7 days. Complete Pharmacare Special Authority Form.
   c. Routine prophylaxis not recommended. Refer to ULKBLIN (blinatumomab) or ULKINOZ (inotuzumab) protocol. Consider prophylaxis against mold infections in very severe AA (ANC < 0.2) with posaconazole (300 mg PO BID x 1 day, then 300 mg PO daily) or voriconazole (6 mg/kg PO BID x 1 day, then 4 mg/kg PO BID – use adjusted weight for BMI > 30). Check trough level after 5-7 days. Not funded under Pharmacare.
   d. Routine prophylaxis not recommended. Risk of infection following therapy with intensive chemotherapy or HSCT may warrant prophylaxis at the discretion of the attending MD.
5. For acute lymphoblastic leukemia patients only, co-trimoxazole DS 1 tab PO BID every Mon & Thurs to start Day 1. Continue until all chemotherapy completed.
   a. Consider prophylaxis in high-risk patients (e.g. HIV, prior infection, etc.).
   b. Pentamidine 300 mg IV q2 to 3 week for 3 – 6 months. Switch to co-trimoxazole DS 1 tab PO BID every Mon & Thurs when ANC > 1 and platelets > 20. May stop prophylaxis if CD4 > 200 cells/mm^3.
6. Refer to BMT Manual Chapter to determine if antiviral prophylaxis required based on hepatitis B risk, as well as duration of prophylaxis and monitoring.

8-2. Outpatient Antibiotic Prophylaxis for Stem Cell Transplantation

SUMMARY OF RECOMMENDED ANTIMICROBIAL PROPHYLAXIS FOLLOWING CELLULAR THERAPY AND TRANSPLANT‡

Indication	HSV+[1]	Antibiotic[2]	Fungal[3]	VZV+[4]	PJP[5]	CMV[6]	EBV[7]	HBV[8] Risk of HBV reactivation: HbsAg+	HBV[8] Risk of HBV reactivation: HbsAg– and HbcAb+	HAdV[9]	Toxo+[10]
Autograft											
MM, POEMS, amyloidosis	Y	Y	Y	Y	N	N/A	N/A	High	High	N/A	N/A
HD, NHL, AML, GCT	Y	N	Y	Y	Y	N/A	N/A	High	High	N/A	N/A
Allograft											
Myeloablative (No ATG)	Y	N	Y	Y	Y	N	N	High	High	N	Y
Myeloablative (ATG)	Y	N	Y	Y	Y	Y	Y	High	High	N	Y
RIC Related (No ATG)	Y	N	N	Y	Y	Y	N	High	High	N	Y
RIC Mismatched (ATG)	Y	N	Y	Y	Y	Y	Y	High	High	N	Y
RIC PTCY	Y	N	Y	Y	Y	N	Y	High	High	N	Y
Haplo	Y	N	Y	Y	Y	Y	Y	High	High	N	Y
DCBT	Y	N	Y	Y	Y	Y	Y	High	High	Y	Y
GVHD											
Acute, steroid	Y	N	Y[3a]	Y	Y	Y[6a]	Y	High	High	N/A	Y
Acute, steroid-refractory	Y	N	Y[3b]	Y	Y	N	Y	High	High	N/A	Y
Chronic	Y	Y[2b]	Y[3c]	Y	Y	N	Y	High	High	N/A	Y
CAR-T	Y	N[2a]	Y[3d]	Y	Y	N/A	N/A	Very High	Very High	N/A	N/A

1. Valacyclovir 500 mg PO BID to start when ANC ≤ 0.5 or per protocol and continue until ANC ≥ 0.5 or mucositis healed, or until off all immunosuppression (refer to Chapter 19).
2. Ciprofloxacin 500 mg PO BID to start when ANC ≤ 0.5 or per protocol and continue until ANC ≥ 0.5 or mucositis healed for outpatients. Dose adjust for renal dysfunction. Modify based on prior infections. Routine prophylaxis for inpatients not recommended.
   a. Routine prophylaxis not recommended. If discharged to Daycare with ANC ≤ 0.5, give prophylaxis with ciprofloxacin. Consider filgrastim if ANC < 0.5 after day +30.
   b. Penicillin V 300 mg PO BID or Septra DS 1 tab daily for functional asplenia or splenectomy. Refer to Chapter 19. For pulmonary GVHD, azithromycin 250 mg on Mondays, Wednesdays, and Fridays.
3. Refer to the BMT Manual for current management of fungal prophylaxis. Modify based on prior infections. If on treatment for invasive fungal infection (IFI), continue treatment until complete resolution of infection and off immunosuppression.
   a. Fluconazole 400 mg PO daily if steroid dose ≥ 1 mg/kg/day. Dose adjust for renal dysfunction. Continue until prednisone dose < 0.5 mg/kg/day.
   b. Posaconazole tabs 300 mg PO BID x 1 day, then 300 mg PO daily if no severe diarrhea or severe liver dysfunction (Pharmacare Special Authorization required). Continue until prednisone dose < 0.5 mg/kg/day.
   c. If starting prednisone ≥ 1 mg/kg/day, fluconazole 400 mg PO daily OR posaconazole 300 mg PO BID x 1 day, then 300 mg PO daily. Continue until prednisone dose < 0.5 mg/kg/day. Posaconazole preferred for pulmonary GVHD. If prior IFI, secondary prophylaxis is recommended with voriconazole (6 mg/kg PO BID x 1 day, then 4 mg/kg PO BID, adjusted weight if BMI > 30) OR *posaconazole tabs. Pharmacare Special Authorization required. Check trough level after 5-7 days. If GVHD of the mouth on oral topical steroid alone, nystatin 5 mL TID-QID.
   d. Fluconazole 400 mg PO daily and continue until ANC > 0.5. Consider micafungin IV for patients who are on long-term or high-dose corticosteroids or who are post-allograft.
4. Valacyclovir 500 mg PO BID. If HSV-/VZV+ start by day + 28. Continue for 12 months post-HSCT and off all immunosuppression (refer to Chapter 19), or 12 months post CAR-T if CD4 > 200 cell/mm^3 (> 0.2 x 10^9/L).
5. Co-trimoxazole DS 1 tab PO BID every Mon & Thurs to start by day + 28, if ANC > 1 and platelets > 20. Continue for 3 months after autograft, 12 months after CAR-T if CD4 > 200 cells/mm^3 (> 0.2 x 10^9/L), or 12 months after allograft and at least 3 months after stopping all immunosuppression (refer to Chapter 19). If intolerant to co-trimoxazole, consider co-trimoxazole oral challenge or desensitization or substitute with pentamidine, atovaquone or dapsone. If starting dapsone, recommend G6PD level prior to initiating. Co-trimoxazole has additional benefit of activity against Nocardia, Listeria, and Toxoplasma; therefore, consider co-trimoxazole despite platelet count for patients at very high risk (e.g. severe steroid-refractory aGVHD).
6. For CMV recipient positive in high-risk protocols only. Refer to BMT Manual for further management of CMV prophylaxis with letermovir.
   a. For CMV recipient positive AND corticosteroid ≥ 1 mg/kg/day initiated for GVHD prior to day +28. Refer to BMT Manual for further management of CMV prophylaxis with letermovir.
7. EBV PCR weekly monitoring recommended in high-risk protocols only. Refer to BMT Manual for further details on EBV monitoring and current management of reactivation

8. Entecavir 0.5 mg PO daily. Continue for 12 months post-autograft, 18 months post CAR-T, or 12 months after discontinuation of all immunosuppression post-allograft. Pharmacare Special Authority required. Dose adjust for renal dysfunction. Refer to BMT Manual for monitoring during and after antiviral discontinuation.
9. HAdV PCR weekly monitoring recommended in high-risk protocols only. Refer to BMT Manual for current management of Adenovirus reactivation
10. Co-trimoxazole DS 1 tab PO daily (preferred) or SS 1 tab PO daily to start by day +28, if ANC > 1 and platelets > 20. Continue for at least 12 months post-allograft and/or 3 months after stopping all immunosuppression (refer to Chapter 19). For co-trimoxazole intolerance, consider co-trimoxazole oral challenge or desensitization, or atovaquone 1500 mg PO daily. Pharmacare Special Authority required.

‡Refer to the BMT Manual - Management of Infectious Complications sections or Chapter 19 - Discontinuation of Antimicrobial Prophylaxis for more details.

References
1. E. Carreras et al. (eds.), The EBMT Handbook, https://link.springer.com/book/10.1007/978-3-030-02278-5#toc Accessed August 17, 2023
2. Ann Oncol. 2022 Mar;33(3):259-275
3. National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections Version 1.2023. June 28, 2023; https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1457 . Accessed August 17, 2023.
4. Biol Blood Marrow Transplant. 2009 Oct;15(10):1143-238
5. Blood. 2015 Jan 22; 125(4): 606–615
6. Cytotherapy. 2020 Jan;22(1):27-34

LEUKEMIA/BMT MANUAL E-EDITION

CHAPTER 9. DIAGNOSIS & MANAGEMENT OF CATHETER-RELATED BACTEREMIA

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9-1. Diagnosis & Management of Catheter-Related Bacteremia

• Bacteremia or fungemia in a patient who has an intravascular device and >1 positive blood culture obtained from a peripheral vein, clinical manifestations of infection (eg: fever, chills and/or hypotension) and no apparent source for bloodstream infection (with exception of the catheter)[1]	• Erythema, induration and/or tenderness within 2 cm of catheter exit site; may be associated with other signs and symptoms of infection, such as fever or purulent drainage emerging from the exit site[1] • Exudate at catheter exit site yields a micro-organism • May or may not involve concomitant bloodstream infection	• Tenderness, erythema and/or induration > 2 cm from the catheter exit site, along the subcutaneous tract of the tunneled catheter[1] • May or may not involve concomitant bloodstream infection
↓	↓	↓
Catheter-Related Bacteremia	**Exit-Site Infection**	**Tunnel Infection**
↓	↓	↓
• Before culture results are known, the decision to pull out the IV catheter and initiate empiric antibiotic therapy is based on the severity of the patient's acute illness, underlying disease and potential pathogens involved[1]. • See Chapter 10. Antifungal Therapy for management.	• Uncomplicated exit site infections (ie: no systemic signs of infection, positive blood cultures or purulence) may be initially managed with topical antibiotics (eg: mupirocin ointment for *S. aureus*).[1] • If it fails to resolve or purulent drainage present, treat with systemic antibiotics. [1,2] • Catheter removal usually not necessary.	• Patients with tunnel infection require removal of the catheter, incision and drainage if indicated, and 7-10 days of antibiotic therapy in the absence of concomitant bacteremia or candidemia.[1]
Considerations: These recommendations were developed based on the current literature. They represent our standard practice, but can be individualized depending on the clinical situation. In a complicated infections such as patients with septic thrombosis, endocarditis, remove Hickman® line and treat with antibiotics for 4–6 weeks; 6–8 weeks for osteomyelitis. In a neutropenic patient, wounds may not have the typical erythema or purulence.		

Staphylococcus aureus[1]	**Coagulase-negative staphylococcus**[1]	**Gram-negative bacilli**[1]	**Candida**[1] **spp.**
• Remove Hickman® line catheter • TTE* should be performed to rule out endocarditis. If short course therapy is being considered, TEE** should be done, ideally 5-7 days after onset of bacteremia to minimize false-negative results. • Treat with antibiotics for 4-6 weeks. A minimum of 14 days can be considered if patient is not immunosuppressed/neutropenic, does not have hardware (e.g. a pacemaker), a TEE is negative and fever & bacteremia have resolved within 72h of antibiotic initiation • If methicillin-susceptible, use cloxacillin 2 g IV q4h • If methicillin-resistant, use Vancomycin, aiming for trough levels of 15-20 mg/L.	• May retain Hickman® catheter • Treat with antibiotics for 5-7 days if catheter is removed, 10–14 days if catheter is retained. • If clinical deterioration, persisting/ relapsing bacteremia, remove Hickman® catheter. Longer courses of antibiotics will be required depending on metastatic spread. **Enterococcus**[1] • May retain Hickman® catheter • Treat with antibiotics for 7-14 days • If clinical deterioration, persisting/ relapsing bacteremia, remove Hickman® catheter and perform TTE. Longer courses of antibiotics will be required depending on metastatic spread.	• **Uncomplicated:** May retain Hickman® catheter and treat with antibiotics for 10–14 days • **Complicated (eg: hypotension):** Remove Hickman® catheter and treat with antibiotics for 10–14 days. Consider commencing meropenem +/- tobramycin due to the increasing incidence of ESBL gram-negative bacilli. • Catheter-related infections due to the following always require removal of the catheter: *Pseudomonas spp; Burkholderia spp.; Acinetobacter baumannii complex; Stenotrophomonas spp;*	• Remove Hickman® catheter • Treat with antifungal therapy for 14 days after the first negative blood culture • All patients require a dilated ophthalmological examination. In neutropenic patients, this should be done or repeated after count recovery as signs of inflammation are obscured by the low neutrophil count.

1. Antibiotic infusions should be rotated among all ports of the Hickman® catheter when left in place.[2]
2. When denoting duration of antimicrobial therapy, day 1 is the first day on which negative blood culture results are obtained.[1]
3. No data support specific recommendations regarding the duration of the therapy for catheter-related infections.
4. Re-insertion of Hickman® catheters should be postponed until after systemic antibiotics are completed, or at least until repeat cultures of blood samples are negative.

* TTE: Transthoracic echocardiogram **TEE: Transesophageal echocardiogram

References:
1. Memel LA, Allon M, Bouza E, et al. Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infections. CID 2009; 49:1-45.
2. NCCN Proceedings. NCCN Prevention and Treatment of Cancer-Related Infections. V.2.2009.
3. Gilbert DN, Moellering RC, Eliopoulos G, et al. The Sanford Guide to Antimicrobial Therapy, 39th Ed, Antimicrobial Therapy Inc.: Hyde Park, 2009.
4. Dugdale DC, Ramsey P. Staphylococcus aureus bacteremia in patients with Hickman® catheters. Am J Med 1990; 89:: 137-41.

CHAPTER 10. ANTIFUNGAL THERAPY

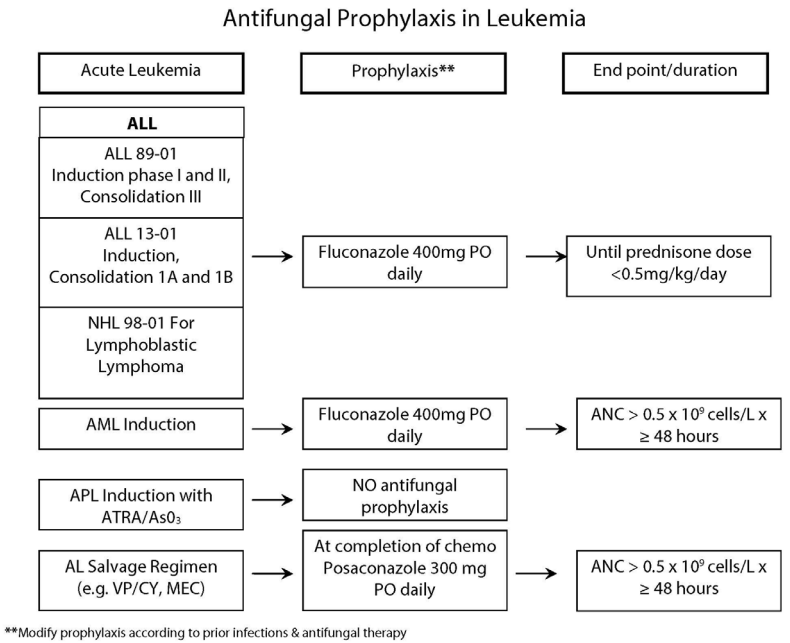
10-1. Prophylaxis and Diagnosis of Invasive Fungal Infection

Serial audits of invasive fungal infection (IFI) have been carried out in the Leukemia and BMT Program. The baseline incidence of IFI is in the order of 20% for both AML and ALL therapy with invasive aspergillus accounting for 85% of these cases. The majority of cases occurred during induction chemotherapy. There is also a high incidence of these infections in patients who have refractory disease.

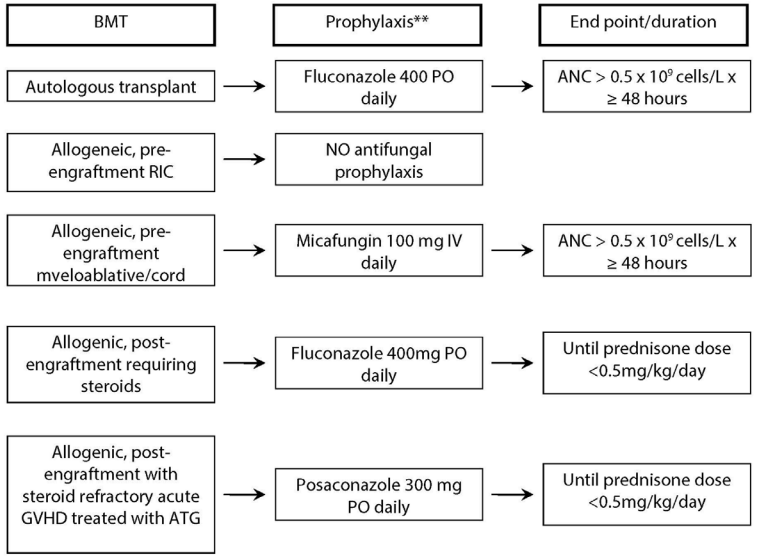
For allogeneic transplant patients the incidence is also in the range of 20% with infections occurring during neutropenia or when on high dose steroids for graft versus host disease. Autologous transplant patients have a very low incidence of IFI at 2%.

Serial prophylactic strategies using mold active agents have failed to reduce the proportion of patients who need to undergo therapy for IFI, prompting a change back to fluconazole prophylaxis for most protocols and a change in emphasis from prophylaxis to early detection and treatment of IFI.

The following outlines our prophylaxis strategy:



Antifungal Prophylaxis in BMT



**Modify prophylaxis according to prior infections & antifungal therapy

Galactomannan Screening in the Diagnosis of Invasive Aspergillus Infection

Routine serum galactomannan antigen screening is NOT performed at VGH.

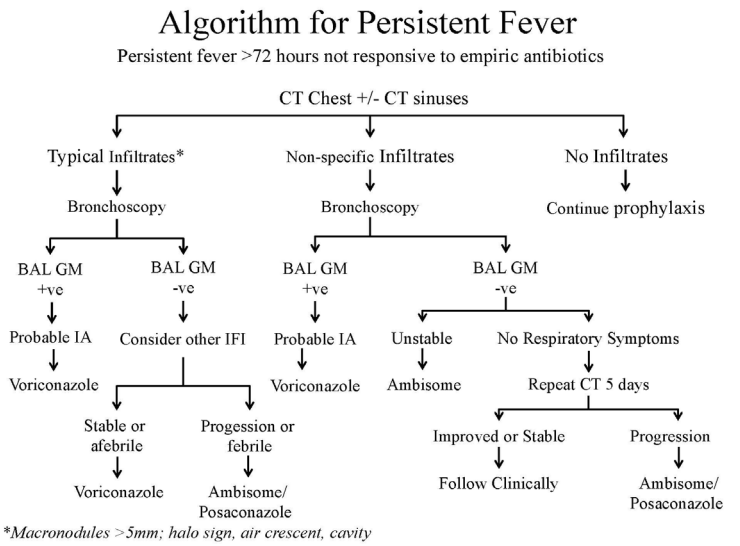
Galactomannan as an adjunct to diagnosis in patients with suspected invasive aspergillosis:

For patients with suspected invasive aspergillus infection on CT scan of chest, a bronchoscopy should still be arranged within 24-48 hours with a BAL sample sent for galactomannan antigen. The specimen to be taken is 10-15 ml of BAL fluid.

As this test is not available to other programs throughout the hospital, we (Leukemia/BMT physicians) need to write the order for the BAL galactomannan antigen on BAL specimen noting “BMT patient” on the requisition. These samples will be sent to an outside laboratory for analysis.

It should be noted that bronchoscopy was shown to give a diagnosis in 30% of L/BMT patients PRIOR to the availability of BAL GM testing. Other diagnoses such as viral or bacterial infection may be made.

10-2. Algorithm for the Management of Persistent Fever



Algorithm for Persistent Fever

- Please note that if the BAL is positive for a bacterial infection (eg staphylococcus aureus) which could explain the CT chest findings, then antifungal therapy should not be continued and CT should be repeated to ensure response to antimicrobial therapy.
- BAL should be performed as soon as possible, target within 24 hours of commencement of empiric anti-mold agents. In a stable patient, it is appropriate to delay the commencement of antifungal agents pending completion of the bronchoscopy.
- Repeat CT in all patients with infiltrates and negative GM after two weeks. If CT is now normal, discontinue antifungal therapy.

If there is a reason for a patient to get a lung biopsy via ultrasound-guided bronchoscopy over a bronchoalveolar lavage, the BMT service should contact either Dr. Renelle Myers or Dr. Eve-Lea Beaudoin directly to arrange this procedure. Lesions need to be relatively central in order for this to be effective.

Reasons for such a biopsy may include:

- progression of nodules on antifungal therapy
- atypical presentations where mucormycosis or cancer (lung ca., pulmonary lymphoma) are higher on the differential
- at the recommendation of Transplant Infectious Disease

10-3. Treatment Protocol for Probable/Proven Candida Infection

An echinocandin (micafungin 100 mg IV daily) is recommended as initial therapy in most scenarios provided the patient has not been on this for antifungal prophylaxis when the fungemia developed. Fluconazole is an acceptable alternative in patients who meet **all** of the following criteria: they are not neutropenic; they are hemodynamically stable; they have had no previous exposure to azoles; and they are not considered at high risk for echinocandin resistant infection. In all other patients, liposomal amphotericin 3-5 mg/kg IV daily is the preferred alternative with certain clinical scenarios requiring the addition of flucytosine (e.g. endocarditis, CNS infection).

1. Echinocandins may not be the drug of first choice in the following scenarios:
   - Endophthalmitis
   - Endocarditis
   - CNS infections
   - Candiduria
   - C. parapsilosis fungemia (classically occurs on echinocandin prophylaxis/treatment)

   Consider consulting Transplant ID for complicated cases of candidiasis.
2. A dilated ophthalmologic exam recommended on all patients with proven IC. In neutropenic patients, this should be done or repeated after count recovery as signs of inflammation are obscured by the low neutrophil count.
3. Intravenous catheter removal is strongly recommended.
4. Start antifungal agent within 24 hours of positive culture.
5. Repeat blood cultures to make sure organism is cleared.
6. Transition to PO azole when species identified and sensitivities known. Limit PO voriconazole to fluconazole-resistant cases (e.g., C. krusei).
7. Duration of therapy:
   - Candidemia: 2 weeks after last positive culture and resolution of signs and symptoms of disease.
   - Disseminated candidiasis: not studied. Consult Transplant ID for complicated cases of candidiasis.
8. Consider adding G-CSF if patient neutropenic.

10-4. Invasive Aspergillosis EORTC Criteria for Diagnosis and Treatment

Proven **Invasive Aspergillosis**

Histopathologic, cytopathologic or direct microscopic examination revealing hyphae with accompanying tissue damage from needle aspiration or biopsy, and/or positive culture result from normally sterile site by invasive procedure (e.g., percutaneous needle aspiration), and clinically or radiologically abnormal site consistent with infection excluding urine, bronchoalveolar lavage and sinus cavity infection.

Probable **Invasive Aspergillosis**

At least one host factor, one mycological criterion and one clinical criterion (see below) from abnormal site consistent with infection.

Possible **Invasive Aspergillosis**

At least one host factor, one clinical criterion (see below) from abnormal site consistent with infection.

Note: These definitions are not limited to Aspergillus alone. A blood culture yielding a mold (e.g. fusarium species) is consistent with proven invasive fungal disease while a sinus swab yielding a mold (e.g. Rhizopus) in a neutropenic host with CT head suggestive of bone invasion is consistent with probable invasive fungal disease, respectively.

Criteria

1. Host Factors
   - Neutropenia (< 500 n/mm2 for > 10 days)
   - Allogeneic stem cell transplant
   - Treatment with cyclosporine/tacrolimus, alemtuzumab, or nucleoside analogues in the previous 90 days
   - Prolonged use (> 21 days) of > 0.3 mg/kg/day equivalent of prednisone
   - Inherited severe immune deficiency
2. Mycologic Criteria
   - Direct test: Positive results of culture of cytologic/direct microscopic evaluation for Aspergillus spp. from sputum, BAL, bronchial brushing or sinus aspirate
   - Indirect test: Positive result for Aspergillus antigen (GMA) in specimens of BAL, CSF or blood samples
3. Clinical Criteria
   - CT chest imaging; any one of the following: dense well circumscribed lesion(s) with or without halo sign, air-crescent sign, or cavity
   - Tracheobronchial ulceration, nodule, pseudomembrane, plaque or eschar on bronchoscopy
   - Radiological evidence suggesting CNS infection including one of the following: focal lesions on imaging or meningeal enhancement on MRI or CT
   - Radiological evidence of sinusitis with one of the following clinical signs: acute localized pain, nasal ulcer with black eschar or extension from paranasal sinus into orbit.

Modified from revised definitions of invasive fungal disease from the EORTC/MSG consensus group. CID 2008, 46:1813–21

10-5. Treatment and Follow-up of Invasive Aspergillosis

Voriconazole is the first line agent of choice for therapy of invasive aspergillosis. Liposomal amphotericin and posaconazole are second line agents which can be used if there is intolerance or progression on voriconazole.

Monitoring response to treatment:

If a patient with "typical infiltrates *" (see footnote) has clinically improved on therapy, a repeated CT scan should be performed in 4 weeks to reassess.

- If there is clinical progression (e.g. persistent fever, ongoing hemoptysis), an earlier CT scan is recommended. It should be noted however that CT scans performed at the time of count recovery can be misinterpreted as showing progression as the lesions of invasive aspergillus will enlarge during this phase even when the disease is responding to therapy.

- Patients who have nonspecific infiltrates should have a CT scan performed at 2 weeks to assess for resolution of CT changes as this would be suggestive of a cause other than invasive fungal infection and antifungal therapy could therefore be discontinued.

All patients who are commenced on antifungal therapy for a suspected IFI should be referred to Dr Alissa Wright in the Transplant ID clinic for an assessment and follow up.

*Macronodules>5mm; halo sign, air crescent, cavity

10-6. Treatment Protocol for Emerging Fungal Infections

There are a number of more unusual fungi that can occur in this patient population. The following are recommended empiric choices.

1. Fusarium –Liposomal amphotericin 3-5 mg/kg IV daily is considered first line. Voriconazole or posaconazole are possible alternatives. Susceptibility can vary between species so consider combination therapy pending full identification. Surgical consult for debridement and/or any reversal of immunosuppression/recovery from neutropenia should be strongly considered.

2. Zygomycetes/Mucormycosis – liposomal amphotericin 5 mg/kg IV daily is preferred. Surgical consult for debridement (if possible) is strongly recommended along with any reversal of immunosuppression/recovery from neutropenia.

3. Cryptococcus – liposomal amphotericin 3-4 mg/kg IV daily + flucytosine 100 mg/kg/day orally in four divided doses is first line therapy. Flucytosine doses should be adjusted for renal function.

Consider consulting Transplant ID for complicated or unusual cases of invasive fungal disease.

10-7. Therapeutic Drug Monitoring of Voriconazole

Voriconazole is a reasonable candidate for therapeutic drug monitoring for the following reasons: it possesses nonlinear saturable metabolism, numerous drug-drug interactions, and wide inter- and intra-patient variability. Furthermore, evidence has supported serum voriconazole concentrations to both its efficacy and toxicity.

A serum tough level is typically ordered at least 5 days after starting therapy to ensure steady state. Results are posted in PCIS on Wednesday.

If a patient is being treated for an invasive fungal infection, weekly monitoring should be done to document therapeutic levels 2 weeks in a row. Thereafter, monitoring can be repeated as clinically indicated.

Below is the suggested Voriconazole Dosage Adjustment Algorithm

Voriconazole Dosage Adjustment Algorithm (Therapeutic Range 1-5.5mg/L)	
Undetectable (<0.3mg/L)	Increase dosage by 25% Repeat level in one week
Well below therapeutic range	Check for accuracy If accurate, increase dosage by 25% Repeat level in one week
Borderline therapeutic	No change in dose Repeat level in one week If still borderline therapeutic, consider dosage adjustment
Therapeutic	No change
Toxic	Hold if symptoms of toxicity Decrease dose by 25% Repeat level in one week

If patient is to be discharged on voriconazole, obtain Special Authority approval from Pharmacare. Pharmacare has been approving voriconazole treatment for 3 months.

10-8. Therapeutic Drug Monitoring of Posaconazole

Posaconazole is currently available on formulary as an oral suspension or delayed release tablet. The oral suspension exhibits highly variable absorption and bioavailability, which is improved with the delayed release tablet. However, both formulations can display large inter and intra-patient variability in pharmacokinetics (1), suggesting that therapeutic drug monitoring for posaconazole be considered. The tablet and oral suspension formulations of posaconazole are not interchangeable due to different dosing and pharmacokinetics.

A serum trough level is typically ordered after at least 7 days of therapy and is processed by St. Paul's Hospital laboratory every Wednesday. For a result to be reported within the same week, the latest time to draw a sample would be Tuesday morning, for arrival at St. Paul's Hospital laboratory by Tuesday afternoon.

The therapeutic range for posaconazole is not clearly established, but studies have suggested trough levels greater than 700 ug/L are effective for prophylaxis (1–3), with higher targets of greater than 1000-1250 ug/L associated with better response for active treatment (1,3,4). Studies have not identified strong correlations between posaconazole levels and toxicity (1,3).

When used for prophylaxis, at least a single level should be documented within target. In the case of active treatment, weekly monitoring should be done until therapeutic levels are documented for 2 consecutive weeks. Thereafter monitoring can be repeated as clinically indicated.

If a patient is to be discharged on posaconazole, Special Authority approval may be obtained from Pharmacare for patients who do not have coverage through private insurance. Pharmacare will likely decline coverage for patients who have assistance with private insurance. For patients who require financial assistance, a referral to the Merck Care Oncology Program for consideration of reimbursement may be made. To enrol a patient, call 1-877-494-0454 or contact a BMT Pharmacist for an enrolment form.

1. Dekkers BGJ, Bakker M, van der Elst KCM, et al. Therapeutic Drug Monitoring of Posaconazole: an Update. Curr Fungal Infect Rep [Internet]. Current Fungal Infection Reports; 2016;10(2):51–61. Available from: http://dx.doi.org/10.1007/s12281-016-0255-4

2. Jang SH, Colangelo PM, Gobburu JVS. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. Clin Pharmacol Ther [Internet]. Nature Publishing Group; 2010;88(1):115–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20505665%5Cnhttp://doi.wiley.com/10.1038/clpt.2010.64

3. Ashbee HR, Barnes RA, Johnson EM, et al. Therapeutic drug monitoring (TDM) of antifungal agents: Guidelines from the british society for medical mycology. J Antimicrob Chemother. 2014;69(5):1162–76.

4. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis [Internet]. 2007;44(1):2–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17143808

10-9. Comparison of Antifungal Agents

Table 1. Activities of antifungal agents common fungal pathogens

Organism	Amphotericin B	Echinocandins	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Aspergillus						
A. flavus	±	+	-	+	+	+
A. fumigatus	+	+	-	+	+	+
A. niger	+	+	-	±	+	+
A. terreus	-	+	-	+	+	+
Candida						
C. albicans	+	+	+	+	+	+
C. glabrata	+	+	±[1]	±	+[2]	+[2]
C. guilliermondi	+[1]	+[3]	+	+	+	+
C. krusei	+	+	-	±	+[4]	+[4]
C. lusitaniae	-	+	+	+	+	+
C. parapsilosis	+	±[3]	+	±[2]	+	+
C. tropicalis	+	+	+	+	+	+
Dimorphic Fungi						
Blastomyces	+	-	+[2]	+	+[4]	+[4]
Coccidioides sp.	+	-	+	+	+[4]	+[4]
Histoplasma sp.	+	-	+[2]	+	+[4]	+[4]

Comparison of Antifungal Agents (cont.)

Table 1. Activities of antifungal agents common fungal pathogens (cont.)

Organism	Amphotericin B	Echinocandins	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Other						
Cryptococcus neoformans	+	-	+	+	+	+
Fusarium sp.	+	-	-	-	+[4]	+[4]
Scedosporium apiospermum	±	-	-	±	+	+
Scedosporium prolificans	±	-	-	-	±	±
Zygomycetes	±	-	-	-	-	+

1 Susceptible with dose escalation.
2 3rd line therapy; least clinical activity.
3 Higher MIC
4 2nd line therapy; less clinical activity

Table 2. Antifungal agents dosing, side effects and drug interactions

	Amphotericin B liposomal (Ambisome®)	Fluconazole (Diflucan®)	Voriconazole (VFEND®)	Posaconazole (Posanol®)	Micafungin (Micamine®)
Dosage	3 mg/kg/d IV (febrile neutropenia) 5 mg/kg/d IV (treatment) 7.5 – 10 mg/kg/d IV (*Zycomycoses* treatment)	400 mg/d IV/PO (febrile neutropenia) 400–800 mg/d IV/PO (candidiasis) 150 mg x 1 dose PO (vaginitis) 100 mg/d (thrush) PO	6 mg/kg IV/PO q12h load x 24h then 4 mg/kg IV/PO BID Manufacturer dose recommendations for weight: Pt ≥ 40 kg: 400 mg PO BID x 2 doses then 200 mg PO BID Pt < 40 kg: 200 mg PO BID x 2 doses then 100 mg PO BID	Delayed Release Tablet: 300 mg PO BID x 2 doses, then 300 mg PO daily (prophylaxis or treatment) Suspension: 200 mg (5mL) PO TID (prophylaxis) 400mg (10mL) PO BID (treatment) **Suspension must be taken with a meal or nutritional supplement**	100 mg IV daily (L/BMT Program prophylaxis and *Candida* treatment)
Renal Impairment	No dose adjustments provided by the manufacturer Consider dose adjustment if renal function declines on therapy to a CrCl < 30 mL/min	Refer to Pharmaceutical Sciences Formulary, prescribing tools section	*Do not use IV in pts with CrCl < 50 ml/min b/c of IV vehicle (cyclodex- trin accumulation)* No adjustment for PO for renal insufficiency	No dosage adjustment for renal insufficiency	No dosage adjustment for renal insufficiency
Hepatic Impairment	No dosage adjustment for hepatic insufficiency	Elimination half- life not affected by impaired hepatic function, but can increase LF Ts – monitor for worsening liver dysfunction & consider benefit / risk	Mild–moderate impairment (Child-Pugh A & B), give standard loading dose & ½ the maintenance dose – not studied in severe hepatic impairment	Use with caution in severe hepatic impairment	No dosage adjustment for mild-moderate impairment. No data in severe impairment.

Table 2. Antifungal agents dosing, side effects and drug interactions (cont.)

	Amphotericin B liposomal (Ambisome®)	Fluconazole (Diflucan®)	Voriconazole (Vfend®)	Posaconazole (Posanol®)	Micafungin (Micamine®)
Adverse Effects	Fever, chills, rigors, nausea, vomiting, hypotension, hypokalemia, hypomagnesemia, nephrotoxicity	Headache (13%) Nausea (7%) Abdominal pain (6%) Hepatitis, ↑ ALP, ALT & AST QT prolongation & torsade de pointes	Visual disturbances (19%) Hallucination (12% - auditory and/or visual and likely serum concentration-dependent Rash (6%) ↑ ALP, ALT , AST & hyperbilirubinemia (19%) QT prolongation & torsade de pointes	Headache (6%), nausea (6%), mild diarrhea, hyperbilirubinemia (up to 10%), ↑ ALP, ALT & AST (up to 17%) QT prolongation & torsade de pointes	Well tolerated Most common ADR's in <5% include: headache, nausea, vomiting, rash, fever, diarrhea, histamine-mediated symptoms; also ↑ LFT's
Contra-indications	Known hypersensitivity	Caution with QT prolongation, torsade de pointes, hepatic dysfunction Contraindicated in patients receiving drugs that are known to prolong QT and are also metabolized by CY3A4 (e.g. erythromycin, citalopram, pimozide, etc)	Caution with QT prolongation, torsade de pointes, hepatic dysfunction Contraindicated with pimozide, quinidine, rifampin, carbamazepine, sirolimus, rifabutin, ritonavir, efavirenz, ergot alkaloids, long-acting barbiturates, and St. John's Wart	Caution with QT prolongation, torsade de pointes, hepatic dysfunction Contraindicated with ergot alkaloids, terfenadine, astemizole, cisapride, pimozide, quinidine, statins metabolized primarily through CY3A4 (e.g. simvastatin, atorvastatin, etc) and sirolimus	Known hypersensitivity

Table 2. Antifungal agents dosing, side effects and drug interactions (cont.)

	Amphotericin B liposomal (Ambisome®)	Fluconazole (Diflucan®)	Voriconazole (VFEND®)	Posaconazole (Posanol®)	Micafungin (**Micamine** ®)
Drug Interactions*	Caution with other renal toxic drugs or drugs that may be affected by hypokalemia	Mild/moderate inhibitor of CYP3A4, moderate inhibitor of CYP2C9, strong inhibitor of 2C19 May increase risk of toxicity of phenytoin, warfarin, NSAIDs, oral hypoglycemics, cyclosporine, sirolimus, calcium channel blockers, statins, TKIs, etc. Use with caution with ATRA Limit fluconazole to 200 mg/d with ruxolitinib, Reduce ibrutinib to 140 mg/d when treating B-cell malignancies, when treating GVHD monitor & dose adjust based on adverse events if needed.	Moderate inhibitor of CYP2C19, CYP2C9, strong inhibitor of CYP3A4 Drugs whose use requires dose ↓ and/or monitoring include tacrolimus (↓ dose by 2/3), cyclosporine (↓ dose by ½), methadone, oxycodone, calcium channel blockers, omeprazole, statins, benzodiazepines, phenytoin, vinca alkaloids (vincristine), cyclophos-phamide, busulfan, etoposide, warfarin, sulfonylureas, HIV protease inhibitors, NNRTIs,TKIs, etc. Use with caution with ATRA Reduce ruxolitinib by 50% Reduce ibrutinib to 140 mg/d when treating B-cell malignancies, when treating GVHD reduce to 280 mg/d	Strong inhibitor of CYP3A4 Concomitant use should be avoided with cimetidine, rifabutin, rifampicin, efavirenz, and phenytoin. Drugs whose use requires dose↓ and/or close monitoring include CSA (↓ dose by 1/4), tacrolimus (↓ dose by 2/3) , calcium channel blockers, atazanavir, ritonavir, vinca alkaloids (vincristine), midazolam, digoxin, statins, TKIs, etc Less well absorbed with PPI or H2 antagonist (suspension formulation only) Use with caution with ATRA Reduce ruxolitinib by 50% Reduce ibrutinib to 140 mg/d when treating B-cell malignancies, when treating GVHD reduce to 280 mg/d	Micafungin may ↑ AUC of nifedipine and sirolimus.

*The drug interactions provided in this table are not inclusive. Refer to the antifungal product monograph or that of the interacting medication for more on monitoring and/or dose adjustments.

CHAPTER 11. VIRAL INFECTIONS

11-1 HSV Prophylaxis

HSV infections are common after chemotherapy, stem cell transplantation (SCT), or CAR-T therapy. The incidence of HSV infections in seropositive patients who do not receive prophylaxis is approximately 50%. Oral HSV infections in immunocompromised patients are often severe and associated with significant morbidity, and may be sites of potential secondary bacterial and fungal infections. HSV prophylaxis reduces this incidence to less than 10%.

Eligibility

Patients who are HSV IgG seropositive and receiving chemotherapy, SCT, or CAR-T therapy should receive HSV prophylaxis. For SCT and CAR-T therapy, prophylaxis should start on day +1 or as indicated in the PowerPlan. For LK protocols, prophylaxis should begin the day after the last chemotherapy dose or at the start of neutropenia as indicated in the PowerPlan. Prophylaxis should continue until engraftment/recovery of blood counts or resolution of mucositis, whichever is longer; most patients require HSV prophylaxis for about 30 days or longer if history of frequency recurrences of HSV.

Antiviral Prophylaxis

Preferred Medication	CrCl (ml/min)	Dosing Interval (hr)
Valacyclovir 500 mg PO	> 30	12
Valacyclovir 500 mg PO	< 30	24
Alternative Medication*	**CrCl (ml/min)**	**Dosing Interval (hr)**
Acyclovir 5 mg/kg IV	> 30	12
Acyclovir 5 mg/kg IV	30–10	24
Acyclovir 2.5 mg/kg IV	< 10	24

*Use ideal body weight for obese patients (BMI ≥ 30 kg/m2)

11-2 VZV Prophylaxis

Varicella zoster virus ("chicken pox") is a common childhood infection. By age 15 over 90% of North American adults have acquired natural immunity to the virus. Universal childhood vaccination has been available in BC since 2004; it is unclear how this will alter the disease course once these individuals reach adult age. Patients who are VZV seropositive prior to stem cell transplant have a risk of reactivation post-transplant. This is highest in the first year with an incidence of 20-25% in those who are only given short course HSV prophylaxis. Patients who are VZV seronegative are at high risk of disseminated disease and death if exposed post-transplantation. All patients being considered for SCT have varicella serology performed as part of their routine pre-transplant serological testing; this helps in decision making around prophylaxis and if exposure occurs.

At VGH, an internal audit of arsenic therapy for newly diagnosed APL, showed 45% of patients developed shingles early in treatment. As a result, prophylaxis is included in arsenic protocols.

Pre-Transplant Prophylaxis

In most cases, it will not be possible to vaccinate patients who are about to undergo SCT as they will be immunosuppressed enough by disease or therapy to raise concerns about dissemination of the attenuated virus. As part of pre-transplant discussions with patients; however, it should be suggested that household contacts who have not clearly had chicken pox should be vaccinated. There is little evidence to suggest that recently vaccinated individuals can transmit the virus to immunocompromised patients, although those who develop a varicella-like rash should avoid physical contact with the patient until the lesions clear.

Post-Transplant Prophylaxis

Patients who are VZV IgG seropositive and receiving arsenic chemotherapy, SCT or CAR-T therapy should receive VZV prophylaxis. Arsenic patients should start prophylaxis on day 1 of treatment and continue for 4 weeks after stopping arsenic. For SCT and CAR-T therapy, prophylaxis should be started before day +28 and given for one year. Prophylaxis may be extended in allogeneic transplant patients who have cGVHD or a continuing need for immunosuppression beyond one year.

Antiviral prophylaxis

Preferred Medication	CrCl (ml/min)	Dosing Interval (hr)
Valacyclovir 500 mg PO	> 30	12
Valacyclovir 500 mg PO	< 30	24

Alternative Medication*	CrCl (ml/min)	Dosing Interval (hr)
Acyclovir 5 mg/kg IV	> 30	12
Acyclovir 5 mg/kg IV	30–10	24
Acyclovir 2.5 mg/kg IV	< 10	24

*Use ideal body weight for obese patients (BMI ≥ 30 kg/m2)

Post-Transplant Exposure

It is difficult to cover each and every eventuality regarding post-transplant exposure and some judgment will need to be used in many cases. In general, patients who were VZV serologically reactive prior to SCT will likely have retained enough immunity that they are at lower risk of disseminated Varicella, but patients who were VZV non-reactive are at high risk and should be given prophylaxis and treated more aggressively.

The following guidelines are suggestions for prophylaxis for most patients; if there are significant questions or concerns about individual patients, the Infection Prevention & Control Service, Transplant ID, the Epidemiology Service at BCCDC or the Vancouver/Richmond Health Board Communicable Disease Control office may prove invaluable resources.

Household contacts of post-SCT patients who have probable contact with VZV and who do not have a clear history of chicken pox should be urgently vaccinated with the VZV vaccine; Household contacts who have a clear history of VZV or who have been vaccinated are unlikely to transmit the virus to the patient, and no prophylaxis is necessary in this case; Post-SCT patients who have definite contact with persons who have active chicken pox or physical contact with an individual with shingles, should receive Varicella Zoster Immune Globulin (VZIG) as soon as contact is documented (ideally within 96 hours). Contact with chicken pox is defined as sharing the same air space.

Patients who are exposed to persons with shingles should avoid physical contact with that person and his/her clothing until the lesions are clearly regressing. Patients in whom the likelihood of exposure is high, or who are known to be non-immune regardless of the likelihood of infection should receive Varicella Zoster Immune Globulin (VZIG) within 96 hours of exposure. The dose of VZIG is 625 units (5 vials) given by deep IM injection for patients weighing more than 40 kg (for doses for smaller individuals, consult the product monograph available from the Blood Transfusion Service). VZIG is obtained by calling Blood Transfusion Services (local 62466) who will order it from Canadian Blood Services; this can be done 24 hours per day.

11-3 HSV/VZV Treatment in the Immunocompromised Host

Type of Infection	Drug, Route & Dosage*§
Herpes Simplex (HSV)	Acyclovir 5 mg/kg IV q8h x 7 days Valacyclovir 1 g PO BID x 7–10 days
Herpes zoster (VZV)	Acyclovir 10 mg/kg IV q8h x 7–14 days (mod–severe) Valacyclovir 1 g PO TID x 7 days
Chicken pox (VZV)	Acyclovir 10 mg/kg IV q8h x 7–10 days
Herpes encephalitis (HSV)	Acyclovir 10–15 mg/kg IV q8h x 14–21 days

*Use ideal body weight for obese patients (BMI ≥ 30 kg/m2)
§See table on next page for dosage adjustment for renal dysfunction

Treatment of Primary Varicella

Any post-SCT patient who develops primary varicella must be hospitalized, placed in strict respiratory isolation, and treated with intravenous acyclovir until clearly resolving (dosage guidelines as above). At that time, valacyclovir may be commenced to complete the course.

Treatment of Herpes Zoster

Patients with skin lesions suspicious for herpes zoster should keep the lesions covered and be isolated when in hospital. Treatment should be started immediately. For mild cases (e.g., thoracic lesions), oral medications may be used. For moderate/severe cases, and those with cranial nerve involvement, intravenous acyclovir should be used.

11-4 HSV/VZV Treatment Dosage Adjustment in Renal Dysfunction

Table 1. Valacyclovir

Usual Dosage Regimen	Creatinine Clearance (ml/min)	Adjusted Dosage Regimen
Valacyclovir 1 g PO BID	> 30 10-29 < 10	No adjustment 1 g Q24H 500 mg Q24H
Valacyclovir 1 g PO TID	> 30 10-29 < 10	No adjustment 1 g Q12H 500 mg Q24H

Table 2. Acyclovir (IV dosing)

Creatinine Clearance (ml/min)	% of Recommended Dose	Dosing Interval (hrs)
> 50	100%	8
30–50	100%	12
10–29	100%	24
< 10	50%	24

References:

Antibiotic, Oral – Adjusting to Estimated Creatinine Clearance, Vancouver Acute Pharmaceutical Sciences Prescribing Tools. Available from: https://www.vhpharmsci.com/prescribing-tools. Accessed June 2023.

Antibiotic, Parenteral – Adjusting to Estimated Creatinine Clearance, Vancouver Acute Pharmaceutical Sciences Prescribing Tools. https://www.vhpharmsci.com/prescribing-tools. Accessed June 2023.

Balfour HH. Antiviral Drugs N Engl J Med 1999; 340(16): 1255–1268.

The Sanford Guide to Antimicrobial Therapy 2020.

Hudson (OH): Lexicomp Inc.: 2021 [updated 7/3/21]. Available from: https://online.lexi.com/lco/action/home. Accessed June 2023.

11-5 CMV Infection Post Transplant

Background

Cytomegalovirus infection is a common complication of allogeneic stem cell transplantation. Reactivation of CMV occurs in approximately 80% of patients who are seropositive before transplantation; about 1/3 of seronegative patients with seropositive donors develop primary CMV infection. Before the introduction of specific prophylaxis, the risk for CMV disease was reported to be 20–35% in seropositive recipients. CMV can cause multi-organ disease after SCT, including pneumonia, gastroenteritis, hepatitis, retinitis and encephalitis. Pneumonia and gastrointestinal disease are the most common manifestations. Previously, the peak incidence of CMV disease occurred between days 45–60 post SCT; however, with current prevention strategies, CMV disease is more frequently diagnosed after day +100.

Transplant Donor Considerations

CMV seronegative patients should (if possible) be transplanted from a CMV negative donor. If only a CMV seropositive donor is available, the risk for CMV transmission by the marrow product to the recipient is approximately 30%.

Risk Factors for CMV Reactivation

The risk of post-transplant CMV infection or disease is significantly influenced by both donor and recipient CMV serostatus. Serostatus is used to help determine the appropriate prophylaxis or pre-emptive strategy. The lowest risk of post-transplant CMV is in CMV-seronegative recipients given grafts from CMV-seronegative donors. Recipients who are CMV-seropositive have the greatest risk of CMV disease (any R+ > R-/D+ > R-/D-). This is especially the case when given grafts from CMV-seronegative donors due to lack of donor-transferred CMV-specific immunity during host reactivation of endogenous latent CMV.

Other risk factors include GVHD and steroid use (esp. >1 mg/kg/day), T-cell depletion (e.g. ATG conditioning or therapy for GVHD) and allograft type (mismatched related or unrelated donors, haploidentical transplants, and cord blood transplants).

Patients can be stratified into high or low risk for CMV reactivation/disease. The highest risk groups should be offered prophylaxis. Patients who are low risk (e.g. any R-, no ATG or high dose steroids, and matched related or unrelated donors) should continue surveillance without therapy.

Pre-emptive therapy initiation should always consider both the patient's risk for CMV progression and their risk of toxicity from therapy, especially (val)ganciclovir. Risk factors for myelosuppression from (val)ganciclovir include allograft type (umbilical cord transplant, bone marrow > PBSC), poor graft function or current neutropenia. This could lead to graft failure. For patients at risk of toxicity, consideration to either continued surveillance without therapy or alternative antivirals should be made. Discuss with the LBMT attending/Transplant ID.

Late CMV disease occurs after day +100. CMV seropositive recipients of umbilical cord blood transplants remain at significantly higher risk for CMV reactivation after day +100 as does anyone who has had CMV disease or reactivation in the first 3 months post-HSCT. Other groups at risk of late CMV include patients with active GVHD or poor marrow function (low CMV specific T-cell immunity, low CD4 counts) as well as those who have undergone T-cell depletion. Consider continued surveillance in this group. For CMV-seropositive recipients who are still on > 0.5 mg/kg/day of steroids at D+100 for GVHD, continued prophylaxis can be considered.

Monitoring for CMV Reactivation

All allogeneic SCT and UCBT	Weekly from day +7 to day +100
CMV seropositive recipient, OR CMV seronegative recipient with seropositive donor, receiving steroids for acute/chronic GVHD* Patients who were treated for CMV early after transplant UCBT	Weekly from day +100 to day +365
*if prednisone <1mg/kg/day in non UCBT	If four consecutive CMV PCR results are <35 IU/mL after day +100, may reduce frequency to every 2 weeks for 4 to 8 weeks. If CMV PCR results are < 35 IU/mL, may reduce or eliminate monitoring.
Patients on letermovir prophylaxis up to day +100	Weekly from day +100 for 4 weeks, then every 2 weeks for 4 to 8 weeks. If CMV PCR results are < 35 IU/mL, may reduce or eliminate monitoring.
Patients on letermovir prophylaxis day +100 to + 200	Every 2 weeks from day +100 to day +200 if no CMV reactivation between day 0 to day +100. After letermovir discontinuation, weekly for 4 weeks, then every 2 weeks for 4 to 8 weeks. If no reactivation, may reduce or eliminate monitoring.

Prophylactic Therapy

Prophylaxis is begun in the absence of detectable virus or disease and is aimed at prevention of CMV infection or reactivation in high-risk patients. Primary prophylaxis using ganciclovir/valganciclovir is generally not recommended due to toxicity. A Phase 3, randomized, double-blind controlled clinical trial of letermovir for prophylaxis compared with placebo demonstrated superiority in reducing the risk of clinically-significant CMV infection for R+ recipients who were post-allogeneic stem cell transplant with a negative baseline CMV viral load. This is now the preferred strategy for high risk patients. HSV/VZV prophylaxis with acyclovir/valacyclovir must still be used for patients on letermovir as

letermovir is only effective against CMV. Alternatively, acyclovir/valacyclovir can be used as herpes prophylaxis with a CMV monitoring strategy in place (pre-emptive therapy) for patients at lower risk of reactivation. The current Pharmacare criteria for letermovir are:

For the prophylaxis of cytomegalovirus (CMV) infection in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)

AND

Who are at high risk of CMV infection meeting the following criteria:

Umbilical cord blood as stem cell source transplant recipients, OR
Haploidentical recipients, OR
Recipients of ex-vivo T-cell depleted grafts, OR
Recipients of related or unrelated mismatched allogenic stem cell transplant, OR
Recipients treated with antithymocyte globulin (ATG) for conditioning, OR
Recipients requiring high-dose steroids (defined as the use of ≥ 1 mg/kg/day of prednisone or equivalent dose of another corticosteroid) for acute graft versus host disease (GVHD), OR
Recipients treated with ATG for steroid refractory acute GVHD treatment, OR
Recipients with documented history of CMV disease prior to transplantation

AND

Patients must have an undetectable CMV DNA at baseline

Patients must be started on therapy before D28 post-transplant. Prophylaxis should be given until day +100 with continued prophylaxis only for those patients on >0.5 mg/kg of steroid for GVHD at that time. Resubmit a Pharmacare Special Authority request for patients requiring prophylaxis beyond day +100.

Patients should still undergo weekly CMV PCR while on prophylaxis as breakthrough infections can occur. Breakthrough should be defined as any CMV PCR >500 IU/mL. If breakthrough is documented, patients should be switched to (val)ganciclovir or foscarnet therapy, depending on their viral load, clinical symptoms, and graft function. Resistance testing can be considered and consultation with Transplant ID should be strongly considered.

Pre-emptive Therapy

Pre-emptive treatment (PET) is started in the absence of disease symptoms but in the presence of detectable virus in the blood. Currently, there is no well validated threshold for the initiation of treatment at the national or international level. Thresholds need to be chosen based on local PCR techniques and patient related factors regarding CMV disease.

CMV viral load and preemptive therapy:
Therapy initiation should always consider both the risk to the patient of CMV and the risk of of toxicity from therapy, especially (val)ganciclovir. Discuss with the L/BMT attending/Transplant ID prior to therapy initiation. Pre-emptive therapy is recommended

when there is a single CMV PCR >1,000 IU/mL for low risk patients, or any patient not receiving letermovir prophylaxis.

CMV PCR Thresholds for Starting PET

Patient Risk Group	CMV PCR
Low risk patients, or any patient not on letermovir prophylaxis	> 1000 IU/mL
Patients on letermovir prophylaxis	> 500 IU/mL

CMV Testing Changes:

As of June 13, 2017, the virology laboratory at St. Paul's Hospital has a new CMV assay. The old CMV assay reported CMV values in copies/mL; however, the new assay reports values in IU/mL (the World Health Organization International CMV standard units). The two assays give similar viral load values despite the change in units. As a result, the current recommended numerical viral load thresholds for pre-emptive therapy will be the same but with units changed from copies/mL to IU/mL. The pre-emptive threshold will now be 1,000 IU/mL instead of 1,000 copies/mL. As of February 5, 2018, quantitative values will be released down to <35 IU/mL (i.e. values will no longer be reported as <1,000 but an actual number will be given). This does not change the pre-emptive threshold, which will remain 1,000 IU/mL.

Treatment Duration:

First episode of CMV reactivation (CMV PCR >1,000 IU/mL for low-risk or no letermovir prophylaxis, CMV > 500 IU/mL on letermovir prophylaxis or CMV disease):
Start treatment doses of antiviral and continue until 2 consecutive CMV PCR results <35 IU/mL are obtained one week apart (typically 3 week's total). This may need to be altered for individual patients who have toxicity to therapy, understanding that there is an increased risk of CMV relapse when therapy is stopped with ongoing viremia. Discuss with the LBMT attending/Transplant ID. Acyclovir/valacyclovir prophylaxis should be stopped when (val)ganciclovir or foscarnet is started and resumed after completion of therapy.

Second or greater episode of CMV reactivation (CMV PCR >1,000 IU/mL for low-risk or no letermovir prophylaxis, CMV > 500 IU/mL on letermovir prophylaxis or CMV disease):
Treat as first episode of CMV reactivation and consider secondary prophylaxis once the viral load has become <35 IU/mL on two consecutive weeks. This may need to be individualized depending on the patient's clinical circumstances (e.g. current steroid dose) and their risk of toxicity from therapy (e.g. neutropenia, risk of graft failure). Refer to secondary prophylaxis section below for more details. Discuss with the LBMT attending/Transplant ID.

Secondary Prophylaxis

Secondary prophylaxis can be given to prevent reactivation in patients who have already had viremia or CMV disease (see Treatment Duration section above). Specific scenarios where secondary prophylaxis may be warranted include the following:

- CMV recipient positive patient who developed early CMV reactivation requiring pre-emptive therapy (prior to day +14) and did not receive letermovir prophylaxis, and CMV PCR is below 35 IU/mL.
- CMV recipient positive patient who developed early CMV reactivation requiring pre-emptive therapy (prior to day +50) and has ongoing risks, including GVHD treatment with systemic corticosteroid (0.5 mg/kg/day or more), poor graft function, and CMV PCR is below 35 IU/mL.
- CMV recipient positive patient who has had 2 or more episodes of CMV reactivation requiring pre-emptive therapy within 6 months post-transplant, and has ongoing risks, such as GVHD treatment and/or poor graft function, and CMV PCR is below 35 IU/mL.

Letermovir is preferred for prophylaxis; however, it is not on the VGH formulary drug list for secondary prevention and appropriate steps need to be taken to access it from Pharmacy. For outpatients, funding may be available through BC Pharmacare for secondary prevention and a Transplant ID consult is required in this scenario. Alternatives include valganciclovir.

Pharmacare will approve a maximum coverage of 100 days of letermovir. There may be patient specific reasons to discontinue earlier (e.g. steroid dose ends up tapered rapidly and no recurrence of GVHD, challenges with deductible and patient felt to be lower risk now).

Antiviral drug resistance:

Drug resistance is relatively uncommon after HSCT. Risk factors include patients who have received prolonged antiviral therapy, especially those with suboptimal drug levels, as well as patients with profound immunosuppression and lack of prior immunity to CMV or low level intermittent viremia. Resistance should be suspected in patients who are on appropriate doses of antiviral drugs for more than 3 weeks and who have had an increasing or stagnant viral load. After initiation of preemptive therapy, viral load increases occur in approximately one-third of BMT patients. They are due to either viral replication dynamics already present at the time of therapy initiation (i.e. the delay between testing and treatment initiation) or underlying immunosuppression (e.g. steroid therapy for GVHD). Reduction of immunosuppression should be strongly considered. If drug resistance is suspected, switch from ganciclovir to foscarnet (if on ganciclovir) or consult Transplant ID, especially if alternative therapies such as maribavir are preferred (refer to Pharmacotherapy section below). Antiviral resistance testing can be sent but this takes several weeks as it has to be sent to the National Microbiology Laboratory in Winnipeg. The test has limited sensitivity when the viral load is <20,000 IU/mL.

Established Disease Therapy

CMV pneumonia continues to be associated with a high mortality. The symptoms are initially non-specific, with dry cough, hypoxemia, and low-grade fever, but it can progress rapidly to respiratory failure. Severe hypoxemia at presentation is a poor prognostic sign, and most patients who require ventilation will succumb to the disease. No clinical or radiological features distinguish CMV pneumonia from pneumonia caused by other pathogens. Thus, the

diagnosis often is made based on pneumonia in the appropriate clinical setting combined with the identification of CMV from the lower respiratory tract in a BAL specimen. However, only a biopsy with the finding of viral cytopathic inclusions can differentiate between CMV pneumonia and asymptomatic pulmonary shedding. The sensitivity of this test is low and obtaining tissue is difficult in a critically ill patient.

A number of non-randomized studies have suggested that combined therapy with ganciclovir and IVIG improves the outcome in CMV pneumonia as compared to single agent therapy. More recent small studies have raised doubt regarding the benefit of IVIG on outcome, but most transplant centers still use a combined regimen consisting of ganciclovir 5 mg/kg b.i.d. and immune globulin. Transfusion Medicine has approved CMV immune globulin as first line for this condition. The dosage is 150 mg/kg IV on days 1, 4, and 7 and the patient has to be failing antiviral therapy. If CMV immune globulin is unavailable, IVIG may be used at a dose of 0.5 g/kg IV given every second day during the first 2 weeks of ganciclovir therapy.[5,6] Reduction of immunosuppression should be strongly considered. Treatment should be continued until peripheral viremia has resolved (two CMV PCR results <35 IU/mL tested 1 week apart) and the patient's clinical symptoms have improved to baseline.

CMV enteritis can occur anywhere from the esophagus to the colon. Thus symptoms vary according to location. At endoscopy, ulcerations are frequently seen, but macroscopic appearance cannot differentiate CMV from other infections (e.g., HSV). Additionally, CMV gastrointestinal disease can occur with acute GVHD of the gut. A clear diagnosis is found with biopsies that show viral inclusions on direct microscopy or through immunohistochemical staining. PCR is more sensitive, but it is difficult to interpret when blood PCR is also positive as this can represent viral shedding. However, tissue PCR of the GI tract could represent true disease if there is no other explanation for the symptoms seen on biopsy (i.e. no GVHD) and blood CMV PCR is <35 IU/mL. It may also be useful when the abnormal tissue cannot be directly sampled. There is no well-established treatment of CMV enteritis. The Infectious Diseases Working Party (IDWP) for EBMT performed a retrospective study showing no advantage in adding IVIG to ganciclovir for CMV enteritis. Most centers use a repeat induction course of ganciclovir 5 mg/kg b.i.d. for at least 3 weeks. Treatment should be continued until peripheral viremia has resolved (two CMV PCR results <35 IU/mL tested 1 week apart) and the patient's clinical symptoms have improved to baseline.

Pharmacotherapy

Ganciclovir is a nucleoside analog with potent in vitro activity against CMV and is considered the first line drug for treatment of CMV reactivation and disease. The half-life is 6 hours. Ganciclovir however causes myelosuppression, particularly neutropenia in up to 30% of treated patients, which increases the risk of bacterial and fungal infections.

If neutrophils fall to < 1 x 10^9/L while on ganciclovir, counts should be maintained with G-CSF. If there is no response to G-CSF therapy after 3 to 5 days, consider holding valganciclovir/ganciclovir and possibly switching to foscarnet. Valganciclovir/ganciclovir dose reduction for leucopenia is not generally recommended, as this increases the chance that the patient will develop resistance due to suboptimal drug levels.

Ganciclovir Dosing:

Creatinine Clearance (mL/min)	Treatment Dose*	Prophylactic Dose
70 or higher	5 mg/kg every 12 hrs	5 mg/kg every 24 hrs
50 to 69	2.5 mg/kg every 12 hrs	2.5 mg/kg every 24 hrs
25 to 49	2.5 mg/kg every 24 hrs	1.25 mg/kg every 24 hrs
10 to 24	1.25 mg/kg every 24 hrs	0.625 mg/kg every 24 hrs
Less than 10	1.25 mg/kg 3 times/week (if on dialysis, dose post dialysis)	0.625 mg/kg 3 times/week (if on dialysis, dose post dialysis)

*Use adjusted weight for obese patients (BMI ≥ 30 kg/m^2)

Valganciclovir is the orally bioavailable pro-drug of ganciclovir that is converted to ganciclovir in vitro after intestinal absorption. Systemic levels of ganciclovir are equivalent after administration of 900 mg of oral valganciclovir or 5mg/kg of intravenous ganciclovir. Absorption of valganciclovir is significantly enhanced when taken with food; thus, patients with poor oral intake (or with severe diarrhea) are NOT good candidates for valganciclovir. Rising viral loads on valganciclovir therapy may be due to poor drug absorption; IV ganciclovir should thus be re-started if this occurs. Valganciclovir (and valacyclovir) should be used with caution in patients with significant liver disease.

The BMT attending physicians, clinical associates, and NPs have a Pharmacare prescriber exemption for valganciclovir. A Pharmacare Special Authority form does NOT need to be completed.

Valganciclovir* Dosing:

Creatinine Clearance (mL/min)	Treatment Dose	Prophylactic Dose
60 or higher	900 mg twice a day	900 mg once a day
40 to 59	450 mg twice a day	450 mg once a day
25 to 39	450 mg once a day	450 mg once every 2 days
10 to 24	450 mg once every 2 days	450 mg twice a week
Less than 10	Not recommended	

*Valganciclovir should be given with food& should only be considered in patients with good

Foscarnet is as effective as ganciclovir but has a different toxicity profile (renal toxicity, electrolyte disturbances). It can be used as an alternative to ganciclovir in situations of neutropenia or suspected/confirmed drug resistance. It is also used for CMV viremia pre-engraftment.

Patients on foscarnet should be hydrated and have their Mg, Ca, phosphate & K levels monitored daily. Hydrate with 0.5–1 L NS with each foscarnet infusion to minimize risk of renal toxicity. The reported frequency of electrolyte abnormalities with foscarnet are as follows: hypocalcemia 15%, hypophosphatemia 8%, hyperphosphatemia 6%, hypomagnesemia 15%, hypokalemia 16%. Other side effects include headache, seizures, nausea, vomiting and diarrhea.

Foscarnet Dosing:

CrCl/wt (ml/min/kg)	Treatment dose for (mg/kg IV)[§]	Prophylactic dose (mg/kg IV)	Dosing for Acyclovir-resistant HSV infection (mg/kg IV)
>1.4	60 q8h* or 90 q12h	90 q24h	60 q12h
> 1-1.4	45 q8h* or 70 q12h	70 q24h	45 q12h
> 0.8-1	50 q12h	50 q24h	35 q12h
> 0.6-0.8	80 q24h	80 q48h	25 q12h
> 0.5-0.6	60 q24h	60 q48h	40 q24h
≥ 0.4-0.5	50 q24h	50 q48h	30 q24h
< 0.4	Not recommended	Not recommended	Not recommended

*q8h dosing preferred for the treatment of CMV end-organ disease
[§]Use adjusted weight for obese patients (BMI ≥ 30 kg/m^2)

Maribavir is an orally available antiviral drug active against CMV, which works against the UL97 viral thymidine kinase. It has been shown to be effective as a therapy for hematopoetic and solid organ transplant patients with CMV infections that are refractory or resistant to standard CMV therapies and/or patients who have life-threatening toxicities to alternative agents with a refractory or resistant infection to first-line therapy. Maribavir is dosed for 8 weeks of therapy at 400 mg PO BID and costs about $58,000/treatment course. It is not on the VGH formulary drug list and is currently not funded by BC Pharmacare. Financial assistance or compassionate supply may be available from the manufacturer. Consultation with Transplant ID for patients who require maribavir should be strongly considered.

Patients on maribavir must be given acyclovir/valacyclovir because maribavir is only active against CMV. The main side effect from maribavir is dysgeusia. Maribavir should not be used for patients with CNS infection including CMV retinitis as these patients were excluded from the trial. Care should be taken if patients have CMV end-organ disease and/or high viral loads as maribavir is thought to have a low-barrier to resistance. It should not be combined with (val)ganciclovir because the mechanism of action is antagonistic with (val)ganciclovir activity.

References:

1. Ljungman R, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). Lancet Infect Dis. 2019;19:e260-72.
2. Hakki M, et al. American Society for Transplantation and Cellular Therapy Series: #3-Prevention of Cytomegalovirus Infection and Disease After Hematopoietic Cell Transplantation. Transplantation and Cellular Therapy. 2021;21:707-719.
3. Pinana JL, et al. Update on Cytomegalovirus Infection Management in Allogeneic Hematopoietic Stem Cell Transplant Recipients. A Consensus Document of the Spanish Group for Hematopoietic Transplantation and Cell Therapy (GETH-TCF). Mediterr J Hematol Infect Dis. 2024;16:e2024065.
4. Hudson (OH): Lexicomp Inc.: 2021 [updated 7/3/21]. Available from: https://online.lexi.com/lco/action/home. Accessed November 2024.
5. https://nacblood.ca/sites/default/files/2024-07/2024-05-30%20National%20Ig%20Shortages%20Management%20Plan.pdf (Accessed August 2025)
6. https://www.unmc.edu/intmed/divisions/id/asp/protected-antimicrobials/cytomegalovirus.html (Accessed August 2025)

11-6 Treatment for Patients with Prior Hepatitis B Infection

Patients with myeloid, lymphoid, and plasma cell malignancies as well as with aplastic anemia undergoing chemotherapy or immunosuppressive treatments, including hematopoietic stem cell transplantation, should be screened for hepatitis B and receive antiviral prophylaxis or serology monitoring depending on risk (Table 1).

Note
Coverage for antiviral prophylaxis (entecavir or tenofovir) may be considered from the BC Pharmacare Special Authority program. Patient specific factors, including specific treatment regimen for the underlying malignancy and the most recent hepatitis serology report, are required with each Special Authority request. As of 2023, lamivudine will no longer be available for coverage under Pharmacare.

Tests

- Baseline*:
    - HBsAg, HBsAb, HBcoreAb.
    - Patients with HBsAg positive and/or HBcoreAb positive also require a baseline HBV DNA.
    - Results do not have to be available to proceed with first treatment, but results must be checked before proceeding with cycle 2 of cancer treatment.
    - ** Baseline serology (particularly HBsAb) should be repeated if patient relapses, and/or needs additional lines of antineoplastic systemic therapy and the patient is not on prophylaxis*
- Every 3 months:
    - Patients with HBsAg positive and HBcoreAb positive or negative: HBV DNA, and ALT, during cancer treatment and at least 12 months after stopping antiviral for HBV prophylaxis
    - Patients with HBsAg negative and HBcoreAb positive: HBsAg, HBV DNA and ALT, during cancer treatment and for at least 12 months after stopping antiviral for HBV prophylaxis

Antiviral Prophylaxis

- Prophylaxis should be initiated before immunosuppressive or cytotoxic therapy
- Consider referral to a hepatology specialist and/or Transplant Infections Diseases to co-manage, particularly in cases with HBsAg or HBV DNA positivity, underlying liver fibrosis/cirrhosis and/or when monitoring may be challenging. These patients might qualify for therapy in the absence of chemotherapy and may need follow-up for complications such as HCC development.

- For HIV-positive patients requiring prophylaxis: follow BC Centre for Excellence in HIV/AIDs guidelines for the treatment of HIV/HBV coinfection.

Drug*§	Dose
entecavir or Tenofovir** (Viread type)	**CrCl 50 mL/min or above: 0.5 mg PO daily** CrCl 30 to 49 mL/min: 0.5 mg PO every 48 hours CrCl 10 to 29 mL/min: 0.5 mg PO every 72 hours CrCl below 10 mL/min: 0.5 mg PO every 7 days **CrCl 50 mL/min or above: 300 mg PO daily** CrCl 30 to 49 mL/min: 300 mg PO every 48 hours or 150 mg PO daily CrCl 10 to 29 mL/min: 300 mg PO twice weekly (every 72 to 96 hrs) CrCl below 10 mL/min: Avoid

*See Table 1 for indication and duration of HBV prophylaxis

§ Consider Hepatology referral for patients with moderate to severe renal impairment for optimal antiviral therapy

**Tenofovir disoproxil fumarate (TDF)

References

1. Coffin CS, et al. Management of hepatitis B virus infection: 2018 guidelines from the Canadian Association for the Study of the Liver (CASL) and Association of Medical Microbiology and Infectious Disease Canada (AMMI). Can Liver J 2018;1:156-217.
2. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370-398.
3. Lau G, et al. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. Hepatol Int 2021;15:1031-1048.
4. Hwang JP, et al. Hepatitis B virus screening and management for patients with cancer prior to therapy: ASCO Provisional Clinical Opinion Update. J Clin Oncol 2020;38:(31):3698-3715.

Table 1: Risk of hepatitis B reactivation with immunosuppressive therapy

Risk of HBV reactivation*	Cancer Treatment*	Serology	Antiviral for HBV prophylaxis	Prophylaxis duration *after end of cancer treatment*	Monitoring including *after prophylaxis discontinued*
Very high	B-cell depleting therapy [e.g., riTUXimab, obinutuzumab, BTK inhibitors, CAR T-cell therapy, plasma cell antibodies (eg. daratumumab, isatuximab), bi-specific anti-B-cell antibodies (blinatumomab), inotuzumab, alemtuzumab]	HBsAg+ **OR** HBcAb+	entecavir†	18 months	Monitor HBV DNA, and ALT (and HBsAg, if negative at baseline) q3months and for at least 12 months after stopping antivirals
High	Autologous or allogeneic stem cell transplant	HBsAg+ **OR** HBcAb+	entecavir†	12 months after completion of all immunosuppressive therapy**	
	High-dose corticosteroids‡, anthracyclines	HBsAg+	entecavir†	6 months¶	
Moderate 1%-10%	Tyrosine kinase inhibitors	HBsAg+	entecavir†	6 months¶	
	Moderate-dose corticosteroids‡	HBsAg+	entecavir†	6 months¶	
	Other highly or moderately immunosuppressive LY/MY/LK protocols*	HBsAg+	entecavir†	6 months¶	
	Tyrosine kinase inhibitors High- or Moderate-dose corticosteroids‡ Anthracyclines Other highly or moderately immunosuppressive LY/MY/LK protocols*	HBsAg- and HBcAb+	If anti-HBs titre > 100 U/L: No prophylaxis If anti-HBs titre ≤ 100 U/L: entecavir†	6 months¶	
Low < 1%	Other low immunosuppressive LY/MY/LK protocols*	HBsAg+ **OR** HBsAg- and HBcAb+	No prophylaxis		Monitor HBV DNA, and ALT (and HBsAg, if negative at baseline) q3months and for at least 12 months after stopping cancer treatment

*	LY/MY/LK are lymphoid, plasma cell, or myeloid malignancy treatment protocols. They are designated as low, moderately, or highly immunosuppressive within the protocols. Refer to specific BC Cancer protocol or Chapter 8 of the L/BMT Manual for designation (Chapter 8 will be updated in the fall 2023).
†	Entecavir is preferred but tenofovir is an acceptable alternative. Tenofovir may cause renal toxicity. Both agents require dose adjustment in patients with pre-existing renal dysfunction. Patients currently on lamivudine do not need to switch therapy; however, consider a switch to entecavir or tenofovir at the next Special Authority renewal.
‡	High-dose = predniSONE equivalent ≥ 20 mg/d for ≥ 4 weeks[3] Moderate-dose = predniSONE equivalent 10 - 20 mg/d for ≥ 4 weeks[3]
¶	Longer duration would require Pharmacare exceptional coverage review and description of patient specific factors requiring extended prophylaxis, including specific treatment regimen for the underlying malignancy and the most recent hepatitis serology report.
**	Refer to Chapter 19 for criteria for discontinuing antiviral prophylaxis in patients on chronic immunosuppression for GVHD.

HBcoreAb and IVIG:

Patients who have received IVIG should not undergo serological testing for HBV for 3 months post-infusion. IVIG contains antibodies to a variety of pathogens. False positive serological tests have been documented for 1. HBcAb, 2. Syphilis, 3. CMV, 4. Toxoplasma among others.[1] Patients who are known to be HBcAb negative prior to an infusion of IVIG with repeat testing positive for HBcoreAb after IVIG infusions do not require hepatitis B antiviral prophylaxis unless there are extenuating circumstances. Testing can be repeated after 3 months (if feasible) if there remains a concern.

Allogeneic Donors with positive serology for HBcoreAb:
Hepatitis B antiviral prophylaxis is not required for recipients of allogeneic stem cell transplants from donors who have positive serology for HBcoreAb but negative HBV DNA levels. There is no risk of transmission in this setting. Refer to Chapter 2-2: Donor Criteria for recommended testing.

References:
Thibault et al. Too Often Forgotten: Passive Transfer of Antibodies. Clin Infect Dis. 2016 Sep 1;63(5):709-10.

11-7 Prevention of EBV- PTLD Post Transplant

BACKGROUND

Epstein-Barr virus (EBV) associated post-transplantation lymphoproliferative disorder (PTLD) is a rare but life threatening complication of allogeneic stem cell transplant (allo-SCT) resulting from the outgrowth of EBV infected B cells that would normally be controlled by an effective EBV-specific cytotoxic T-cell response. The most important risk factors for EBV-PTLD are the use of anti-thymocyte globulin for GVHD prevention/treatment (in vivo T cell depletion) and umbilical cord blood (UCB) transplantation [1]. The reported incidence of PTLD following in vivo T cell depletion is 11% [2] and 4.5% after UCB transplantation [3].

Reduction of immunosuppression on its own is not a useful approach to management of PTLD because the immune system cannot recover fast enough to eradicate the malignancy. As most cases of PTLD arise in donor or recipient derived B-cells, first line therapy with rituximab is recommended for proven or probable EBV-PTLD in addition to reduction of immunosuppression where possible [5]. In established PTLD 4-8 doses of rituximab are need to obtain clinical improvement and to reduce the EBV-DNA load [5]. A phase 2 clinical trial using rituximab to treat PTLD reported a response rate of 44% at day 80 [6], hence waiting until the patient develops clinically evident PTLD may lead to failure in a significant proportion of patients.

Clinical symptoms are frequently lacking in the early stages of EBV reactivation and are often only recognized in the later stages if they coincide with progressive EBV- LPD. Serial measurement of EBV-DNA load in the peripheral blood can identify patients at risk of

developing PTLD. Many studies have demonstrated that EBV "load-guided" preemptive therapy with rituximab is effective in preventing EBV-PTLD in alloSCT patients at high risk [7-9].

EBV PCR Surveillance: Post-transplant Monitoring Guidelines
Weekly Day + 7 until day +100

- Patients receiving anti-thymocyte globulin in the conditioning regimen
- Haploidentical transplants
- Cord blood patients
- Patients who receive post-transplant cyclophosphamide
- Patients who require anti-thymocyte globulin for treatment of GVHD

Beyond day + 100
Consider longer monitoring if the patient has a history of EBV reactivation requiring treatment or EBV-related PTLD or if the patient has severe, acute (especially steroid-refractory) or chronic GVHD requiring intensive immunosuppressive therapy.

**Please note: The EBV assay at SPH will be changing soon to a new assay. Results from the two assays will be different. The old assay uses copies/mL. The new assay, once launched, will be in IU/mL and will have a warning flag about the change in units.

** Currently there is a lack of uniformity and consistency among the assays available indicating the need for caution when attempting to determine significant cut-offs for treatment. In order to validate our assay, we need to capture the clinical data as outlined in Appendix X on **ALL** patients with EBV reactivation.

PRE-EMPTIVE TREATMENT FOR EBV REACTIVATION

* If a patient has a PCR > 2,000 IU/mL and < 5,000 IU/mL (> 5,000 copies/mL but < 15,000 copies/mL), and no symptoms or signs of PTLD, the PCR needs to be repeated weekly until < 2,000 IU/mL (<5,000 copies/mL). More frequent monitoring may be considered. If the level has doubled or increased on **two** further occasions, give a single dose of rituximab 375 mg/m^2 (*) (Cerner PowerPlan BMT LPDRIT).

* If single PCR reading is > 5,000 IU/mL (>15,000 copies/mL), give a single dose of rituximab (Cerner PowerPlan BMT LPDRIT).

* In addition to rituximab, reduce the dose of immunosuppressive drugs by 20% if possible, except in patients with uncontrolled severe acute or chronic GVHD.

* Repeat PCR one week following the 1st dose of rituximab, and if still > 2,000 IU/mL (>5,000 copies/mL)(even if decreasing), give another dose. Continue weekly rituximab until the PCR is below 2,000 IU/mL (<5,000 copies/mL). Based on the small amount of literature, about half clear after a single dose and in most patients it is cleared after 2 doses [7].

Note pre-emptive rituximab is reimbursed by BC Cancer for up to 2 doses (**BMTLPDRIT**). If more than 2 doses of rituximab are required for pre-emptive treatment of EBV reactivation,

a BC Cancer CAP request for additional doses must be submitted prior to pharmacy dispensing.

For patients with proven or probable EBV-PTLD, give a total of 4 doses of rituximab (LYRITUX). If more than 4 doses of rituximab are required for PTLD treatment, a BC Cancer CAP request for additional doses must be submitted before pharmacy dispensing.

References:

1. Landgren, O., et al., Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation. Blood, 2009. 113(20): p. 4992-5001.
2. Podgorny, P.J., et al., High rabbit-antihuman thymocyte globulin levels are associated with low likelihood of graft-vs-host disease and high likelihood of posttransplant lymphoproliferative disorder. Biol Blood Marrow Transplant, 2010. 16(7): p. 915-26.
3. Brunstein, C.G., et al., Marked increased risk of Epstein-Barr virus-related complications with the addition of antithymocyte globulin to a nonmyeloablative conditioning prior to unrelated umbilical cord blood transplantation. Blood, 2006. 108(8): p. 2874-80.
4. Zutter, M.M., et al., Epstein-Barr virus lymphoproliferation after bone marrow transplantation. Blood, 1988. 72(2): p. 520-9.
5. Styczynski, J., et al., Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after hematopoietic stem cell transplantation: Sixthe European Conference on Infections in Leukemia (ECIL-6) guidelines. Haematologica, 2016. 101(7):803-811.
6. Choquet, S., et al., Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood, 2006. 107(8): p. 3053-7.
7. Coppoletta, S., et al., Rituximab treatment forepstein bar virus (ebv) dna-emia, after alternative donor transplants. Biol Blood Marrow Transplant, 2010.
8. Blaes, A.H., et al., Monitoring and preemptive rituximab therapy for Epstein-Barr virus reactivation after antithymocyte globulin containing nonmyeloablative conditioning for umbilical cord blood transplantation. Biol Blood Marrow Transplant, 2010. 16(2): p. 287-91.
9. Van Esser, J.W., et al., Prevention of Epstein-Barr virus-lymphoproliferative disease by molecular monitoring and preemptive rituximab in high-risk patients after allogeneic stem cell transplantation. Blood, 2002. 99(12): p. 4364-9.

11-8 Guidelines for Diagnosis and Treatment of Adenovirus Infection in Cord Blood Transplant Patients

Human adenovirus (HAdV) infections are increasingly recognized as important pathogens in patients receiving a cord blood transplant (CBT).

The spectrum of HAdV-associated disease in CBT ranges from mild gastrointestinal or respiratory symptoms to severe hemorrhagic enteritis, hemorrhagic cystitis, nephritis, hepatitis, pneumonia, encephalitis, and myocarditis. It is frequently associated with hepatic failure. Fatal HAdV disease is reported in up to 50% of infected patients.

Monitoring of patients for HAdV load in peripheral blood using qPCR is recommended on a weekly basis for patients receiving a CBT. The duration of monitoring should be adapted to duration of immune suppression and to degree of immune reconstitution (e.g. continued as long as patient has severe lymphopenia <200 cells/ul).

Although adenovirus can rarely cause disease in other stem cell transplant recipients, there is limited evidence for monitoring or pre-emptive therapy in these groups. Therefore, adenovirus testing should not be routinely ordered on stem cell transplant recipients outside of the cord blood setting. This includes the haploidentical transplant recipients using the current protocol at VGH. Any patient with symptoms or signs of disease that could be due to adenovirus infection should be referred to Transplant ID for evaluation and testing.

Testing

Please draw 10 mL red top q weekly on Tuesday. BC C&W Microbiology Laboratory will run the PCR on Wednesday with same day turn around for the result.

Testing should be carried out between day +7 and day +100. Testing is not recommended beyond this period unless the patient has a reactivation that is being treated or monitored. All samples need to be collected at Vancouver General Hospital. This test will not be processed in community laboratories.

Indications for pre-emptive antiviral treatment

1. Any plasma viral load >1000 without symptoms, or
2. Initial plasma viral load <1000 without symptoms but rising on repeat testing. Patients with VL <1000 should have their viral loads repeated immediately upon receiving this result. If the repeat level is increasing or the patient becomes symptomatic, the patient should be treated even if the repeat level is still <1000. Microbiology will have to be notified to expedite testing as this test is only run once a week unless a special request is made.

Patients with symptoms consistent with HAdV disease and any detectable adenovirus viral load

should be considered to have proven/probable HAdV disease and treated accordingly, regardless of exact value of the viral load. Alternative etiologies for these symptoms should also be ruled out.

Preemptive Treatment

Cidofivir 3 to 5 mg/kg IV weekly for 2-3 weeks, thereafter every other week. Therapy should be continued until the viral load has become negative.

Cidofovir is not on the formulary drug list at VGH and appropriate steps need to be taken.

Proven or Probable HAdV disease

Immune suppression should be reduced or withdrawn whenever possible. Cidofovir 5 mg/kg IV weekly for 2-3 weeks, thereafter every other week. Therapy should be continued until the viral load has become negative and the patient has symptomatically improved.

Cidofovir is highly nephrotoxic. Normal saline (NS) 1 L must be infused over 1 to 2 hours immediately prior to each cidofovir dose. If possible, a second litre of NS should be initiated at the start of the infusion or immediately after the infusion. Infuse second liter over 1 to 3 hours.

Probenacid must be administered concurrently with each cidofovir dose. Give probenacid 2 g PO 3 hours prior to cidofovir, then 1 g PO 2 hours and 8 hours post infusion).

Cidofovir is contraindicated in the following situations:

- patients with a CrCl $\leq$ 55 mL/min or having proteinuria $\geq$ 2+ ($\geq$ 100 mg/dL).
- patients with hypersensitivity to cidofovir
- patients with a history of clinically severe hypersensitivity to probenecid or other sulfa-containing medications

Every effort should be made to stop concurrent nephrotoxic agents (e.g. amphotericin, aminoglycosides, etc.) within 7 days of starting cidofovir.

Treatment of Concurrent HAdV and CMV

Cidofovir has activity against both HAdV and CMV. If treatment for both CMV and HAdV required, cidofovir monotherapy is acceptable. In this case, give cidofovir 5 mg/kg IV weekly for 2 to 3 weeks, followed by every other week. Therapy should continue until HAdV and CMV viral loads are negative. If HAdV viral load becomes negative first, treatment with cidofovir may be discontinued and another appropriate antiviral agent (ganciclovir, foscarnet, etc.) may be used until CMV viral load is negative.

11-9 Community-Associated Respiratory Viral Infection

Community associated respiratory viral (CARV) infections comprise a wide-spectrum of viral infections. They include both RNA viruses – including COVID-19, influenza, respiratory syncytial virus (RSV), human metapneumovirus, parainfluenza, rhinovirus, enterovirus, and coronavirus – and DNA viruses such as adenovirus. Infection with these in the pre- and post-transplant period can cause significant morbidity and mortality, particularly when upper tract infection progresses to lower tract pneumonia and/or respiratory failure. Most of these viruses do not have targeted antiviral therapy except for influenza and the only therapy in severe cases is minimization of immunosuppression.

Any patient who presents with upper or lower respiratory symptoms should be evaluated for CARV infection with a Baylor wash. Testing should be sent for both influenza and other respiratory tract viruses (preferably by Biofire testing). Baylor wash should also be strongly considered for febrile patients with no localizing symptoms, particularly if it is influenza season and/or other routine diagnostic testing has not yielded a source of fever.

Influenza

Patients diagnosed with influenza infection should be given oseltamivir if they are symptomatic regardless of how much time has passed since the onset of infection. If the patient has recovered from their symptoms by the time testing is done, consideration for therapy can still be made if the patient is highly immunosuppressed (i.e. recently transplanted, on immunosuppression for active GVHD). However, patients may shed virus for weeks after infection so patients who continue to be positive by Baylor wash but are clinically well will likely not benefit from further therapy, particularly if they are farther out from transplant without GVHD. Prolonged therapy or repeat therapy may be considered for those who are still symptomatic after five days of oseltamivir or highly immunocompromised.

Post-transplant patients who are in close contact with someone diagnosed with influenza infection should be offered post-exposure prophylaxis with oseltamivir if they are within the first 3 months and/or highly immunocompromised (i.e. on immunosuppression for active GVHD).

COVID-19

Patients diagnosed with mild to moderate COVID-19 who have active hematological malignancies or are post-HSCT or CAR-T therapy are eligible for therapy to prevent progression to severe/critical COVID-19. There are two therapeutics available - nirmatrelvir/ritonavir p.o. or remdesivir IV. The main limitation to nirmatrelvir/ritonavir is drug-drug interactions. Please see the COVID-19 Treatment page on the BCCDC website for more information regarding the options and how to prescribe.

http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/treatments

Remdesivir must be given at a hospital in the patient's catchment area (e.g. patients who live in the Fraser Health Authority region must be sent to a hospital there).

Transplantation after a diagnosis of community-associated respiratory viral (CARV) infection

The most difficult scenario is when one of these infections is detected immediately pre-stem cell transplant. Several guidelines and societies have recommended that conditioning should be delayed in patients who have a CARV infection detected pre-transplant because of the increased risk of adverse outcomes. This includes COVID-19 as rebound disease has occurred in some patients who proceed to transplantation. However, certain viruses have more data than others (e.g. COVID-19, RSV vs. entero/rhinovirus) and the risk may not be the same between all viruses.

Except for influenza, patients who are found to be positive for a CARV pre-transplant should have their conditioning delayed until they are negative on a follow-up Baylor wash/respiratory samples. The following principles would apply.

1. The delay should apply regardless of whether patients are asymptomatic or only mildly symptomatic.
2. The delay applies to both autologous and allogeneic stem cell transplant recipients. Delay may be more feasible for patients with non-malignant or well-controlled disease. In patients with relapsed or refractory disease, the risk of progression during the delay must be weighed against the risk of adverse outcomes (including death) with proceeding despite infection. Patients who go ahead with conditioning despite infection should be counselled on the risks.
3. Patients should have follow-up screening on a weekly basis via Baylor wash to determine when they convert from positive to negative. Data suggests that this takes an average of 4 weeks.
4. Patients who are still positive at 4 weeks after infection should have their case reviewed. At that time, the risk of waiting further might outweigh the risk of proceeding to transplant, particularly if the patient is clinically well despite the positive results.

Patients who are found to have influenza should be treated appropriately with oseltamivir and have their Baylor wash repeated after therapy is complete before proceeding to transplant. Similarly, patients who are found to be COVID-19 positive should be treated appropriately with follow-up testing prior to proceeding.

References:

1. Peck AJ, Corey L, Boeckh M. Pretransplantation respiratory syncytial virus infection: impact of a strategy to delay transplantation. Clin Infect Dis. 2004 Sep 1;39(5):673-80.
2. von Lilienfeld-Toal M et al. Community acquired respiratory virus infections in cancer patients-Guideline on diagnosis and management by the Infectious Diseases Working Party of the German Society for haematology and Medical Oncology. Eur J Cancer. 2016 Nov;67:200-212.

3. Hirsch HH et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for Diagnosis and Treatment of Human Respiratory Syncytial Virus, Parainfluenza Virus, Metapneumovirus, Rhinovirus, and Coronavirus. Clin Infect Dis. 2013 Jan 15; 56(2): 258–266.
4. Zaia J, Baden L, Boeckh MJ, Chakrabarti S, Einsele H, Ljungman P, McDonald GB, Hirsch H; Center for International Blood and Marrow Transplant Research; National Marrow Donor Program; European Blood and Marrow Transplant Group; American Society of Blood and Marrow Transplantation; Canadian Blood and Marrow Transplant Group; Infectious Disease Society of America; Society for Healthcare Epidemiology of America; Association of Medical Microbiology and Infectious Diseases Canada; Centers for Disease Control and Prevention. Viral disease prevention after hematopoietic cell transplantation. Bone Marrow Transplant. 2009 Oct;44(8):471-82.

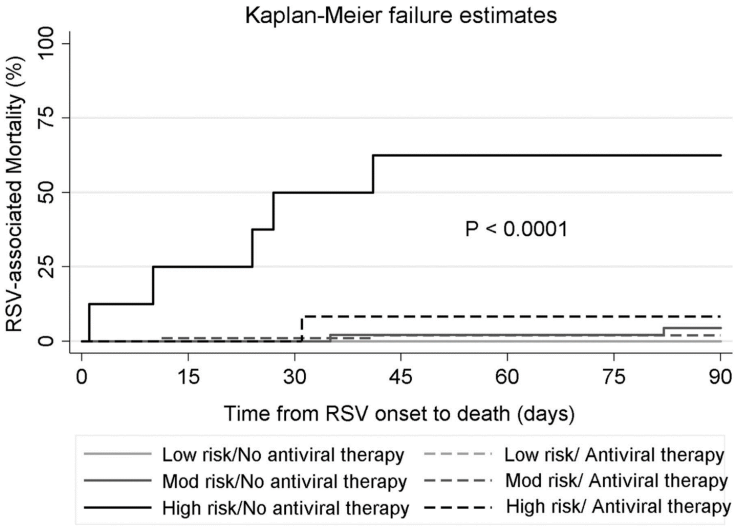
11-10 Respiratory Syncytial Virus Infection Management in Allogeneic Stem Cell Transplant Recipients

Respiratory Syncytial virus (RSV) infection in allogeneic stem cell transplant recipients can lead to significant morbidity and mortality. Certain risk factors increase the risk of mortality from RSV.

Table 2: Immunodeficiency scoring index for allogeneic HSCT recipients (adapted from Shah D et al. Blood 2014)

Characteristic	Score
Absolute Neutrophil Count <500/µL	3
Absolute Lymphocyte Count <220/ µL	3
Age ≥40 years	2
Myeloablative conditioning regimen	1
GVHD (acute or chronic)	1
Pre-engraftment or within 30 days of engraftment	1

Low risk score: 0-2, Intermediate risk score: 3-6, High risk score: 7-12



Allogeneic stem cell transplant recipients with a high ISI score are at greatest risk of RSV-associated mortality. Unfortunately, ribavirin – a nonspecific viral inhibitor – is no longer available for therapy. Patients should have their immunosuppression reduced, if possible. Otherwise, they should be offered supportive care. These high-risk patients should have immunoglobulin levels measured and if IgG is below 4 g/L, they should receive IVIG 0.5 g/kg x 1 dose.

CHAPTER 12. PNEUMOCYSTIS JIROVECII (PNEUMOCYSTIS CARINII) & TOXOPLASMA GONDII

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12-1. PJP Prophylaxis & Schedule

PJP is a serious problem in the post transplant setting and has occurred in approximately 10% of allogeneic transplant patients not receiving PJP prophylaxis, as well as in a small number of autologous transplant patients, patients treated for ALL, and patients on prolonged immunosuppressive therapy. Patients treated with fludarabine and alemtuzumab are also at a higher risk of developing PJP. Prophylaxis is important in these patients since the fatality rate of PJP post-transplant is approximately 50%. The ideal prophylactic regimen, duration and definition of relative risk for developing PJP have not been defined, but we currently recommend prophylaxis in the following groups:

Pneumocystis jirovecii Prophylaxis Regimens

1. First line prophylaxis

TMP-SMX (co-trimoxazole) DS 1 tab PO BID q Mon/Thur is effective and is the preferred regimen for all patients. TMP-SMX also provides some protection against other pathogens, including *Toxoplasma* and *Nocardia*. Although dapsone and atovaquone may provide some protection against *Toxoplasma*, the broader spectrum of TMP-SMX is among the reasons it is preferred. For patients identified as having a history of allergic reaction to sulfa medications prior to a planned transplant, a referral for TMP-SMX challenge is recommended (see management algorithm on page 5).

a. Attempts should be made to limit drug interruptions of TMP-SMX to < 2 weeks. G-CSF should be considered if the main toxicity is felt to be neutropenia.

b. If rash develops, refer to TMP-SMX allergy management algorithm on page 5

2. Second line prophylaxis

IV pentamidine is currently recommended by our program if TMP-SMX cannot be tolerated or the patient cannot be re-challenged or desensitized. This recommendation is based on the following:

a. The incidence of PJP in our program with TMP-SMX as primary prophylaxis and IV pentamidine as the most common secondary prophylaxis appears to be < 1.5% since this strategy was adopted in the early 1990's.

b. The optimal dosing and scheduling of IV pentamidine in the post transplant setting remains unclear, but the current recommendation is 300 mg IV q 2 weeks. If patients are at low risk for PJP and have limited access to IV pentamidine, it may be given every 3–4 weeks. If patients are at high risk for PJP, attempt to administer q 2 week therapy.

c. Compared to IV pentamidine, aerosolized pentamidine is more difficult to administer and is associated with concerns about staff exposure.

Prophylaxis & Schedule (cont.)

3. Third line prophylaxis

Atovaquone 1,500 mg PO daily will be considered for third line therapy if the patient can afford it (approximately $900/month and the drug is not a Pharmacare benefit). The optimal dose and interval of administration of atovaquone for PJP prophylaxis in BMT patients is unknown. Clinical trials in BMT have used 1,500 mg 3 days per week, but these studies were too small to evaluate efficacy. In HIV infected persons, both 750 mg daily and 1,500 mg daily have been evaluated and 1,500 mg may be modestly more effective. Side effects include rash, GI, transaminitis.

An alternative third line prophylaxis is dapsone 50 mg BID but PJP rates > 5% have been reported in some trials. The cost is approximately $60/month, but patients who are intolerant to TMP-SMX frequently do not tolerate dapsone, and there are many side effects including GI, methemoglobinemia, myelosuppression and hemolytic anemia. Dapsone should not be given to people with G6PD deficiency; G6PD levels must be checked prior to starting therapy.

Table 1. Pneumocystis jirovecii prophylaxis schedule

	Initiate PJP Prophylaxis	Discontinue PJP Prophylaxis	Special Considerations
Autologous HSCT (HD, NHL, AML)	Initiate before day 28 **Use IV pentamidine until ANC >1.0 and platelets > 20K**	3 months post transplant	If the patient cannot tolerate TMP-SMX, is not a candidate for rechallenge or desensitization consider discontinuing.
Patients given fludarabine, alemtuzumab, other T-cell depleting agents	Start of therapy	6 months post completion of therapy	Consider measuring CD4 count and continuing if <200 cells/mm3
Allogeneic HSCT (all patients)	Initiate before day 28 **Use IV pentamidine until ANC >1.0 and platelets > 20K**	1 year post therapy and/or 3 months following discontinuation of immunosuppressive therapy	See Chapter 19 for recommendations about prophylaxis discontinuation in patients with ongoing need for immunosuppression.
Acute lymphoblastic leukemia patients	Start of chemotherapy	On completion of chemotherapy	--------
CAR-T	Initiate before day 28 **Use IV pentamidine until ANC >1.0 and platelets > 20K**	6 months post CAR-T	If the patient cannot tolerate TMP-SMX, is not a candidate for rechallenge or desensitization consider discontinuing. Consider measuring CD4 count at 3 months and discontinuing if >200 cells/mm3

12-2. Toxoplasma gondii Prophylaxis & Schedule

Toxoplasmosis is a serious, infection complication following allogeneic HSCT with clinical reactivation reported to occur in 2% to 6% of recipients who are seropositive prior to transplant. Risk factors in addition to positive serology include, no TMP-SMX prophylaxis, severe GVHD, ablative conditioning regimens, T cell depletion, cord blood source, or use of antithymocyte globulin (ATG). Most cases after allogeneic HSCT are reported to have occurred between 3 and 26 weeks after transplant, but later occurrences have been reported in patients receiving long-term immunosuppression. Prophylaxis is important in these allograft patients as infection can lead to rapid mortality. Except for the rare patient with pretransplant toxoplasmic chorioretinitis, who may benefit from secondary prophylaxis, autologous transplant recipients are at negligible risk for toxoplasmosis reactivation. No prophylaxis is recommended for autologous transplant recipients.

Toxoplasmosis Prophylaxis Regimens

1. First line prophylaxis

TMP-SMX (co-trimoxazole) DS 1 tab PO daily appears to offer protection against toxoplasmosis and is the preferred regimen for toxoplasma seropositive patients. Alternative TMP-SMX dosing may be considered in patients with poor graft function, including 1 SS tab daily. Reports of breakthrough toxoplasmosis have been reported with TMP-SMX dosing of less than 3 days per week. Start after engraftment and administer as long as patient remains on immunosuppressive therapy. For patients identified as having a history of allergic reaction to sulfa medications prior to a planned transplantation, a referral for TMP-SMX challenge is recommended (see management algorithm on page 5).

a. Attempts should be made to limit drug interruptions of TMP-SMX to < 2 weeks. G-CSF should be considered if the main toxicity is felt to be neutropenia.

b. If rash develops, refer to TMP-SMX allergy management algorithm on page 5.

2. Second line prophylaxis

Atovaquone 1,500 mg PO daily is currently recommended by our program if TMP-SMX cannot be tolerated and the patient cannot be re-challenged or desensitized (see TMP-SMX allergy management algorithm on page 5). Data supporting its use in HSCT patients is scarce and breakthrough infections have been reported. Atovaquone is not a Pharmacare benefit. Coverage should be discussed with the patient before initiating atovaquone ($900/month).

References:

1. J Clin Oncol. 2018; 36:3043-3054
2. J Antimicrob Chemother 2016; 71: 2397–2404
3. Bone Marrow Transplant. 2016; 51(4): 573–580
4. Blood 2020 Aug 20;136(8):925-935

12-3. Management of TMP-SMX (Sulfonamide) Allergy

Patients identified as having a history of allergic reaction to TMP-SMX or other sulfonamide antibiotic (dapsone, sulfadiazine) prior to a planned transplant should be referred to Pharmacy for allergy assessment. Patients who meet criteria for an oral TMP-SMX challenge will be referred to the Antibiotic Allergy Clinic (Dr. R. Mak) in the Diamond Health Centre for testing. Others may have testing in Daycare if criteria are met. Patients who develop new, non-severe rash while on TMP-SMX can be considered for desensitization. Any patient with severe cutaneous rash or rash with mucosal involvement to sulfonamide antibiotics should avoid TMP-SMX.

TMP-SMX oral challenge will consist of 1 single strength tablet (80-400 mg), followed by a 1 hour observation period. If no adverse reaction, TMP-SMX prophylaxis can be dosed as above.

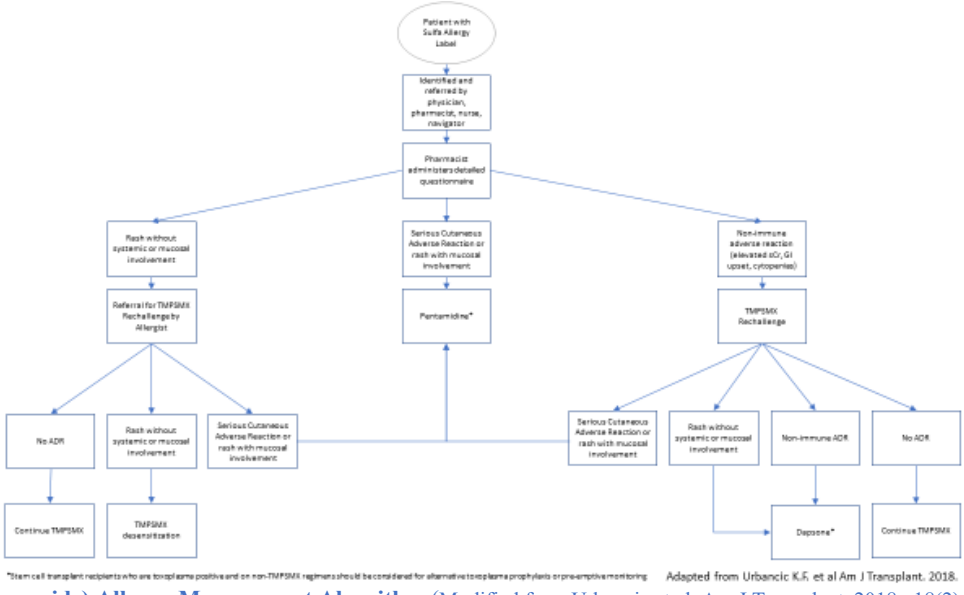

Figure 1. TMP-SMX (Sulfonamide) Allergy Management Algorithm (Modified from Urbancic et al. Am J Transplant. 2018 ; 18(2): 462-466)

12-4. TMP-SMX Desensitization

Indication

Gastrointestinal symptoms or mild rash secondary to TMP/SMX. The rash should have been an isolated cutaneous reaction without fever, mucocutaneous membrane or other organ involvement (e.g. liver/kidneys).

Basic Solution

Dilute 1 mL of pediatric suspension (contains 8 mg trimethoprim and 40 mg sulfamethoxazole) with 9 mL normal saline

DAY	SEPTRA (mL basic solution)	SULFAMETHOXAZOLE (mg)
1	0.25	1
2	0.5	2
3	1	4
4	2	8
5	5	20
6	10	40
7	15	60
8	20	80
9	25	100
10	50	200
11	0.5 regular tab BID	400
12	1 regular tab BID	800
13	1.5 regular tab BID	1,200
14	start 2 regular or 1 DS daily	1,600

Modified from Purdy et al. Ann Intern Med 1984, 100: 514–5.

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CHAPTER 13. TUMOR LYSIS SYNDROME AND DISSEMINATED INTRAVASCULAR COAGULATION

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13-1. Prophylaxis

Patients at Highest Risk

- Burkitt's Lymphoma
- B-cell ALL (L3-ALL)
- Lymphoblastic lymphoma
- Acute leukemia with hyperleukocytosis particularly AML M4 (WBC > 100 x 10^9/L)

Complications of Tumour Lysis Syndrome

- Acute renal failure (urate nephropathy)
- Electrolyte/metabolic disturbances (↑ K, ↑ PO_4, ↓ Ca)

Strategies in Prophylaxis

- Aggressive hydration (3 L/m^2/24h) to achieve urine output > 100 ml/hr.
- Alkalinize urine only if the uric acid is elevated to increase solubility of urate (use $NaHCO_3$ IV or PO to maintain pH > 7.0).
- Allopurinol (to ↓ urate formation) 600 mg PO initially then 300 mg PO q6h x 6 doses then 300 mg PO daily x 5–7 days.
- If PO_4 becomes elevated add Amphojel® (Aluminum hydroxide) 15–30 ml PO q4h. Remove $NaHCO_3$ if it has been added.
- Rasburicase can be considered on a case by case basis as described in the following section.

Laboratory Monitoring re: Tumour Lysis

Baseline: K, Ca, PO_4, urea, creatinine, LDH, uric acid (q6h x 24–48hrs)
* If baseline creatinine elevated (or other significant metabolic derangements)

1. U/S kidneys (to R/O obstruction)
2. Consult nephrology
3. If obstruction – consult urology

13-2. Rasburicase

Rasburicase is a recombinant urate-oxidase enzyme. It converts uric acid into a more soluble metabolite, allantoin. This inactive metabolite is easily excreted in the kidneys. The elimination half-life of rasburicase is 16–22 hours. The manufacturer recommended dosing for treatment of hyperuricemia is 0.2 mg/kg IV daily x 5–7 days which is based on the dosing schema used in the original clinical trials. Trifilio et al. suggested that a fixed dose of 3 mg (the contents of 2 vials) repeated in 24 hours if necessary, appeared to be effective in lowering serum uric acid levels in most patients. Due to the high cost of the drug the latter dosing schedule is favored. To measure uric acid levels after rasburicase has been given, blood must be collected into pre-chilled tubes containing heparin anticoagulant. Samples must be immediately immersed in an ice water bath before being sent to the lab.

Rasburicase Criteria for Use

1. Hyperuricemia (≥ 476 µmol/l)

PLUS

2. **one** of the following hematologic malignancies with high tumour burden:
   - Burkitt's lymphoma with LDH > 2 x ULN
   - Lymphoblastic lymphoma with LDH > 2 x ULN
   - Acute leukemia with WBC > 50,000/mm^3

PLUS

3. Evidence of tumour lysis which includes **one or more** of the following:
   - Potassium ≥ 6.0 mmol/L
   - Phosphorus ≥ 1.45 mmol/L
   - Calcium ≤ 1.75 mmol/L
   - LDH > 2 x ULN
   - Creatinine clearance < 50 ml/min

PLUS

4. Immediate need for chemotherapy (within 72 hours)

OR

Above (1, 2 & 4) plus hypersensitivity/allergic reaction to allopurinol

OR

Above (1, 2 & 4) plus unable to ingest oral allopurinol

Dose: 3 mg IV x 1 dose (cost $263) May repeat in 24 hours if magnitude of decline in serum uric acid is insufficient.

13-3 Diagnosis and Management of Disseminated Intravascular Coagulation (DIC) in Acute Leukemia

Disseminated intravascular coagulation (DIC) is a systemic process where coagulation and fibrinolysis become abnormally activated within the vasculature. Many clinical conditions can be associated with DIC (sepsis, pregnancy, trauma, some solid tumors and acute leukemias). In acute leukemia, procoagulant substances in the leukemia cells are felt to lead to rapid activation and consumption of coagulation factors and increased fibrinolysis and platelet consumption. This leads to an increased risk of serious hemorrhagic complications. Thromboembolic manifestations can also occur in DIC (VTE or arterial thrombosis), but are more commonly seen in chronic DIC in the setting of solid tumors. Amongst acute leukemia subtypes, AML (particularly APL and monocytic subtypes of AML) is more commonly associated with DIC than ALL, but DIC can be seen in all subtypes of acute leukemia.

Clinical and laboratory findings consistent with acute DIC include:

- Bleeding and ecchymosis at sites of trauma, catheters, drains
- Thrombocytopenia
- Prolonged PTT and INR
- Low plasma fibrinogen
- Elevated plasma D-dimer
- Abnormalities of other coagulation testing (Increased TT, low factor VII, X, V, II, AT, protein C/S)
- Microangiopathic changes (MAHA) in peripheral blood

Management of DIC in the context of acute leukemia is an emergency and includes treatment of the underlying cause (leukemia) and administration of platelets and coagulation factors, especially in those cases with markedly deranged coagulation profiles and/or active bleeding or planned invasive procedures. The specific thresholds for transfusion and amount of product to be given should be individualized to the specific clinical setting and patient factors such as volume status and severity or risk of bleeding.

The following thresholds for replacement are suggested as a guideline:

- Platelet transfusion to keep platelet count > 30
- Fibrinogen concentrate or cryoprecipitate to keep fibrinogen >1.5
- FFP to keep INR <1.5

The administration of antifibrinolytic agents (Tranexamic acid or epsilon-aminocaproic acid) is generally contraindicated, since blockade of the fibrinolytic system may increase the risk of thrombotic complications. However, these agents may be appropriate in cases of severe bleeding in association with a hyperfibrinolytic state.

During the acute presentation and management of DIC in acute leukemia, frequent monitoring (every 6-8 hrs) of the coagulation parameters (PPT, INR, fibrinogen and platelet count) is suggested and the coagulation parameters should be checked after the infusion of the replacement product (cryoprecipitate, fibrinogen concentrate, FFP, platelets etc) to ensure adequate replacement has occurred.

Generally DIC resolves after a few days of acute leukemia treatment, however if abnormalities should persist , then a further work-up of other potential etiologies should be explored (eg. liver disease).

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CHAPTER 14. ANTIEMETIC PROTOCOL

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14-1. Emetogenic Potential of Chemotherapy

Level	Agent	
High emetic risk (>90% frequency of emesis)	Carboplatin Carmustine Cisplatin Cyclophosphamide >1,500mg/m^2 Melphalan ≥140mg/m^2 (IV) Total Body Irradiation (TBI)	
Moderate emetic risk (30%-90% frequency of emesis)	Alemtuzumab Azacitidine Bendamustine Busulfan Cyclophosphamide ≤1500mg/m^2 Cytarabine >200mg/m^2 Daunorubicin Doxorubicin	Idarubicin Ifosfamide Imatinib Interferon alfa ≥10 X10^6 IU/m^2 Melphalan <140 mg/m^2 (IV) Methotrexate ≥250mg/m^2 Midostaurin Temozolomide Thiotepa Treosulfan
Low emetic risk (10%-30% frequency of emesis)	Arsenic trioxide Blinatumomab Bortezomib Carfilzomib Cytarabine 100-200mg/m^2 Daratumumab Dasatinib Etoposide	5-Fluorouracil Gemtuzumab Ibrutinib Inotuzumab Interferon alfa 5-10 X10^6 IU/m^2 Lenalidomide Methotrexate 50-250mg/m^2 Mitoxantrone Ponatinib
Minimal emetic risk (<10% frequency of emesis)	Asparaginase Bleomycin Cytarabine <100mg/m^2 Dexrazoxane Fludarabine Hydroxyurea Interferon alfa ≤5 X10^6 IU/m^2 Melphalan (oral low-dose) Mercaptopurine Methotrexate ≤50mg/m^2	Pegaspargase Pomalidomide Rituximab Ruxolitinib Sorafenib Thalidomide Thioguanine Tretinoin Venetoclax Vinblastine Vincristine

14-2. Antiemetic Protocol

To determine emetogenic classification of chemotherapy, please refer to tables in the Leukemia/BMT Manual.

FOR HIGHLY EMETOGENIC AGENTS/COMBINATIONS (i.e. greater than 90% frequency of emesis – e.g. BEAM, or for any protocol containing cyclophosphamide doses greater than 1.5g/m^2 or total body irradiation (TBI))**:**

On day 1 _____(indicate date), 30 minutes prior to first dose of chemotherapy, give:

ondansetron 8 mg PO BID ***AND***
dexamethasone 8 mg PO x 1 dose ***AND***
aprepitant 125 mg PO x 1 dose

On days 2 and 3 _____ and _____ (indicate dates), 30 minutes prior to first dose of chemotherapy, give:

ondansetron 8 mg PO BID ***AND***
dexamethasone 8 mg PO x 1 dose ***AND***
aprepitant 80 mg PO x 1 dose

On day 4 and continue until the last day of chemotherapy _____ (indicate dates), 30 minutes prior to first dose of chemotherapy, give:

ondansetron 8 mg PO BID ***AND***
dexamethasone 8 mg PO daily

After completion of chemotherapy, give dexamethasone 8 mg PO daily x 2 days _____ and _____ (indicate dates) for prevention of delayed nausea and vomiting.

FOR MODERATE EMETOGENIC AGENTS/COMBINATIONS (30-90% frequency)**:**

On _____ (indicate dates), 30 minutes prior to first dose of chemotherapy, give:

ondansetron 8 mg PO BID ***AND***
dexamethasone 8 mg PO daily

FOR LOW RISK AGENTS/COMBINATIONS (10-30% frequency)**:**

On _____ (indicate dates), 30 minutes prior to first dose of chemotherapy, give:

ondansetron 8 mg PO daily

FOR MINIMAL RISK agents/combinations (less than 10% frequency), routine prophylactic treatment is NOT needed.

BREAKTHROUGH NAUSEA AND VOMITING ANTIEMETICS:

prochlorperazine 10 mg PO Q6H PRN

metoclopramide 10 to 20 mg PO/IV Q6H PRN

LORazepam 1 mg PO/IV Q6H PRN

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CHAPTER 15. TOTAL PARENTERAL NUTRITION

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15-1. Total Parenteral Nutrition (TPN)

1. **To initiate TPN, a verbal order must be obtained from a L/BMT Attending Physician. Subsequent orders may be written by the clinical pharmacist. The macronutrient requirements are calculated by the Dietitian. Clinical pharmacist decides on the electrolytes based on bloodwork and completes the TPN order form.**
2. It is preferable to initiate TPN orders ***prior to*** a weekend as there is no consistent pharmacy support available on weekends and the on-call Dietitian will provide macronoutrient recommendations only.
3. **TPN order form must be received by TPN Dispensary before 1pm for same day delivery.**
4. Initial TPN total calorie requirements should not exceed 20 calories/kg based on Actual Body Weight. If Actual Body Weight is greater than 130% of their Ideal Body Weight, use Corrected Body Weight to calculate initial caloric requirements (refer to Chapter 4 for calculation formulas).
5. Convert total calories to protein, carbohydrate and fat calories to provide the optimum ratio of each substrate:
    - Protein: 20% (0.2 x total calories)
    - Carbohydrate 50% (0.5 x total calories)
    - Fat 30% (0.3 x total calories)
6. Convert calories of each substrate to grams:
    - Protein: 4 calories/gram
    - Carbohydrate: 3.4 calories/gram
    - Fat: 10 calories/gram.
7. Check to ensure maximum amounts are not exceeded for each substrate:
    - Protein: 2.5 g/kg
    - Carbohydrate (maximum for refeeding): 2-3g/kg
    - Fat: 1.5g/kg
8. Choose from the available solutions:

    <u>Amino Acids Solution</u>
    - 10% amino acid solution is available without electrolytes.
    - Order in 50 mL (5 g) increments

Dextrose Solutions

- Available in Dextrose 70%, 50% or 20%
- Dextrose 50% is preferable to avoid fluid overload

Lipid Emulsion

- Order as 100 mL, 250 mL or 350 mL
- Intralipid® 20% provides 2 kcal/mL (1.8 kcal from fat, and 0.2 kcal from glycerin)
- Intralipid® contains soybean oil emulsified with egg phospholipids. Caution if patient has severe egg or soy allergies.
- Intralipid® 20% contains vitamin K 53 mcg/100 mL; 200 mL/day will generally meet daily vitamin K requirement. If Intralipid® dose is less than 200 mL/day, add 2 mg vitamin K once weekly, unless patient is on warfarin.

9. Discontinue and/or reassess maintenance IV fluids when TPN starts to avoid overfeeding dextrose and fluid overload.
10. Discontinue peripheral vitamin K if it has been ordered on admission.
11. Discontinue peripheral H2 antagonists and proton pump inhibitors if they have been added to the TPN bag.
12. Complete the pre-printed orders for TPN bloodwork.
13. Discontinue TPN when patients are able to meet >50% of their estimated needs. Consult with the Dietitian to order calorie counts and assess nutritional adequacy.
14. To modify ongoing TPN, the following guidelines apply. However, these may be individualized for each patient depending on renal function and other factors.

Electrolytes	Target Ranges
K	• 4–4.5 mmol/L
CO2	• 22–31 mmol/L
Ca	• Correct for albumin to get therapeutic range • For every 10 g decrease in albumin from normal, add 0.2 to calcium value
Glucose	• 24 hr TPN: 6.6–9.9 mmol/L; 12 hr TPN: 10–15 mmol/L
Electrolyte Management	
K+	• For every 0.1 mmol/L increase desired in serum K, add 10 mmol KCl
Phos	• Add as K Phos unless K is high then add as Na Phos, add in multiples of 3 mmol (watch total K addition)
Mg	• Add in multiples of 2 mmol (2 mmol = 4 mEq = 0.5 g Mg)
CO2	• If low, add in form of K or Na Acetate (multiples of 2 mmol) • If high, remove Acetate if in TPN, otherwise no change
Ca	• Add in multiples of 2.3 mmol (2.3 mmol = 4.6 mEq Ca)
Glucose	• Do not add insulin unless serum glucose > 10 • If > 10, add 1 unit of regular human insulin for every mmol of glucose, round to nearest 5 units (i.e., serum glucose = 14; add 15 units of Humulin R) • Remove insulin if glucose < 7 (would rather run glucoses a little high than low) • Monitor blood glucose daily if insulin in TPN; watch steroid dose • If requiring insulin in TPN, refer to Endocrinology for follow-up
Miscellaneous	
Trace elements	• 0.5 ml daily
Zinc	• Replenish 12-15 mg for each L of diarrhea
Thiamine	• Give 200 mg daily x 7 days to abate electrolyte shifts that may occur with Refeeding Syndrome.
Vitamin C	• Give 100 mg daily to promote would healing with mucositis
Lipids	• Maximum 12 hr infusion for 2-in-1 TPN; lipids in 3-in-1 TPN may still be infused over 24 hr
Creatinine	• Adjust ranitidine dosing for decreased renal function

Electolyte Replacement

- Electrolyte levels (K, Mg, PO4) should be normal prior to the start of TPN to avoid Refeeding Syndrome.
- Refeeding Syndrome is characterized by a rapid drop in intracellular K, Mg and P04 levels post-infusion of carbohydrates to malnourished patients.
- If Refeeding Syndrome occurs, electrolytes should be aggressively repleted with boluses.
- K & Mg wasting is common when on cyclosporine, FK-506, amphotericin B & diuretics.
- Patients on cyclosporine/FK-506 generally require magnesium replacement therapy.
- Oral replacement is preferable but can be associated with GI disturbance (diarrhea).
- Serum Mg level is generally a poor reflection of body stores.
- Hypo Mg increases risk of cardiac dysrhythmias (e.g., Torsades des Pointes) (↑ QT interval with ↓ Mg).
- If K sparing diuretics are used, must do so with caution re: risk of precipitating hyperkalemia.

As of September 2002, we have been using 3-in-1 TPN solutions for patients requiring parenteral nutrition support when possible within the guidelines set out below. A 3-in-1 TPN solution is a combined solution containing Travasol® (amino acids), dextrose, and lipids (fat), facilitating the use of a single IV pump and tubing set. This method of administering TPN is more efficient, however, there are restrictions as to the amount of additives allowed in order to maintain compatibility of the solution.

Solutions will be compatible as a 3-in-1 formulation if:

- The concentration of amino acids, dextrose, and fat are within the range specified (see Formulation Concentrations table below).
- The formulation contains any combination of additives at or below the maximum concentration limits listed in the table.

Table 1. Formulation concentrations

Component	Acceptable Concentration Range/Maximum Limit
Protein	15-65 g/L
Dextrose	50-250 g/L
Fat Emulsion	15-50 g/L
Sodium	154 mEq/L
Potassium	138 mEq/L
Chloride	300 mEq/L
Acetate	110 mEq/L
Calcium Magnesium Ca + Mg	20 mEq/L 20 mEq/L < 20 mEq/L
Phosphate	15 mmol/L
Multivitamins	10 ml/L
Vitamin K	10 mg/L
Folic Acid	3.3 mg/L
Trace Element Solution	1 ml per admixture
Zinc	13.3 mg/L
Thiamine	50 mg/L
Ranitidine	100 mg/L
Insulin	65 units/L
Ascorbic Acid	100 mg/L
Selenium	100 mcg/L

Trace Elements

- Trace Element solution protocol is 0.5 mL daily (Micro+6 Concentrate®)

Trace Element	Daily Requirement [1]	0.5 mL Dose
chromium (Cr)	10 - 15 mcg [2, 3]	5 mcg
copper (Cu)	0.3 - 0.5 mg [4]	0.5 mg [4]
iodine		37 mcg
manganese (Mn)	60 - 100 mcg [4]	250 mcg [4]
selenium (Se)	20 - 60 mcg [3, 5]	30 mcg
zinc (Zn)	2.5 - 5 mg [6]	2.5 mg

[1] ASPEN 2004 Recommendations
[2] Oley Foundation 2007 recommends daily chromium dose of 5-10 mcg
[3] Reduce Cr and Se doses in renal dysfunction, as excretion is impaired
[4] Consider reducing or holding Cu and Mn doses in hepatobiliary disease or patients on long-term TPN, as excretion is impaired. May consider use of single entity products
[5] Selenium supplementation recommended in long-term TPN (over 30 days), for patients with chronic GI disease (e.g.Crohn's; short bowel; prolonged diarrhea; high output ostomy) and in cystic fibrosis
[6] Increase Zn dose for elevated intestinal fluid losses, metabolic stress, or severe wounds

Single Trace Element Products: Chromium 4 mcg/mL Selenium 40 mcg/mL Zinc 5 mg/mL

CHAPTER 16. OTHER REGIMEN RELATED TOXICITIES

16-1. Busulfan: Seizure Prophylaxis Disease

Busulfan enters the cerebrospinal fluid (CSF) rapidly after administration and achieves a CSF concentration similar and in some cases exceeding that in the plasma. High dose busulfan is reported to result in seizures within 2 to 4 days of initiation in the absence of metabolic disturbance. Temporary prophylactic anticonvulsant therapy is recommended for all patients receiving high dose busulfan as part of their conditioning regimen.[1]

Prophylactic Regimen

Lorazepam 1mg PO/SL/IV Q6h starting at 9:00 of the first day of busulfan administration and continuing for 24h after the last dose of busulfan..

16-2. Veno-Occlusive Disease (Sinusoidal Obstruction Syndrome) Prophylaxis & Treatment

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of conditioning during hematopoietic stem cell transplantation (HSCT). This historically reported mean incidence of VOD/SOS is 13.7% post-HSCT, with approximately 1/3 of these cases developing severe disease (1). Typical symptoms of VOD/SOS may include hyperbilirubinemia, painful hepatomegaly, weight gain, and ascites. VOD/SOS usually occurs within the first 30 days following allogeneic stem cell transplant, though it is possible to have a later presentation. Clinical diagnosis using the EBMT Criteria (2) includes the following:

Classical SOS/VOD In the first 21 days after HSCT	*Late onset SOS/VOD* >21 Days after HSCT
Bilirubin ⩾2 mg/dL and two of the following criteria must be present:	Classical VOD/SOS beyond day 21
	OR
Painful hepatomegaly	Histologically proven SOS/VOD
Weight gain >5%	OR
Ascites	Two or more of the following criteria must be present: Bilirubin ⩾2 mg/dL (or 34 µmol/L) Painful hepatomegaly Weight gain >5% Ascites AND Hemodynamical or/and ultrasound evidence of SOS/VOD

Clinically, VOD/SOS manifests along a spectrum of severity, from mild to severe and life-threatening. Severe VOD/SOS has previously been defined by the presence of multiple organ dysfunction/ multiple organ failure (MOD/MOF) in patients who develop with respiratory, renal and encephalopathy as a result of VOD/SOS. Severe disease with MOD/MOF is associated with a mortality of 80% (3).

The revised EBMT criteria include severity grading that better reflect the dynamic nature of VOD/SOS (2).

New EBMT criteria for severity grading of a suspected SOS/VOD in adults

	Mild[a]	*Moderate*[a]	*Severe*	*Very severe - MOD/MOF*[b]
Time since first clinical symptoms of SOS/VOD[c]	>7 Days	5–7 Days	⩽4 Days	Any time
Bilirubin (mg/dL) Bilirubin (μmol/L)	⩾2 and <3 ⩾34 and <51	⩾3 and <5 ⩾51 and <85	⩾5 and <8 ⩾85 and <136	⩾8 ⩾136
Bilirubin kinetics			Doubling within 48 h	
Transaminases	⩽2 × normal	> 2 and ⩽5 × normal	>5 and ⩽8 × normal	>8 × Normal
Weight increase	< 5%	⩾5% and <10%	⩾5% and <10%	⩾10%
Renal function	<1.2 × baseline at transplant	⩾1.2 and <1.5 × baseline at transplant	⩾1.5 and <2 × baseline at transplant	⩾2 × baseline at transplant or others signs of MOD/MOF

Risk Factors

Risk factors for post-HSCT VOD/SOS may be patient related (eg, age, history of liver diseases, active hepatitis, prior treatment, primary disease) or transplant related (eg, type of transplant, conditioning regimen intensity, GVHD prophylaxis).

Table 1. Factors that Increase the Risk of Severe Sinusoidal Liver Injury Resulting from the Conditioning Regimen

Liver Diseases at Baseline	Specific Conditioning Regimens	Concomitant Drugs During Conditioning Therapy
Inflammatory diseases	**Cyclophosphamide-based**	Itraconazole
Chronic hepatitis B or C	CY 120 mg/kg + TBI	Sirolimus (rapamycin)
Nonalcoholic steatohepatitis	(greater risk with higher TBI dosing)	Norethisterone
Alcoholic hepatitis	BCV (BCNU + CY + VP-16)	
	BU + CY (greater risk without therapeutic drug monitoring of BU)	
Fibrotic diseases	**Melphalan-based**	
Cirrhosis	BU + MEL + thiotepa	
Lobular fibrosis	BU + MEL	
Extramedullary hematopoiesis with sinusoidal fibrosis		
Cholestatic disorders	**Other regimens**	
Jaundice caused by intrahepatic cholestasis	BU + TBI (greater risk with higher TBI dosing)	
Past history	Gemtuzumab ozogamicin-containing myeloablative regimens	
Prior SOS from conventional chemotherapy	High-dose radiolabeled antibody myeloablative regimens	
Recent exposure to gemtuzumab ozogamicin		
Prior liver irradiation		
Prior myeloablative hematopoietic cell transplant		

Prophylaxis

Interventions to prevent the development of VOD/SOS have also been studied. These include the synthetic bile acid ursodeoxycholic acid (UDCA). Other therapies that have been investigated include low dose heparin, low molecular weight heparin, defibrotide, and perhaps the use of peripheral blood progenitor cells as a stem cell source (4,5). Only the prophylactic use of ursodeoxycholic acid (Ursodiol) has ever been shown to reduce the risk of VOD/SOS after stem cell transplant. In a systematic review that pooled the results of three randomized studies, the relative risk of hepatic SOS developing in patients receiving ursodiol prophylaxis compared to no prophylaxis was 0.34 (95% CI: 0.17-0.66) (6). As a result, ursodiol prophylaxis has formed our standard of care in the L/BMT Program of BC.

Ursodeoxycholic acid is used for prophylaxis at VGH for all allografts and select autografts (those receiving conditioning regimens containing VP/CY/TBI and Bu/Cy. The dose, based on a trial by Ruutu et al.(7), is 12mg/kg/day (in 2 divided doses) starting the day before conditioning and continued until day 90 post transplantation.

Fluid balance is monitored by daily weights and careful documentation of input and output. Patients should be kept near their admission weight. Furosemide is generally adequate to maintain fluid balance.

Treatment

Treatment of VOD/SOS has traditionally been supportive, with judicious fluid management. Supportive management includes vigorous diuresis, sodium restriction, and narcotics for painful hepatomegaly. These measures often suffice for mild cases. In July 2017, Health Canada approved the use of defibrotide for patients with severe VOD/SOS defined by renal or pulmonary dysfunction. Defibrotide is thought to be effective in VOD/SOS via its profibrinolytic, antithrombotic, and anti-inflammatory actions. The literature consistently indicates a survival advantage with the use of defibrotide as compared to the historical outcomes of patients with severe VOD/SOS (5, 8-11). Furthermore, several jurisdictions have demonstrated cost savings in terms of reduced ICU and hospital length stay associated with the use of defibrotide.

The L/BMT Program recommends the use of defibrotide for patients with severe VOD/SOS (ie, with MOD/ MOF or severe grade VOD/SOS per EBMT criteria). The recommended dosing is 6.25 mg IV q6h for a minimum of 21 days or until symptom improvement. Defibrotide is contraindicated in patients with active bleeding. In early 2021, Defibrotide was added to the hospital formulary list of approved medications for the treatment of hepatic sinusoidal obstructive symptoms in patients meeting the older Baltimore diagnostic criteria (bilirubin ≥34 μ/mol/L within the first 21 days of transplant, plus two of the following criteria 1. weight gain ≥ 5%, 2. painful hepatomegaly, 3. ascites). This formulary restriction excludes cases presenting greater than 21 days following transplant. However, discussion of these cases is encouraged for patients with later presentations severe VOD/SOS. Defibrotide is an expensive medication (eg. ~$110,000 for a 70kg person for a 21 day course). As such, in addition, approval is required from the L/BMT Program Director prior to use. Of practical consideration is that defibrotide is not stocked at Vancouver General Hospital and as such cannot be initiated over a weekend.

References:

1. Coppell JA, Richardson PG, Soiffer R et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant. 2010 Feb;16(2):157-68.
2. Mohty M, Malard F, Abecassis M et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. BMT. 2016 Jul; 51(7): 906–912

3. Corbacioglu S and Richardson PG Defibrotide for children and adults with hepatic veno-occlusive disease post hematopoietic cell transplantation**.** Expert Rev Gastroenterol Hepatol. 2017 Oct;11(10):885-898
4. Imran H, et al. Use of prophylactic anticoagulation and the risk of hepatic veno-occlusive disease in patients undergoing hematopoietic stem cell transplantation: a systematic review and meta-analysis. BMT 2007, 37:677-685.
5. Dignan F. BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following hematopoietic stem cell transplantation. BJH 2013, 163:444-457
6. Tay J et al. Systematic review of controlled clinical trials on the use of ursodeoxycholic acid for the prevention of hepatic veno-occlusive disease in hematopoietic stem cell transplantation. BBMT 2007, 13:206-217.
7. Ruutu T, et al. Improved survival with ursodeoxycholic acid prophylaxis in allogeneic stem cell transplantation: long term follow-up of a randomized study. BBMT 2014, 20:135-138.
8. Chopra R, Eaton JD, Grassi A et al. Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. Br J Haematol. 2000 Dec;111(4):1122-9

9. Bulley SR, Strahm B, Doyle et al. Defibrotide for the treatment of hepatic veno-occlusive disease in children. Paediatric Blood & Cancer. 2007. 48, 700–704.

10. Richardson P, Tomblyn M, Kernan N et al. Defibrotide (DF) in the Treatment of Severe Hepatic Veno-Occlusive Disease (VOD) with Multi-Organ Failure (MOF) Following Stem Cell Transplantation (SCT): Results of a Phase 3 Study Utilizing a Historical Control. Blood (ASH Annual Meeting Abstracts) (2009) 114, 654.

11. Richardson PG, Riches ML, Kernan NA et al Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood. 2016 Mar 31;127(13):1656-65

12. NHS England Clinical Commissioning Policy: Use of defibrotide in severe veno-occlusive disease following stem cell transplant
https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/b04-use-defibrotide.pdf
13. Mohty M, Malard F, Abecassis M et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation Bone Marrow Transplant. 2016 Jul; 51(7): 906–912

16-3. Engraftment Syndrome

This syndrome has been predominantly described in patients receiving an autologous stem cell transplant although it is increasing recognised in those receiving an allogeneic SCT as well. It is associated with increased treatment related mortality. If treated early with corticosteroids, it can result in a significantly improved outcome. To guide recognition of this syndrome, criteria proposed by TR Spitzer is presented below.

Major Criteria
• Temperature of ≥ 38.3ºC with no identifiable infectious etiology • Erythrodermatous rash involving more than 25% of body surface area and not attributable to a medication • Noncardiogenic pulmonary edema, manifested by diffuse pulmonary infiltrates consistent with this diagnosis, and hypoxia

Minor Criteria
• Hepatic dysfunction with either total bilirubin ≥ 2mg/dl or transaminase levels > two times normal • Renal insufficiency (serum creatinine of ≥ two times baseline) • Weight gain ≥ 2.5% baseline body weight • Transient encephalopathy unexplainable by other causes

1. A diagnosis is established by the presence of all three major criteria or two major criteria and one minor criterion.
2. Engraftment syndrome should occur within 96h of engraftment. It may present just prior to engraftment.
3. In the setting of allogeneic HSCT, additional clinical and pathological symptoms and signs of GVHD should at least initially be absent.
4. Infections must be ruled out and bronchoscopy should be considered.
5. Therapy should consist of methylprednisolone 1–2 mg/kg/day divided in twice daily doses.
6. Adjustments are to be made based on response.
7. A diagnosis of pulmonary hemorrhage must be considered as there is a close association with the engraftment syndrome. For those diagnosed with pulmonary hemorrhage treatment should include pulse steroids (0.5–1.0 gm of methylprednisolone daily for 3 days followed by a taper) and transfusion support to correct for coagulopathies.

References:
Spitzer, BMT 27, pp. 893-898, 2001.
Lavoie et al, Blood 98, pp. 777a, 2001.

16-4. Hemorrhagic Cystitis

Background

Although many chemotherapeutic agents (as well as radiation) can cause hemorrhagic cystitis (HC), the most common in our practice are the oxazaphosphorine derivatives cyclophosphamide and ifosfamide. One of the principle metabolic by-products of these agents is acrolein which is highly toxic to the uroepithelium (including not only the bladder but also the renal collecting system). In addition to their direct toxic effects, there is strong suspicion that exposure of the uroepithelium to acrolein may render it more susceptible to infection with viruses, especially adenovirus, CMV, and BK virus. It is these infections which are likely responsible for late onset cystitis (that which occurs beyond a time at which direct toxic effects should be expected to have diminished).

Prophylaxis

The mainstay of prophylaxis for patients receiving high dose cyclophosphamide (since we use little ifosfamide) is hyperhydration with intravenous fluids. Although the sulfhydryl compound 2-mercaptoethan sulfonate (mesna) has been shown to decrease HC in ifosfamide treated patients, a number of randomized studies (including our own) have shown that it is no more effective than standard hyperhydration in BMT patients.

Standard hyperhydration consists of Normal Saline or ½ Normal Saline at a rate of 3.0 L/m^2 of body surface area per 24-hour period. Depending on the patient's electrolyte status, KCl and $MgSO_4$ are generally added to the fluid. Hyperhydration is started at least 4–6 hours prior to the start of Cy or Ifos and is continued for 24–48 hours after completion of the last dose of Cy or If.

In patients in whom there is a specific contraindication to the use of hyperhydration, mesna would be considered a reasonable alternative but this should be discussed prior to administration.

Treatment of Early Cystitis

The first line of therapy for patients developing HC in the early transplant period is to reintroduce hyperhydration at the above rate. Patients in whom there are visible clots in the urine or who are experiencing bladder spasm should also have a 3-way bladder irrigation catheter inserted for continuous bladder irrigation (CBI).

Hyperhydration and/or CBI is generally continued for at least 48 hours after the urine returns to normal colour and the symptoms have resolved. When being withdrawn, it is generally advisable to do so gradually as some patients will relapse if the hydration is decreased too quickly.

Hemorrhagic Cystitis (cont.)
Treatment of Early Cystitis (cont.)

If frontline treatment fails, contact Urology for 2nd line treatment. Second line therapy of early cystitis may be with bladder irrigation with Alum (aluminum potassium sulfate). It is important to remember that Alum contains significant amounts of aluminum and that in patients with renal dysfunction or requiring prolonged therapy, aluminum levels should be checked to avoid aluminum toxicity. In rare cases, HC is resistant to all above measures and in a few cases, bladder fulguration with formalin or other chemical is necessary. Thankfully, this is uncommon enough not to need to be discussed in detail here.

Evaluation of Late Onset Cystitis

As noted previously, some patients will develop HC at a time when the inciting chemicals have long passed through the urinary tract. Many of these cases are likely due to secondary viral infection or bacterial infection superimposed on an injured mucosa. In such cases, urine for bacterial culture and blood for CMV PCR and should be undertaken prior to instituting therapy. Adenovirus testing is not routinely recommended. If the patient has suspected disseminated disease/other sites of involvement which could be due to adenovirus infection, they should be referred to Transplant ID for evaluation and testing.

Primary therapy of late onset HC is with hyperhydration ± bladder irrigation. If a specific pathogen is identified, this should be treated appropriately (ganciclovir or foscarnet for CMV, antibiotics for bacterial infections). There is no specific antiviral treatment for either BK or adenovirus. Additional manoeuvres such as noted above (alum, carboprost etc.) are rarely used in these cases and are generally not effective.

16-5. BCNU Pneumonitis

Carmustine (BCNU) is an agent with proven efficacy in autologous BMT preparative regimens for relapsed Hodgkin's disease (CBV, CBVP, BEAM, BEAC etc.).[1-2] Doses of BCNU > 450 mg/m^2 may be associated with the development of acute lung injury in approximately 20% of patients.[3-4]

In our experience BCNU pneumonitis ("BCNU lung") typically occurs between 30 and 100 days following autologous transplantation for Hodgkin's disease. A previous review of this entity at our centre pointed out that the major predictor for development of this was prior nitrosourea therapy, nevertheless, this can occur in patients who have never received prior therapy with nitrosoureas.[5]

Patients with BCNU pneumonitis may present with features that resemble pneumonia with a clinical picture of fever, cough, dyspnea and pulmonary infiltrates on x-ray. While this may represent pneumonia it may also represent BCNU pneumonitis and the latter requires urgent therapy with corticosteroids. The following recommendations are proposed:

1. All patients discharged from hospital following autologous bone marrow transplant for Hodgkin's disease, where the conditioning regimen has included BCNU, should receive appropriate instructions regarding the possibility of development of BCNU pneumonitis.

2. If patient lives locally, he/she should be evaluated immediately by BMT physician for any pulmonary symptoms.

3. If not living locally, he/she should be given a prescription for prednisone in a dose of 1 mg/kg b.i.d. (3 days' supply) and have this filled at discharge to be available should they develop pulmonary symptomatology. He/she should have the prednisone with them if they are to travel away from home during the period of highest risk. The patient should be instructed, if he/she develops typical symptoms of BCNU pneumonitis, to commence prednisone and to contact both his/her local physician as well as the Leukemia/BMT Program to ensure appropriate investigations are undertaken.

4. When the patient is reviewed the following tests should be performed:
   - Baseline laboratory work (blood counts, routine chemistries, renal and hepatic function)
   - Chest x-ray
   - Pulmonary function studies (to look for restrictive change)
   - Oxygen saturation and arterial blood gas to assess oxygenation
   - High resolution CT scan of the chest should be arranged ASAP looking for interstitial changes. Note on requisition **high resolution CT query or R/O BCNU pneumonitis**.

BCNU Pneumonitis (cont.)

5. Urgent consultation with Respiratory Medicine. Bronchoscopy should be considered in order to rule out infection such as PCP, atypical pneumonia, CMV, etc. Patients with suspected BCNU pneumonitis should be maintained on systemic corticosteroids in the form of prednisone 2 mg/kg/day or equivalent until a firm diagnosis is reached. Empiric use of appropriate antibiotics such as TMP-SMX, erythromycin, etc. should also be used as indicated.

6. Management of proven BCNU pneumonitis – prednisone should be continued for approximately 8 weeks as follows: prednisone at a dose of 2 mg/kg/day x 4 days, then 1.5 mg/kg/day x 4 days, then 1 mg/kg/day to be tapered over the next 7 weeks. Adjustments of this dosing regimen may be necessary on clinical grounds.

References:

1 Reece, DE, Connors, JM, Spinelli, JJ et al. "Intensive therapy with cyclophosphamide, carmustine, etoposide + cisplatin and autologous bone marrow transplantation for Hodgkin's disease in first relapse after combination chemotherapy', Blood 83, pp. 1193–1199, 1994.

2 Chopra, R, McMillan, AK. , Linch, DC. et al. "The place of high-dose BEAM therapy and autologous bone marrow transplantation 81, pp. 1137–1145, 1993.

3 Phillips, GL, Fay, JW, Herzig, GP et al. "Intensive 1,3-bis (2-chloroethyl) -1,-nitrosourea (BCNU), and cryopreserved autologous marrow transplantation for refractory cancer. A phase I/II study'. Cancer 52, pp. 1792–1802, 1983.

4 Wheeler, C, Antin, JH, Churchill, WH et al. "Cyclophosphamide, carmustine and etoposide with autologous bone marrow transplantation in refractory Hodgkin's disease and non-Hodgkin's lymphoma: A dose-finding study". Journal of Clinical Oncology 8, pp. 648–656, 1990.

5 Sayegh, A, Reece, D, Barnett, M et al. "Interstitial pneumonitis (IP) following high-dose chemotherapy (CT) with cyclophosphamide, BCNU, etoposide + cisplatin (CBV+ P) and autologous bone marrow transplantation for advanced Hodgkin's disease (HD): Incidence, risk factors and outcome. J Cell Biochem, 1992; (Suppl 16a): 205a.

16-6. Primary Graft Failure

Primary graft failure is the failure to achieve a neutrophil count of 0.5 x 10^9/L for 3 consecutive days some time after myeloablation. With conventional marrow stem cell transplants, 99% of patients undergoing matched sibling SCT and 95% of patients undergoing matched unrelated donor transplant will engraft. If a patient has not achieved an ANC $\geq$ 0.1 x 10^9/L by day 21, graft failure should be considered. The peripheral blood smear should be examined for the presence of neutrophils. If no neutrophils are seen, G-CSF should be started at 5–10 µg/kg/day. If there is no significant improvement by day 28, a bone marrow aspirate and biopsy should be performed and consideration for a second transplant should be made.

Risk Factors for Graft Failure

- Unrelated donor transplant
- Mismatched donor transplant (related & unrelated)
- Risk is greater with HLA class 1 mismatches
- Suboptimal stem cell dose
- T-cell depleted marrow transplant
- Reduced intensity stem cell transplant
- Umbilical cord blood transplant (criteria for graft failure and the use of growth factors are different)

References:
Wolff, BMT 29, pp. 545–552, 2002.
Petersdorf et al, Blood 92, pp. 3515–3520, 1998.
Weisdorf et al, Blood 99, pp. 1971–1977, 2001.
Nemunaitis et al, Blood 76, pp. 245–253, 1990.

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Weisdorf et al, Blood 99, pp. 1971–1977, 2001.
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LEUKEMIA/BMT MANUAL E-EDITION

CHAPTER 17. OBTAINING G-CSF FOR OUTPATIENTS

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17-1. Process for Obtaining G-CSF (Filgrastim) for Outpatients

There are two filgrastim products available in Canada. Grastofil is a subsequent entry biologic of filgrastim based under the reference product Neupogen. Both Grastofil and Neupogen have been approved by Health Canada for the same indications, but are not considered interchangeable products. In BC, PharmaCare covers Grastofil under the Special Authority Program for all indications. In addition, PharmaCare will continue to cover Neupogen for donors requiring filgrastim for stem cell collection. Procedures for obtaining Grastofil or Neupogen are outlined below.

Neupogen for Donor Stem Cell Mobilization

Neupogen is the preferred filgrastim product for donors undergoing stem cell collection in our Program. In order to obtain coverage through the PharmaCare Special Authority program, the following must be done:

1. Complete the Neupogen template PharmaCare Special Authority Request form available on BMT Accuro. Sections 1, 2 and 3 MUST be filled in completely and the form signed by the prescriber in the appropriate section in order for PharmaCare to process the request. Ensure that the date of BMT is included in Section 3.

2. Fax the completed form to **PharmaCare** at **1-800-609-4884** at least TWO working days before the donor requires the prescription. PharmaCare will NOT accept telephone requests for Neupogen. Once approval is granted, it is good for 3 months. After that time, a new request will need to be sent should the patient require another prescription.

3. Fax prescription to Macdonald's Prescriptions at 746 West Broadway. Specify Neupogen on the prescription and indicate *No Substitution* along with the directions for use and quantity to fill. Neupogen is available in 300 mcg or 480 mcg pre-filled syringes or single-use vials.

Grastofil for Autologous Stem Cell Mobilization

Grastofil is the preferred filgrastim product for autologous stem cell mobilization in our Program. In order to obtain coverage through the PharmaCare Special Authority program, the following must be done:

1. Complete the Grastofil template PharmaCare Special Authority Request form available on BMT Accuro. Sections 1, 2, 3 and 4 MUST be filled in completely and the form signed by the prescriber in the appropriate section in order for PharmaCare to process the request. Ensure that the date of BMT is included in Section 4.

2. Fax the completed form to **PharmaCare** at **1-800-609-4884** at least TWO working days before the patient requires the prescription. PharmaCare will NOT accept

telephone requests for Grastofil. Once approval is granted, it is good for 6 months. After that time, a new request will need to be sent should the patient require another prescription.

3. Provide a prescription to the patient. Specify Grastofil on the prescription and include the directions and quantity. Grastofil is available in 300 mcg or 480 mcg pre-filled syringes.

4. Instruct the patient to go to Macdonald's Prescriptions at 746 West Broadway or a pharmacy of their choice.

Patients who require financial assistance for Grastofil can be referred to the Answers Program. Complete the Answers Patient Enrolment Form available on BMT Accuro.

Grastofil for Indications Other than Stem Cell Mobilization

For patients who need to have Grastofil filled immediately, and cannot wait the turnaround time for Special Authority approval (e.g. febrile neutropenia), the following must be done:

1. Complete the Grastofil template PharmaCare Special Authority Request form available on BMT Accuro. Sections 1, 2, 3 and 4 MUST be filled in completely and the form signed by the prescriber in the appropriate section in order for PharmaCare to process the request. Fax the completed form to **PharmaCare** at **1-800-609-4884**. Telephone requests are not accepted. Once approval is granted, it is good for 6 months.

2. Photocopy the completed form and keep a copy for the patient's chart. Provide the original form to the patient along with a prescription. Specify Grastofil on the prescription and include the directions and quantity. Grastofil is available as 300 mcg or 480 mcg pre-filled syringes.

3. Instruct the patient to go to Macdonald's Prescriptions at 746 West Broadway or Shoppers Drug Mart in the Diamond Centre to fill the prescription. The patient may go to a pharmacy of their choice, but there will likely be a delay in drug procurement.

Patients who require financial assistance for Grastofil can be referred to the Answers Program. Complete the Answers Patient Enrolment Form available on BMT Accuro.

18-1. Platelet Transfusion Policy

1. 'Standard' platelet transfusion threshold for both inpatients and outpatients is **10 x 10^9/L**. Platelets are **not** to be routinely requested from the BTS by the nursing staff, i.e., a doctor's order must be on the chart, verbally or in writing, before platelets are requested.

2. Patients to be assessed each morning for the following factors, and the threshold to be adjusted upward for that day if one or more of these factors exist.

   a. Temperature > 38˚C at any time in the preceding 24 hours .....**20 x 10^9/L**
   b. Fresh minor bleeding (not requiring a RBC transfusion).....**20 x 10^9/L**
      e.g., petechiae or mucosal bleeding
   c. Major bleeding (including retinal) .....**> 50 x 10^9/L**
   d. Invasive procedure required.....**> 50 x 10^9/L**

3. Patients with APL, DIC or other coagulation abnormalities .....**> 50 x 10^9/L**

4. The standard aliquot of platelets from the BTS is a pooled unit of buffy coats harvested from 4 ABO-matched whole blood donations. Although platelets ABO-matched for the recipient are preferred, they may not be routinely available. If so, unmatched platelets may be issued. Single donor platelets are also collected by Canadian Blood Services. Most of these collections are issued to patients on a first come, first served basis to supplement the supply of pooled platelet concentrate. If a patient is actively bleeding, it may be useful to request single donor platelets as they usually contain a higher number of platelets. All platelets products are leukodepleted.

5. Platelets HLA-matched for the recipient (Class 1 matching only) can be obtained from the Canadian Blood Services (CBS) for patients who fulfill the following criteria:

   a. Poor 15 minute to one hour post transfusion platelet count increments after a minimum of 2 unmatched transfusions. A poor response is defined as a corrected count increment (CCI) of less than 5:

$$CCI = \frac{(\text{post platelet count} - \text{pre platelet count}) \times \text{BSA of patient } (m^2)}{\text{Number of platelets transfused } (\times 10^{11})}$$

   (The mean number of platelets in a bag of pooled buffy coat is 3.3 x 10^{11})

   b. The presence of HLA or anti-platelet antibodies in patient serum. (Performed by the CBS).

   c. No obvious cause (such as splenomegaly or DIC) for the poor response.

Platelet Transfusion Policy (cont.)

d. No recent administration of ATG which can cause a false positive ELISA antibody screen. A request for HLA-matched platelets is made by completing the "Request for HLA-matched Platelets" form and faxing it to the BTS. **Please note that this form must be filled out completely in order for the CBS to process your request. In particular, the Class 1 HLA typing of the patient is absolutely required as part of this request. If the HLA typing is not available on the patient chart it can usually be obtained from one of the BMT Navigators 604-875-4863.** It will be at least 48 hrs (and frequently longer) from the time a request is received to the time that the HLA-matched cells will be available for transfusion. Due to limitations in the number of donors available, most HLA-matched platelet products will **not** be ABO-matched for the recipient. Post transfusion platelet counts must be performed on HLA-matched products.

18-2. Indications for Red Cell & Platelet Irradiation

See current Blood Transfusion Service requisition for cellular blood products for guidelines.

Reference:

Provincial Blood Co-ordinating Office Medical Policy Manual Version 3.0, 2015 -03-06

18-3. Bone Marrow Processing

Major blood group incompatibility between the bone marrow donor and recipient is dealt with in the following ways:

1. If the donor plasma is not compatible with recipient red cells, the marrow is plasma reduced in the Clinical Cell Therapy Laboratory at the B.C. Cancer Research Centre. The processed marrow will have a total volume of 100 to 200 ml and will be accompanied by a report indicating the number of nucleated cells present. Approximately 80% of the nucleated cells in the original marrow harvest are recovered by this procedure so that the dose of cells per kg patient weight should still be ~ 2–3 x 10^8/kg.

2. If donor red cells are incompatible with recipient plasma, the marrow is red cell depleted in the Cell Separator Unit (CSU). Since the volume of the marrow harvest is reduced from 1–1.5 L to 100–200 ml, marrow that is red cell depleted in the CSU is also plasma depleted, i.e., it should never be necessary for marrow to undergo plasma depletion in the Cell Therapy Lab if it is being processed in the CSU.

   The goals of the red cell depletion procedure are to:

   a. Reduce the volume of incompatible packed red cells transfused to less than 10 ml.
   b. Recover at least 80% of the total mononuclear cells (lymphocytes + monocytes) from the original marrow. Because a large proportion of the nucleated cells in the marrow are neutrophils, nucleated RBCs and other cell types that are not recovered in the red cell depletion process the overall nucleated cell recovery is quite low (typically 20–30%) and

the dose of nucleated cells/kg patient weight less than 1 x 10^8.

When the processed marrow is delivered to the ward it will be accompanied by a report indicating the % recovery and total number of mononuclear cells and the volume of packed RBC that the product contains, as well as the total cell dose per kg of recipient weight.

18-4. Infusion of Cryopreserved Stem Cell Products

1. All cryopreserved stem cell & DLI infusions are to be booked by the physician (staff or fellow) with the Clinical Cell Therapy Lab (604-675-8000 ext. 7745) before commencing conditioning or with appropriate notice (e.g., 1 week) in the case of DLI. Date and time of re-infusion to be indicated on order sheets.

2. Premedication

   a. Hydrocortisone 100 mg IV (1 h pre)
   b. Diphenhydramine 50 mg IV (30 min pre)
   c. Acetaminophen 650 mg PO (30 min pre)
   d. Additional antiemetics/anxiolytics as required

3. The stem cell product/DLI will be administered by the physician immediately after thawing into a saline IV (non-filtered tubing) via a central venous catheter. The stem cell product should be infused as quickly as tolerated (generally 8–12 ml/min). Other medications should be held during re-infusion.

4. Patients will be monitored via pulse oximeter during infusion of the stem cell product and for 15 minutes post completion. Vital signs (pulse, BP, temp) + O_2 saturation are to be monitored Q15MIN for 1 hour post completion of infusion.

5. If patients are to receive large volume re-infusion (i.e., > 10 ml/Kg recipient body weight) of cryopreserved cells, then consideration should be given to dividing this into 2 (or more) aliquots for separate re-infusions (e.g., successive days).

18-5. Guide to the Infusion of Cryopreserved Products

Types	Autologous or Allogeneic Hematopoietic Progenitor Cells (Marrow/Apheresis/Cord); Therapeutic Cells (T-cells)
Who Administers	Specially trained RN administers with MD present in the patient room for the entire duration of the infusion.
Administration Tubing/Solution Note: Do not use an infusion pump	Use standard blood product administration set with 170–260 micron pore. Y-connect to a nonfiltered IV tubing with distal access port and attach to largest CVC lumen (all primed with NS). Retain the blood tubing package for verification during double- checking of product to be infused. **White cell filter is absolutely contraindicated.**
Vital Signs	Obtain baseline VS prior to infusion; Repeat Q15MIN during infusion and for 1 hour post infusion. Notify MD of fever during or after infusion.
Cardiac Monitoring	Not required
Emergency Equipment	Suction and oxygen equipment in patient.
Pulse Oximetry	Continuous monitoring until 15 minutes post-infusion, then Q15MIN until 1 hour post infusion.
Physician Presence on Ward	MD on patient ward for the entire infusion and will remain on the ward for 15 minutes after completion.
Duration of Infusion	10 ml per minute as tolerated. Volumes > 300 ml may require more than one infusion (due to amount of DMSO). A physician order is required for rate and number of infusions.
Pre-medications	As ordered – hydrocortisone 100 mg IV 1 hour pre-infusio, diphenhydramine 50 mg IV 30 minutes pre-infusion; acetaminophen 650 mg PO 30 minutes pre-infusion; antiemetics PRN.
Administration of medications during infusion	Physician order required. In the usual circumstances all IV infusions/medications except cyclosporine are held during infusion.
Administration of medications pre/post infusion	• All chemotherapy except melphalan: at least 48 hours must elapse between completion of last dose and commencement of marrow infusion • Melphalan: at least 24 hours must elapse between completion of last dose and commencement of marrow infusion • Methotrexate (if applicable) – 24 h must elapse between completion of marrow or PBSC infusion and first dose • Post infusion: fluids and medications will be resumed unless otherwise ordered.
Administration of blood products pre/ post-infusion	As ordered. Generally avoid transfusions 12–24 h pre and up to 24 h post infusion.
Administration following TBI	Bone marrow or PBPC may be administered without a waiting period following **completion** of TBI
Potential complications during infusion	Severe nausea, hypertension, bradycardia, heart block, allergic reaction/anaphylaxis secondary to DMSO (marrow preservative), pulmonary edema, emboli.Transfus Med Rev . 2018 Jun 1;S0887-7963(18)30023-3
Storage if infusion delayed	N/A - given immediately after thawing
Additional information	DMSO creates a strong taste and smell (described as garlic, corn or oyster-like) which lasts 12–24 hours. The patient may have red coloured urine post infusion due to destruction of red blood cells in thawing
Double-checking product prior to infusion	All CTP are to be double-checked by two staff members (RN and another RN, BMT Coordinator, TFL Technician, or MD) in accordance with standards outlined in the Patient Care Guidelines. A physician's order must be written prior to infusion of any product that does not meet standard criteria.

18-6. Guide to the Infusion of Non-Cryopreserved Products

Types	Autologous or Allogeneic Hematopoietic Progenitor Cells (Marrow/Apheresis/Cord); Therapeutic Cells (T-cells)
Who Administers	Specially Trained RN 1:1 in patient's room for entire infusion
Administration Tubing/Solution Note: Do not use an infusion pump	Use standard blood product administration set with170–260 micron pore. Y-connect to a non-filtered IV tubing with distal access port and attach to largest CVC lumen (all primed with NS). Retain the blood tubing package for verification during double-checking of product to be infused. **White cell filter is absolutely contraindicated.** To administer T cells A via syringe, (< 10 mL fresh) use standard IV tubing primed with NS. Use CVC or peripheral IV access. Run NS via gravity. Chose port as close as possible to patient on the IV line and attach syringe. Clamp line above (use bull dog clamp). Infuse cells over 1-5 minutes. Flush port with 10 mL NS. Stop IV fluids when line clear of cells.
Vital Signs	Obtain baseline VS prior to infusion, then Q15MIN x 4 and Q1H for duration of infusion. Notify MD of fever during or after infusion.
Cardiac Monitoring	Not required
Emergency Equipment	Suction and oxygen equipment in patient room.
Pulse Oximetry	Not required
Physician Presence on Ward	MD on ward for first 15–30 minutes of infusion; if no complications, available by pager for remainder of infusion
Duration of Infusion	Physician order required. Determined by volume to be infused and status of patient
Pre-medications	As ordered – usually not required. Consider pre-medication for history of blood product reactions or ABO incompatibility.
Administration of medications during infusion	Physician order required. In the usual circumstances all IV infusions/medications except cyclosporine are held during infusion.
Administration of medications pre/post infusion	• All chemotherapy except melphalan – 48 hours must elapse between completion of last dose and commencement of marrow infusion • Methotrexate (if applicable) – 24 h must elapse between completion of marrow infusion and first dose • Post infusion, fluid and medications will be resumed unless otherwise ordered
Administration of blood products pre/ post infusion	As ordered. Generally avoid transfusions 12–24 h pre and up to 24 h post marrow infusion.
Administration following TBI	Bone marrow or PBSC may be administered immediately following completion of TBI
Potential complica-tions during infusion	Pulmonary edema, pulmonary emboli, allergic reaction/anaphylaxis
Storage if infusion delayed	Storage conditions are on the product label. If not given immediately unmanipulated products can be stored at room temperature. Overnight storage must be in Blood Bank at 4°C.
Double-checking product prior to infusion	All CTP are to be double-checked by two staff members (RN and another RN, BMT Coordinator, TFL Technician, or MD) in accordance with standards outlined in the Patient Care Guidelines. A physician's order must be written prior to infusion of any product that does not meet standard criteria.

18-7. Allogeneic Stem Cell Transplant Immunoglobulin (IgG) Replacement Guidelines

Routine assessment of IgG levels as Day 100 post allogeneic stem cell transplant.

All haplo-identical and cord blood allogeneic stem cell transplant recipients should have their IgG levels checked beginning at day 30 and be given monthly replacement if IgG levels < 4 g/L as outlined in the L/BMT transplant protocols. These patients are highly immunosuppressed and can be expected to take a longer time for immune reconstitution.

For other allogeneic stem cell transplant recipients (unrelated donor and sibling-matched) consider checking IgG levels between Day 30 and 100 if recurrent bacterial infections (particularly sinopulmonary infections) or multiple or difficult to treat viral reactivations (CMV, EBV).

Intravenous Immunoglobulin (IVIg) or Subcutaneous Immunoglobulin (SCIg) Replacement

IVIg or SCIg replacement should be avoided prior to Day 30 following allogeneic stem cell transplant due to an increased risk of Sinosoidal Obstructive Syndome (SOS).

- For IgG levels above 6g/l, replacement with IVIg or SCIg is likely not required. IF recurrent infections are problematic with IgG levels above 6 g/L, suggest Ig subclass testing to detect subclass deficiencies (eg CD 4) and a Transplant ID consult.

- IgG level 4-6g/L: replacement with IVIg or SCIg at physician's discretion. Consider IVIg 400 mg/kg Q monthly or SCIg replacement if the patient is on high doses of immunosuppression for GVHD treatment or if there is a history of recurrent/ refractory infection. Reassess every 6 months.

- IgG level < 4g/ L: replacement IVIg 400 mg/kg Q monthly or SCIg at physician's discretion. Data to support replacement at this level exists. Reassess every 6 months.

For all replacement IVIg or SCIg ordered, there should be a trough IgG level redrawn on the day prior to the sixth monthly dose. This should be used in combination with the patient's clinical history to determine whether further replacement is warranted. In general, the maximum period for IVIg or SCIg replacement post allogeneic stem cell transplant is 1 year. In very select circumstances (eg. profound immunosuppression related to GVHD, recurrent infections after IVIg or SCIg is stopped) the period of replacement can exceed 1 year at the discretion of the ordering physician.

References:

Lachance S, Christofides AL, Lee JK, Sehn LH, Ritchie BC,‖Shustik C Stewart, Toze CL. Haddad E & Vinh DC. A Canadian perspective on the use of immunoglobulin therapy to reduce infectious complications in chronic lymphocytic leukemia. *Current Oncology*. 2016 Feb; 23(1): 42–51.

Raanani, P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L and Shpilberg, O. Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation. *Cochrane Database of Systematic Reviews*, 2008(4). doi:10.1002/14651858.CD006501

LEUKEMIA/BMT MANUAL E-EDITION

CHAPTER 19. GRAFT VERSUS HOST DISEASE (GVHD)

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19-1. Acute GVHD

Risk Factors Considered in the Model

Step 1: Perform staging of individual organ systems for acute GVHD.

a. Skin Stage

- +1 Maculopapular eruption involving less than 25% of the body surface
- +2 Maculopapular eruption involving 25–50% of the body surface
- +3 Maculopapular rash > 50% of the body surface
- +4 Generalized erythroderma with bulla formation and often with desquamation

b. Liver Stage*

- +1 Bilirubin 35–50 µmol/L
- +2 Bilirubin 51–100 µmol/L
- +3 Bilirubin 101–255 µmol/L
- +4 Bilirubin > 255 µmol/L

* If patient has documented GVHD of the liver and documented alternative cause of hyperbilirubinemia (i.e., veno-occlusive disease) then downstage liver GVHD by 1 stage

c. Gut Stage**

Severity is categorized according to volume of diarrhea (average of two consecutive days) or the presence of nausea/vomiting.

- +1 Diarrhea volume = 500–900 ml/day or persistent nausea (+ vomiting) with histological proof of GVHD within the gut
- +2 Diarrhea volume = 1,000–1,500 ml/day
- +3 Diarrhea volume > 1,500 ml/day
- +4 Severe abdominal pain or ileus

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

Step 2: Add organ staging together to determine overall clinical grade.

Table 1. Clinical grading of severity of acute GVHD

Grade	Skin	Liver	Gut
0 (none)	0	0	0
I (mild)	+1 to +2	0	0
II (moderate)	0 to +3†	+1 and/or	+1
III (severe)	——	+2 to +3 and/or	+2 to +4
IV (life-threatening)‡	+4 or	+4	——

† Skin stage 3 alone is also considered overall grade II
‡ Severe decrease in performance status due to GVHD should be considered grade IV irrespective of the organ stages
From Przepiorka et al: Consensus conference on acute GVHD grading. Bone Marrow Transplant 15: 825-8, 1995.

Acute GVHD (cont.)

GVHD Prophylaxis

Usual regimen is cyclosporine (CSA)+ methotrexate:

Cyclosporine: **1.5 mg/kg/dose* IV Q12H** to be given at 06:00 and 18:00. Start on day -2 (18:00) or as per protocol**

Check whole blood trough level at 05:30* (30-60 minutes prior to IV dose).**
Target cyclosporine trough level (mcg/L, 12 hours post-dose)

†Day +1 until tapered: 200 - 300‡

* Actual body weight
** Because of variable absorption kinetics, it is recommended to leave the patient on IV cyclosporine for approximately 3 weeks before switching to oral cyclosporine with myeloablative SCTs.
***Trough levels for oral cyclosporine should be drawn at 07:30 (30-60 minutes prior to PO dose)
† Cyclosporine doses should not be increased before day +1, to allow for steady state levels to be reached.
‡ Target low end of therapeutic range until completion of methotrexate doses.

Dosage adjustment based on whole blood concentration:

Dose adjustments should be based on **steady state levels** which may take 4-5 days to achieve. Consider trends when levels are drawn prior to steady state.

If CSA level < 200, ↑ by 25%; if 300-400, ↓ by 25%; if > 400, skip one dose and ↓ by 25-50%.

IV: PO conversion. 1: 1 or 1:1.5 (e.g. 1 to 1.5 times the IV dose = PO dose) with a level drawn 2 days later. Historically, conversion from CIVI to PO have been converted at 1:2 IV:PO though similar conversions with q12h IV dosing have led to supra-therapeutic dosing. A range of 1:1 or 1:1.5 IV: PO conversion is recommended depending on the patient's renal and liver function.

PO cyclosporine is continued until day +60 to +100 (depending on risk of disease relapse) when it can be tapered (in the absence of GVHD) by 25–50 mg/week.

For patients who receive myeloablative conditioning with ATG or PTCy and do not have acute GVHD by D+60, a CSA taper can be started at 25-50mg per week at D+60. The speed of taper can be further adjusted based on chimerism results.

- CSA levels should not be monitored once tapering starts.

The following equation may be used to guide dose adjustments:

$$\text{New dose} = \frac{(\text{current dose})(\text{target whole blood level})}{(\text{current whole blood level})}$$

Methotrexate: Delivery target ≥ 80% of total scheduled MTX dose

Myeloablative regimen	**RIC Regimen**
15 mg/m^2‡ (IV) day +1 10 mg/ m^2‡ (IV) day +3, +6, +11	5 mg/m^2‡ (IV) day +1, +3, +6

‡ Adj50 BSA when ideal weight is less than actual weight

GVHD Prophylaxis: Cyclosporine & Methotrexate Dose Modifications

Table 1. Cyclosporine dose calculation

Cyclosporine Dose Calculation *(add % reduction from each category for total % reduction)*				
Dose Reduction	**0**	**25%**	**50%**	**100%**
Direct Bilirubin	< 34	34-50	51–100	———
Serum creatinine	< 1.6 baseline	1.6–1.9 x baseline	———	> 1.9 x baseline
MAHA	———	———	LDH > 600	LDH > 1,000 or neurologic symptoms

Table 2. Methotrexate dose calculation for standard allografts and MUD transplants

Methotrexate Dose Calculation for Standard Allografts and MUD Transplants *(add % reduction from each category for total % reduction)*				
Dose Reduction	**0**	**25%**	**50%**	**100%**
Direct Bilirubin	< 34	34–50	51–100	> 100
*Creatinine clearance	> 85	65–84	50–64	< 49
*Significant fluid collection	None	Drained	———	Undrained

Mucositis	Grade 0–I or Mild Grade II	Moderate Grade II	Severe Grade II	Grade III

$$\text{Creatinine Clearance (ml/min)} = \frac{(140 - \text{age})\ (\text{Females x } 0.85)}{\text{Serum creatinine x } 0.011\ (\mu\text{mol/L})}$$

* Every attempt should be made to minimize nephrotoxic drugs (including cyclosporine) and to drain third space fluid collection (especially pleural) by inserting a drainage tube in order to optimize methotrexate dose delivered.

GVHD Prophylaxis: Cyclosporine & Methotrexate Dose Modifications (cont.)

Methotrexate Dose Calculation for RIC Transplants* *(add % reduction from each category for total % reduction)*			
Dose Reduction	**0**	**25% total if <u>two</u> of these criteria**	**25% for <u>each</u> of these criteria met**
Direct Bilirubin	< 50	51–100	> 100
Creatinine clearance	> 65	40–64	< 40
Significant fluid collection	Drained or none	———	Undrained
Mucositis	Grade 0–I or Moderate Grade II	Severe Grade II	Grade III

$$\text{Creatinine Clearance (ml/min)} = \frac{(140 - \text{age})\ (\text{Females x } 0.85)}{\text{Serum creatinine x } 0.011\ (\mu\text{mol/L})}$$

* The goal is to administer as much of the methotrexate as possible with minimal dose adjustments as the overall methotrexate dosage is considerably reduced from that administered in a standard allograft. If clarification is required, please discuss with Clinical Director.

Tacrolimus Dosage Guidelines

Tacrolimus 0.03 mg/kg/day CIVI (PO dose = 0.06 mg/kg BID)
Target Level **Day +1 to +21: 8-12 mcg/L***
Day +22 until tapered: 4–12 mcg/L
*In patients with multiple comorbidities and/or at high risk of renal toxicity, consider target of 4-12 ug/L.

Table 1. Tacrolimus dose adjustments based on whole blood concentration**

Tacrolimus Whole Blood Level	IV	PO
< 4	increase by 25-50%	increase by 25-50%
4-7	no change *OR* increase by 25%	no change *OR* increase by 25%
8-12	no change	no change
13–19	decrease by 25%	decrease by 25%
20–24	hold x 6 hr and resume at 50%	hold one dose and resume at 50%
> 24	hold and resume at 25% when level < 15	hold and resume at 25% when level < 15

**This guide is intended for patients with normal renal function and does not replace clinical judgment. Consider renal function when determining dose adjustment.

The following equation may be used to guide dose adjustments:

$$\text{New dose} = \frac{(\text{current dose})(\text{target whole blood level})}{(\text{current whole blood level})}$$

Table 3. Tacrolimus dose adjustments based on renal insufficiency

Serum Creatinine	Dosage Adjustment
1.0–1.5 x baseline	75–100% current dose
1.6–1.9 x baseline	25–50% current dose
> 1.9 x baseline	Hold and resume at 0–50% current dose if renal dysfunction is stable

Mycophenolate Mofetil (MMF) Dosage Guidelines

Haploidentical Transplants	Umbilical Cord Transplants
• If patient >50 kg: 1 g IV/PO BID • If patient 50 kg or less, 15 mg/kg IV/PO BID Start day +5 to day +60	• 1000 mg PO TID Start day -3 to day +60

Therapeutic drug monitoring of MMF is not routinely performed at our centre.

IV:PO conversion = 1:1

References:

Quan DJ, Winter ME. Immunosuppressants: Cyclosporine, Tacrolimus and Sirolimus. Basic Clinical Pharmacokinetics 5th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2010.p.250-276.

Penack O, Marchetti M, Ruutu T, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol. 2020 Feb;7(2):e157-e167. doi: 10.1016/S2352-3026(19)30256-X. PMID: 32004485.

Neoral and Sandimmune product monograph. Novartis Pharmaceuticals Canada Inc. Date of Revision: January 9, 2015.

Sandoz-tacrolimus product monograph. Sandoz Canada, Inc. Date of Preparation: June 12, 2019.

Acute GVHD (cont.)

Table 4: Pharmacokinetic Interactions of Cyclosporine (CSA) & Tacrolimus (FK)

Drug	Possible Mechanism	Severity	Onset	Adverse Effects	Management	Documentation
Anticonvulsants:						
• Phenytoin	Induction of the enzymes → ↑ CSA/FK metabolism	major	Delayed	↓ effectiveness of CSA/FK → ↑ risk of GVHD	↑ CSA/FK dose by 30% and monitor levels	probable
• Carbamazepine		moderate				possible
• Phenobarbital		major				suspected
• Primodone						
Antimicrobial:						
• Erythomycin	↓ CSA/FK metabolism, ↑ rate of absorption, ↓ vol of distribution	major	delayed	↑ CSA/FK levels, ↑ risk of toxicity	↓ CSA/FK dose by 30-50%, monitor level	established
• Clarithromycin						
• Ketoconazole		moderate	delayed	same as above	Monitor level, may need to ↓	probably
• Itraconazole		moderate	delayed	same as above	CSA/FK by 30-50%	suspected
• Voriconazole		moderate	delayed	same as above	Reduce CSA by 50%; FK by 66%	established
• Posaconazole		moderate	delayed	same as above	Reduce CSA by 25%; FK by 66%	established
• Fluconazole	↓ CSA/FK metabolism	moderate	rapid	neurotoxicity, confusion, tremor	Monitor level, occurs with doses > 200 mg/day;	suspected
• Imipenem	Same as above, may be additive toxicity				Consider other antibiotic	
• Nafcillin	Induction of hepatic enzymes	moderate	delayed	same as above	Monitor CSA/FK levels	possible
• Rifampin	Same as above	major				suspected
• Sulphonamide + Trimethoprim (iv)	Unknown	major				suspected
• Letermovir	↓ CSA/FK metabolism CSA ↓ letermovir metabolism	moderate major		↑ CSA/FK levels ↑ letermovir exposure	Monitor CSA/FK levels Reduce letermovir to 240 mg/day	suspected established

Acute GVHD (cont.)

Pharmacokinetic Interactions of Cyclosporine (CSA) & Tacrolimus (FK)

Drug	Possible Mechanism	Severity	Onset	Adverse Effects	Management	Documentation
Octreotide	↓ oral absorption of CSA/FK by inhibiting the secretion of pancreatic lipase or bile acids	major	Delayed	Same as above	↑ oral CSA/FK dose by 30-50%	suspected
Imatinib	↑ intestinal absorption of CSA via CYP3A and/or the drug transporters p-glycoprotein and/or breast cancer resistance protein (BCRP, ABCG2)	moderate	Unknown	↑ CSA/FK levels, ↑ risk of toxicity	Monitor for CSA level and/or toxicity	suspected
NSAIDs: • Ibuprofen • Naproxen • Indomethacin	↑ CSA/FK exposure	major	Early	↑ nephrotoxic effects of CSA/FK	Avoid	established
Antidepressant: • Nefazodone • Fluoxetine • Fluvoxaminel	↓ CSA/FK metabolism	moderate	Delayed	↑ CSA/FK levels, ↑ risk of toxicity	Consider another antidepressant and/or monitor CSA/FK levels closely	suspected
Cardiovascular: • Diltiazem • Verapamil • Nicardipine • Amiodarone	May inhibit hepatic metabolism of CSA/FK	major moderate moderate	delayed delayed delayed	↑ CSA/FK levels same as above same as above	Monitor CSA/FK levels on start, stopped or dose alteration of CSA/FK	established probable suspected

Acute GVHD (cont.)

Pharmacokinetic Interactions of Cyclosporine (CSA) & Tacrolimus (FK)

Drug	Possible Mechanism	Severity	Onset	Adverse Effects	Management	Documentation
Gastrointestinal: • Metoclopramide • Domperidone	↑ absorption of CSA/FK	moderate	Delayed	CSA/FK toxicity	Monitor level, may need to ↓ CSA/FK by 30-50%	suspected
Corticosteroids: • Methylpredniso-lone • Prednisone	Reduced liver degradation of either or both drugs	moderate	Delayed	Therapeutically beneficial for transplantation, may also ↑ toxicity	May need to adjust the dosage of either drug if signs of toxicity	possible
Acetazolamide:	Unknown	moderate	Delayed	↑ CSA/FK levels, nephrotoxicity & neurotoxicity	Monitor CSA/FK levels and Cr and adjust dose accordingly	Possible

Acute GVHD (cont.)
Pharmacokinetic Interactions of CSA & FK-506

Drug	Possible Mechanism	Possible Effects
HMB-Reductase Inhibitors (Statins): lovastatin, simvastatin, pravastatin, etc.	CSA/FK may ↓ metabolism of these agents and/or CSA may inhibit OATP1B1/SLCO1B1-mediated hepatic uptake of these agents → accumulation of drug and toxicity	Myalgia, myopathy, rhabdomyolysis Coadministration with rosuvastatin or pravastatin is preferred with CSA. Limit rosuvastatin to 5 mg/day and pravastatin to 40 mg/day. CSA coadministration with simvastatin, atorvastatin, lovastatin, fluvastatin may be harmful. Monitor very closely for toxicity. No dose adjustments required when FK is administered with statins. Monitor for statin toxicity.
Digoxin	↓ volume of distribution of digoxin by 50–70% ↑ half-life by 30–40%, and increased digoxin levels	Digoxin toxicity such as vomiting, cardiac arrhythmias, serum digoxin levels, and symptoms of digoxin toxicity should be closely monitored
Nifedipine, Phenytoin Interactions with CSA only	Unknown	In addition to altering the levels, may also ↑ the frequency of gingival hypertrophy

Acute GVHD

Treatment of Acute GVHD

First Line Treatment

Methylprednisolone (MP) IV: 2 mg/kg/day (divided in twice daily doses) x 5 days (10 doses)

OR

Prednisone PO: 2.5 mg/kg/day (divided in twice daily doses) x 5 days (10 doses)

Treatment should be started within 12 hours of establishing the diagnosis of ≥ grade II GVHD based on clinical symptoms/signs (pathologic confirmation is not mandatory to commence treatment).

Suggested steroid taper if response: give 1–1.5 mg/kg/day methylprednisolone x 3–4 days then reduce by 10% every 3–4 days as tolerated.

Second Line Treatment

a. Commence if:
   1. Progression of GVHD after 6 doses of MP
   2. Persistence of ≥ grade II GVHD after 10 doses of MP
   3. Significant flare of acute GVHD prior to tapering to ≤ 1 mg/kg/day of MP
   4. Any flare of acute GVHD unresponsive to MP
   5. More than 1 flare of symptoms on prednisone taper at any dose

Steroid refractory GVHD is a very challenging clinical problem associated with a high morbidity and mortality. Steroid refractory GVHD of the gut carries a mortality of 80%. Patients with steroid responsive GVHD –eg acute GVHD that responds to prednisone though flares on taper to relatively low doses can often have a good long-term prognosis though patients often face increased morbidity from repeated steroid course[1]. Isolated cutaneous skin GVHD also generally has a more favourable prognosis relative to other organ sites.

Historically, ATG (thymoglobulin), etanercept and MMF have been used. Program review of long-term outcomes has been very disappointing. Review of 1127 allograft recipients from 2000-2016 demonstrates a overall survival for patients with steroid refractory graft vs host disease by therapy received as follows: ATG: 10%; etanercept 17 %; MMF 0%[2]. Patients receiving basiliximab had an overall survival of 30% though this likely represents groups with isolated skin GVHD with a better overall prognosis. These disappointing results for steroid refractory acute GVHD are comparable to the published literature[3-4]. With use of some of newer therapies (eg ruxolitinib) below we are hopeful for improved outcomes.

i. Ruxolitinib

The REACH2 randomized controlled trial comparing ruxolitinib 10mg PO bid (target dose) to other standard GVHD treatment options[5]. This trial, demonstrated superior response rates relative to other commonly used second line agents including ECP, ATG, etanercept and MMF grouped together in the Best Alternative Therapy (BAT) Arm. The Overall Response Rate was 62.3 % vs 39.4 % in the BAT ($p < 0.001$) at 28 days. The median failure-free survival was also longer with ruxolitinib than with BAT control therapy (5.0 months vs. 1.0 month Hazard ratio, 0.46 (95% CI, 0.35–0.60)). REACH2 established ruxolitinib as the preferred second-line treatment for steroid refractory/depending acute GVHD.

The target dose of ruxolitinib is 10mg PO bid. However, patients on moderate to strong CYP3A4 inhibitors including, posaconazole and voriconzole require dose reduction 5mg PO bid. Fluconazole dosing should not exceed 200mg and requires dose reductions to 5mg PO bid. Dose reductions for cytopenias are also common. It is recommended that patients receive transfusional support and growth factors (eg GSCF) to facilitate administration of the highest tolerable dose ruxolitinib where possible. Among responding patients, the general treatment duration is 6-12 months, with general practice of tapering off corticosteroids prior to ruxolitinib taper.

Funding for ruxolitinib is provided under Pharmacare Special Authority for patients with grade II-IV steroid refractory/dependent acute GVHD who are not receiving other therapies lines for acute GVHD other than steroids and calcineurin inhibitors. Exceptions to the use of other concurrent therapies may be considered for patients with rapidly progressing life-threatening acute GVHD. Ruxolitinib is also available for inpatients on hospital formulary listing meeting the same above criteria.

ii. Basiliximab

For patients with isolated Steroid-resistant cutaneous acute GVHD, a treatment of choice is IL-2 receptor antibody basiliximab 20mg IV on days 1 and 4. Dosing may be repeated once weekly thereafter based on response. Responses are generally observed by the 4th dose. The usual treatment course is 4-6 doses. Dose is diluted in 50 ml NS or D5W and infused over 20-30 min. No pre-medications are required. Cyclosporine or FK-506 are not discontinued

iii. Extra-corporeal photopheresis

Extra-corporeal photopheresis (ECP) has the best evidence for acute GVHD of the skin and acceptable response rates for skin and liver, though studies evaluating this therapy are small and single-centered from selected populations. ECP is a therapeutic apheresis procedure that entails the separation of activated T lymphocytes from the patient's blood, exposure to psoralen, a photosensitizer, followed by UV light. The therapeutic mechanism of ECP is thought to be via the selective removal of alloreactive GVHD-inducing T cells. These alloreactive T cells

are preferentially susceptible to psoralen and UV light-induced apoptosis relative to T –regulatory cells. ECP can also be considered immunomodulatory rather than immunosuppressive.

Patients require a HCT > 27 and Platelets 20 to safely undergo the procedure, though can be supported with transfusions to facilitate this

A challenging patient group for ECP are those with steroid refractory GVHD of the gut as the ECP procedure may take several hours and this is difficult for a patient to endure with large volume diarrhea. Patients who are unable to tolerate extra corporeal fluid shifts are also unable to complete this procedure.

While it is possible to complete ECP via peripheral vein access, many patients will require central access via tri-fusion line (rather a than a Hickman line).

Another population of patients for whom ECP is a useful strategy are those with challenging infectious complications where further immunosuppression is especially undesirable. Those with steroid refractory/dependent GVHD and recurrent CMV or EBV reactivations post-HSCT are examples of this patient type.

The ECP schedule for acute GVHD in an intensive twice weekly session schedule x 1 month. As these patients are generally followed closely by either the inpatient service or L/BMT day care ward, direct discussion with the Apheresis Unit Physicians is required to accommodate the patient on the intensive twice weekly schedule. If patients require blood product support to complete ECP, the L/BMT inpatient or day ward will arrange for this.

Patients who do not respond within 1 month or those unable to taper their steroids in 1 month should discontinue ECP. In responding patients, ECP is tapered to weekly or 2 sessions every other week after 1 month on the twice weekly schedule. The duration of ECP therapy for acute GVHD is approximately 3 months to 6 months. There is no consensus on how to taper patient from ECP. Tapering with reduced frequency over a couple of months is reasonable.

Other therapies for steroid refractory acute GVHD

Anti-thymocyte globulin

Anti-thymocyte globulin (ATG) is less frequently used therapy since its addition to the conditioning regimens for most myeloablative transplant as prevention and the high frequency of serious infectious complications associated with ATG in this context. The use of thymoglobulin is, in general, for patients who have not previously received it as part of GVHD prevention in their conditioning regimen and for those who have failed other therapies. The thymoglobulin regimen consists of 1 mg/kg actual weight x 4 doses on day 1, 3, 5 and 7. Hold cyclosporine (or FK-506) for 7 days.

If the patient was on CSA before the administration of the thymoglobulin, they may

be switched to FK-506 after the thymoglobulin. See page 8 for FK-506 dosage guidelines.

Etanercept.

Etanercept typically used for steroid-refractory GVHD of the gut who have not responded to other agents. The dosing 25 mg subcutaneously twice weekly x 4 weeks, then once weekly x 4 weeks.

Mycophenolate mofetil 1 gm PO/IV b.i.d.

Evidence for MMF for treatment of acute GVHD is very limited though may be used where options are limited.

Immunosuppression Taper

Patients without prior acute GVHD (related and unrelated):
Patients who have received myeloablative fully matched donor transplant with ATG conditioning and do not have any GVHD by D+60 can begin taper of calcineurin inhibitor taper. The usual rate of taper is 25-50mg per week. The speed of taper can later be adjusted/increased when chimerism results are available.

Patients who have undergone reduced intensity transplants can develop acute GVHD later relative to patients with myeloablative conditioning. The decision on timing of tapering of calcineurin inhibitors in reduced intensity conditioned patients should be individually tailored based on relapse risk with some patients being appropriate for tapering beginning around D+60 (eg high risk myeloid diseases).

Discussions around commencement of immunosuppression taper should take place with the M1C2 physician and/or primary attending.

References

1. Newell NF, Holtan SG,. Acute GVHD: think before you treat. Hematology Am Soc Hematol Educ Program. 2021 (1): 642–647
2. Nevill, T. Program Quality Review Data
3. Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2012.18(8):1150-63
4. Westin JR, Saliba RM, De Lima M et al. Steroid-refractory acute GVHD: predictors and outcomes. Adv Hematol. 2011; 601953–601953
5. Zeiser RR, von Bubnoff N, Butler J et al. Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease. NEJM. 2020 382:1800-1810
6. Tang Fei Fei, Cheng YF, Xu F. Basiliximab as Treatment for Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric Patients after Haploidentical Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2020. 26(2): 351-357,
7. Greinix HT, Knobler RM, Worel N, et al. The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. Haematologica. 2006 Mar; 91(3):405-8.

19-2. Chronic GVHD

Chronic Graft vs Host Disease (cGVHD) differs phenotypically from acute GVHD and is a pleomorphic syndrome with both inflammatory and fibrotic manifestations. Chronic GVHD is a major barrier to otherwise successful allogeneic stem cell transplant, a major cause of NRM and a major impediment to quality-of-life post-transplant. The median onset is 6- months post-transplant and is generally first diagnosed in the first year following transplant[1]. The skin, liver, eyes and GI tract are the most commonly involved sites at diagnosis. Bronchiolitis obliterans and sclerodermatous skin cGVHD are among the highly morbid forms of cGVHD and a challenge to manage. Chronic GVHD is classified and graded according to NIH consensus criteria described below[2].

Definitions and Classification in Chronic Graft vs Host Disease

The following are definitions of chronic GVHD based on its onset:

Progressive: Chronic GVHD evolving directly out of acute GVHD. This subtype is generally associated with a more challenging clinical course

Quiescent: Chronic GVHD arising after complete resolution of prior acute GVHD (being off Prednisone and Cyclosporine for a period of time is NOT required for the "quiescent" designation)

De novo: Chronic GVHD in patients never showing signs of acute GVHD

The National Institutes of Health (NIH) criteria are used to classify the organ site of involvement, clinical features and severity[2]. The NIH criteria were developed to standardize assessment at treatment responses. The criteria are also particularly useful is different clinicals are assessing a patient over time for consistency.

Acute vs Chronic GVHD

Acute and Chronic GVHD

The broad category of **acute** GVHD includes:

1. Classic acute GVHD (maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic hepatitis) occurring within 100 days after transplantation or DLI (without diagnostic or distinctive signs of chronic GVHD) ***AND***
2. Persistent, recurrent, or late acute GVHD when features of classic acute GVHD are present without diagnostic or distinctive manifestations of chronic GVHD occurring beyond 100 days of transplantation or DLI (often seen after withdrawal of immune suppression). Late acute GVHD can

generally be treated with a shorter duration of immunosuppression relative to chronic GVHD.

The broad category of chronic GVHD includes:

1. Classic chronic GVHD without features characteristic of acute GVHD ***AND***
2. An overlap syndrome in which features of chronic and acute GVHD appear together.

Clinical Grading of Chronic GVHD

Table 1. NIH grading criteria for chronic GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				

Chronic GVHD (cont.)
Table 1. NIH grading criteria for chronic GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: % FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Chronic GVHD (cont.)
Clinical Grading of Chronic GVHD (cont.)

Table 1. NIH grading criteria for chronic GVHD (cont.)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)

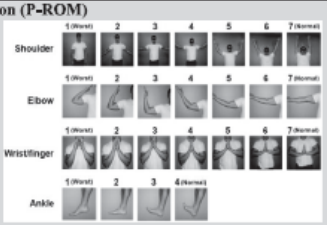

Figure 1. (*continued*).

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0–3) based on its functional impact where applicable (none = 0; mild = 1; moderate = 2; severe = 3)

Esophageal stricture or web	Pericardial effusion	Pleural effusion
Ascites (serositis)	Nephrotic syndrome	Peripheral neuropathy
Myasthenia Gravis	Cardiomyopathy	Eosinophilia > 500 µl
Polymyositis	Cardiac conduction defects	Coronary artery involvement
Platelets < 100,000/µl	Progressive onset	
Other: (Specify) _____		

Notes:
Organ scoring of chronic GVHD. * AP may be elevated in growing children, and not reflective of liver dysfunction.
† Pulmonary scoring should be performed using both the symptom and pulmonary function testing (PF T) scale whenever possible. Whenever discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring.

GVHD, graft versus host disease; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, Body Surface Area.

Clinical Grading of Chronic GVHD (cont.)
Final Grading of Chronic GVHD

Mild	_____	Overlap	_____
Moderate	_____	Late Acute	_____
Severe	_____		

Mild chronic GVHD involves only 1 or 2 organs or sites (except the lung: see below), with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). Mild chronic GVHD can often be treated with topical therapies.

Moderate chronic GVHD involves:

1. At least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) ***OR***
2. 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). A lung score of 1 will also be considered moderate chronic GVHD.

Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GVHD.

A summary of GVHD Grading and Treatment response are provided in Tables 2 and

3. Reponses to therapy are generally assessed at 3 months, though may take longer for some fibrotic manifestations such as scleroderma, which take a minimum of 6 months to see response.

Table 2: Overall National Institutes of Health Chronic GVHD Grading[2, 3]

No. of Organs Involved	Mild Grade	Moderate Grade	Severe Grade
1	Score 1	Score 2	Score 3
2	Score 1	Score 2	Score 3
3		Score 1	Score 3
Lung		Score 1	Score 2

Mild grade: 1 or 2 organs (but not lung) with maximum score of 1. Moderate grade: lung score 1 or ≥3 organs at score 1 or at least one organ at score 2. Severe grade: lung score 2 or score 3 in any organ.

Table 3: Definitions of NIH Response for Chronic GVHD[2, 3]

Response	Definition
Complete response (CR)	(1) Resolution of all manifestations in each organ or site, and PR is defined as improvement in at least one organ or site without progression in any other organ or site. (2) The skin, mouth, liver, upper and lower GI tract, esophagus, lung, eye, and joint/fascia are considered to evaluate the overall response. (3) The genital tract and other manifestations are not included due to a lack of validated response measures. (4) The CR category may not apply to organs with irreversible damage.
Partial response (PR)	An improvement in score from baseline that reflects a genuine clinical benefit and exceeds the measurement error of the assessment tool, as follows: an improvement of one or more points on a 4-to-7-point scale or an improvement of two or more points on a 10-to-12-point scale.
Disease progression (DP)	(5) For skin, eye, esophagus, and upper and lower GI tract, a worsening of one point or more on the 0 to 3 scale is considered progression, except a change from 0 to 1, which is considered trivial progression since it often reflects mild, non-specific, intermittent, self-limited symptoms and signs that do not warrant a change of therapy. (6) For joint/fascia, a worsening of one point or more on the 0 to 3 scale is considered progression, even if from 0 to 1. For joints assessed using the P-ROM, a worsening of one or more points on the 7-point scales (wrist, elbow, or shoulder) and one or more points on the 4-point scale (ankle) is considered progression. (7) Worsening of liver GvHD is defined by an increase of two or more times the upper limit of normal for the assay for alanine transaminase, alkaline phosphatase, or total bilirubin. (8) For patients with lung involvement, absolute worsening of FEV1 by 10% predicted or more (e.g., 50% to 40%) is considered progression.
Mixed response	A new category defined as CR or PR in at least one organ accompanied by progression in another organ, while the cases that do not meet the criteria for CR, PR, DP, or mixed response are considered unchanged.

Chronic GVHD (cont*)*

Treatment of Chronic GVHD

First Line Treatment:

1. Enroll on a clinical trial (either observational or therapeutic) if available. Future therapeutic strategies in cGVHD involve the use upfront
2. Commence prednisone 0.5–1 mg/kg/day and then taper as tolerated. An alternate day dosing may be used to minimize steroid-related side effects (Seattle protocol (N drive: supportive care).
3. Increase cyclosporine dose if onset occurs in the context of cyclosporine taper or consider adding in cyclosporine as a steroid sparing agent particularly
5. For isolated elevation in transaminases, cyclosporine as a single agent can be effective.
6. Start appropriate prophylaxis (see Antimicrobial Prophylaxis in Chronic GVHD for more details).

The median duration of immunosuppression for chronic GVHD is 2.5 to 3.5 years and a small proportion of patients need to remain on immunosuppression long term. Approximately 50 % of patients will fail frontline immunosuppression with steroids +/- calcineurin inhibitors and require second line therapies for GVHD[1].

The following second-line agents for chronic GVHD are approved by Health Canada: Ibrutinib (2017); Ruxolitinib (2022); Belumosudil (2023). Axatilimab has received FDA approval in 2024 and Health Canada Approval is hoped for over 2025/2026.

i. Ruxolitinib

Ruxolitinib, a Janus kinase (JAK) inhibitor, is, in general, the preferred second line agent for many chronic GVHD manifestations. This follows from the REACH 3 randomized control trial published in 2021[4]. This trial compared ruxolitinib 10mg PO bid to a selection of commonly used Best Alternative Therapies (BAT) mainly in second line. Ruxolitinib was superior in terms of failure free survival (5.6 months in the Best Alternative Therapy Arm vs not reached in the ruxolitinib arm P<0.001), improvement in GVHD-related symptoms as well as overall response (76.4% vs 60.4% in BAT arm p<0.001) as well as sustained response at 12 months (68.5 vs 40.3% in BAT p=0.05). The highest response rates were highest for skin, organ, GI tract and joint and fascial manifestations.

Similar to acute GVHD, access to ruxolitinib is funded via Pharmacare Special

Authority for patients with NIH grade 2-3 chronic GVHD who are steroid refractory/dependent and not receiving any other therapy lines other steroids/CNIs. However, exceptional access may be considered for ruxolitinib and other therapies for patients with rapidly progressing, highly morbid forms of cGVHD or those who have a new organ involvement while other involved organs remain under good control with previous therapies.

Dosing adjustments to 5mg PO bid for concomitant therapy with azoles is required. Weekly bloodwork for the first month is recommended due to risk of cytopenias.

ii. Ibrutinib

Ibrutinib is a Bruton's tyrosine kinase inhibitor that has been shown to be effective in the treatment of cGvHD. It works by blocking the activation of B cells and B/T cell signaling and T cell activation. Phase 2 clinical trials have shown that ibrutinib can lead to improvements in cGVHD (ORR 67%) and effectiveness in reduction of steroids in heavily pre-treated patients[5]. However, real-world experience has not shown a similar level of efficacy[3]. Bruising, sometimes significant, is a frequent side effect due to antiplatelet effects of ibrutinib.

Although, the 420 mg dosing was used in clinical studies, lower dosing may have equal efficacy.

Patients on concomitant azoles require empiric dose adjustments to 140 mg PO daily.

Re-imbursement for ibrutinib is a limited, though some patient may have access via their private drug plans

iii. Belumosudil

Belumosudil is a selective inhibitor of rho-associated coiled-coil kinase 2 (ROCK2), which promotes the signaling pathways that lead to inflammation, tissue damage and fibrosis in cGvHD. Belumosudil is thought to have anti-fibrotic effects helpful in the treatment of sclerotic and mild-to moderate pulmonary GVHD[6]. The ROCKstar Phase 2 clinical trial demonstrated a 74% NIH Overall Response Rate for patients with cGVHD who had failed a median of 2 prior therapy lines, many of whom had already failed ruxolitinib and ibrutinib.

Our Program experience with 42 patients who received belumosudil on compassionate access program has not indicated the same response rate (ORR~25-

30% at 6 months) though a greater number of patients have had success with belumosudil as a steroid-sparing agent[7].

Belumosudil is dosed at 200 mg daily. Co-administration with Proton-pump inhibitors requires an increased dose to 200 mg PO bid. Some patients may be able to replace their PPI with an H2 blocker, though others may not tolerate this switch and require bid belumosudil dosing and stay on their PPI. There is also an interaction between belumosudil and statins. Clinical and CK monitoring may be helpful for patients on potent/high dose statins. Although belumosudil is generally well-tolerated, nausea and liver toxicities are occasionally encountered.

Funding for belumosudil is hoped for via Pharmacare in 2025/2026

iv. Axatilimab

Axatilimab is a colony stimulating factor 1 (CSF-1) inhibitor and fits into the biologic model of cGVHD via inhibition of CSF-1 driven monocytes and macrophages contribute to inflammation and ongoing fibrosis. Axatilimab has shown impressive results in the AGAVE study, where heavily pre-treated patients (median 4 prior treatment lines) demonstrated an Overall Response Rate of 74% at 6 months in the 0.3 mg/kg q 2weekly dosing cohort[8]. Many of the patients in this study had severe scleroderma and lung GVHD.

Axalitimab is generally well tolerated. Transaminitis as well as elevations in lipase are common though represent delayed enzymatic clearance with axatilimab rather than hepatotoxicity**.** Peri-orbital edema is also common, though unlikely to require drug discontinuation and often improved with subsequent dosing cycles.

Axatilimab received FDA approval in August 2024 and Health Canada approval is hoped for in the near future. Axatilimab is available via compassionate access program, though a Health Canada Special Access Program application is required.

v. Extra-corporeal Photopheresis for Chronic GVHD

As described in the acute GVHD section above, ECP is a therapeutic apheresis procedure that entails the separation of activated T lymphocytes from the patient's blood, exposure of the T lymphocytes to photosensitizing agent (Psoralen) and UV light. ECP has the highest response rates in steroid refractory/dependent cGVHD of the eye, mouth and skin, though studies examining this therapy are for the most part small and retrospective [9-11] (Figure 1). ECP is frequently used in the setting of sclerotic GVHD in Canadian practice. In the real-world setting, it is often used in

combination with other therapies. ECP also has the advantage of being considered immunomodulatory, rather than immunosuppressive. It may be advantageous for patients with complicated infections -eg challenging CMV or PTLD - who are unable to tolerate immunosuppression.

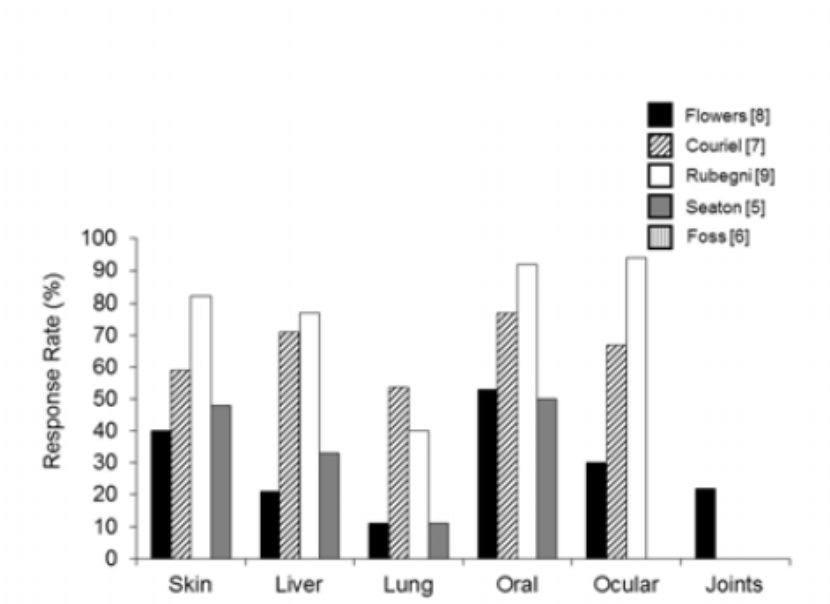

Figure 1: NIH Response Rates for Extracorporeal Photopheresis across Organ sites in Chronic GVHD.

Referrals for ECP therapy are made to the apheresis unit to initiate therapy.
The initial cGVHD schedule for chronic GVHD is 1 weekly session or 2 back-to-back sessions every second week. The latter scheduling may work better for out-of-town patients who are travelling to for treatment.

Patients require a minimum frequency of assessment every 3 months while on therapy. Several months of ECP may be needed before tangible improvement can be seen. For sclerotic cGVHD, a minimum of 6 months is often needed to see results. The usual time on therapy for patients who respond is approximately 1 year, with no consensus as to how to taper ECP, though general practice is a taper of frequency of sessions over a period of 3-6 months. Tapering of frequency at the 6 month mark could take place for early responding patients who achieve a complete response by 3 months.

The requirements and exclusion for ECP therapy are listed in Box 1. The

advantages of ECP should be weighed against need for a central venous access if required and frequent travel to the L/BMT Program for treatments vs other available options.

Box 1: Exclusions for Extra-corporeal Photopheresis

Patients with aphakia

Pregnancy

Previous history of HIT (if using heparin)

Untreated thrombocytopenia (plt <20 x 109/L)

Neutrophil count <1 x 109/L

Untreated hematocrit <0.27L/L

Patients who are unable to tolerate extracorporeal volume shifts associated with ECP treatment due to the presence of any of the following conditions: uncompensated congestive heart failure, pulmonary oedema, renal failure.

Patients exhibiting a known sensitivity to psoralen compounds such as 8-MOP.

Selection of second line therapies and beyond for chronic GVHD

A treatment algorithm is suggested in Figure 2. While ruxolitinib is generally considered a preferred second-line agent, it is recognized that therapeutic approaches should be individualized and based on: specific organ involvement, severity of organ involvement, side-effects, patient preference and reimbursement. Ruxolitinib is thought to have more anti-inflammatory properties, whereas axatilimab and belumosudil are more fibrosis-specific. Organ-specific response rates for the cGVHD therapies described above are outlined in Table 4. Depending on the clinical manifestation and suspected pathogenesis of cGVHD in a particular patient, the most appropriate could be selected.

Table 4: Organ Specific Responses by Therapy for Chronic Graft vs Host Disease

Organ System	**Ruxolitinib[4]**	**Belumosudil[6]**	**Axatilimab[8]**	**Ibrutinib[5]**	**ECP[9-11]**
Mouth	50%	55%	52%	88%	50-90%
Eye	26%	42%	30%	37%	30-90%
Skin	41.2%	37%	24%	88%	40-80%
Lung	8.6%	27%	46%	--	10-50%

Other systemic therapies in chronic GVHD

The following systemic therapies are often used for chronic GVHD

1. Low dose weekly methotrexate (eg 10-12.5 mg weekly orally in combination with leucovorin) may be helpful in patients with morphea or cGVHD-related arthralgias
2. Imatinib. Low dose imatinib (100mg PO daily) may be used in patients with fibrotic type manifestations such as bronchiolitis obliterans or scleroderma. Efficacy in the literature is reported at around 26%[12].
3. Rituximab. Patients with autoimmune-type manifestations (immune-mediated cytopenias, myositis, glomerulonephritis) may respond well to rituximab. Dosing is 375mg/m2 weekly x 4 weeks (or closest available dosing in the subcutaneous formulation). Patients with a partial response may undergo a repeat course. This "off-label" use of rituximab is available via compassionate access program. Rituximab limits vaccine efficacy and routine immunizations (eg excluding seasonal influenza and COVID vaccines) are delayed 6 months post last rituximab dose.
4. Total Lymphoid Irradiation (TLI), also known as Total Nodal Irradiation or Thoraco-abdominal Irradiation involves the delivery of low dose irradiation (1 Gy) in a single fraction to nodal areas of the chest, abdomen and pelvis. The mechanism of action of TLI is not fully understood though proposed to be via promotion of immune tolerance via a reduction in cytotoxic T cell activity against donor and enhanced T-regulatory function. Review of our Program Data in a small number of heavily pre-treated patients (n=26) indicated a response rate of 20% though reductions in steroid dosing was observed in a majority. Post-radiation cytopenias, often significant and requiring hospitalization, occurred in 20% of patients[13].
5. Mycophenolate Mofetil (MMF -dosing 15 mg/kg, generally 1-1.5 gm per day) has little demonstrated efficacy in steroid refractory/dependent cGVHD, though is generally accessible and may be tried in patients who have failed other available options. MMF may be associated with a higher risk of infectious complications and hematologic malignancies[3].

Specific Chronic GVHD Organ manifestations/sub-types

i. Sclerodermatous cGVHD

Sclerodermatous cGVHD is a highly morbid sub-type, with a generally later onset in the clinical course of cGVHD[2]. The onset of scleroderma is at a median of 19 months post-transplant and it can occur as other previously diagnosed organ involvement is well-controlled on tapering immunosuppression. The development of scleroderma may begin with an inflammatory edematous phase. Early intervention with systemic steroids may be helpful at this stage, though as the fibrotic pathophysiology takes effect, steroids have a more limited role.

Frequent sites of scleroderma include the extremities, particularly the lower extremities, leading to joint contractures, ulceration and disability. The chest and abdomen are particularly troublesome sites of involvement, which may lead to chest wall restriction, breathlessness and high-risk of morbidity/mortality from respiratory infections.

Patients with well- established scleroderma generally require longer time (minimum 6 months) to assess the effectiveness of new therapy lines. The role of supportive care is of particular importance in this patient population. Adjunctive physiotherapy as well as strength and movement exercises such as yoga, Tai Chi or Qi gong have potential to improve flexibility, strength and balance in those with sclerosis. These adjunctive exercises also have the benefit of muscle strengthening for those with muscle weakness from previous systemic steroid exposure. Expert wound care is often needed for lower extremity ulcerations.

ii. Bronchiolitis Obliterans Syndrome

Bronchiolitis Obliterans Syndrome (BOS) is associated with high morbidity/ mortality. BOS involves inflammation and fibrosis of the small airways. BOS occurs in 15-20% of patients with cGVHD[2] It is typically diagnosed later the course of cGVHD and can have an insidious onset, while other active cGVHD are under good control with tapering immunosuppression. BOS rarely occurs as the sole manifestation of cGVHD. As such, routine pulmonary function testing/spirometry monitoring is required for patients in the first 2 years post alloHSCT and for those with established chronic GVHD. The characteristic pulmonary function pattern is a non-reversible obstructive pattern with air trapping. Early decreases in the FEV1 and drops in FEF 25/FEF50 may be the first signs of BOS development prior to the onset of any symptoms.
Early initiation of inhaled combined steroid and long-acting bronchodilator (e.g. **F**luticasone propionate/Salmeterol – Advair-250TM, one inhalation BID),

Azithromycin (250 mg qM/W/F) and **M**ontelukast 10 mg daily (referred to as "FAM") is a mainstay of BOS therapy. Systemic steroids may be helpful early after diagnosis (see below) but long-term use is not recommended (see below). The value of long-term use of Azithromycin is uncertain and it has been suggested that it can increase the risk of relapse of an underlying hematologic neoplasm. While follow-up studies have not shown a higher rate of relapse in patients taking Azithromycin, its use should be evaluated in BOS patients after 6 months and ongoing use individualized.

Box 2: National Institute of Health 2014 Consensus Criteria for Bronchiolitis Obliterans Syndrome[2]

1. FEV1/VC < 0.7 or the 5th percentile of predicted.
    a. FEV1= Forced Expiratory Volume in 1 second.
    b. VC= Vital Capacity (Forced Vital Capacity "FVC" or Slow Vital Capacity "SVC", whichever is greater).
    c. The 5th percentile of predicted is the lower limit of the 90% confidence interval.
    d. For pediatric or elderly patients, use the lower limits of normal defined according to NHANESIII calculations
2. FEV1 < 75% of predicted with ≥ 10% decline over less than 2 years. FEV1 should not correct to > 75% of predicted with albuterol, and the absolute decline for the corrected values should still remain at ≥ 10% over 2 years.
3. Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as chest radiographs or computed tomographic scans or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, bronchoalveolar lavage).
4. One of the two supporting features of BOS:
    a. Evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by high-resolution chest CT OR
    b. Evidence of air trapping by PFTs: RV (Residual Volume) > 120% of predicted or RV/TLC elevated outside the 90% confidence interval (RV/Total Lung Capacity).

If a patient already carries the diagnosis of chronic GVHD by virtue of organ involvement elsewhere, then only the first three criteria above are necessary to document chronic GVHD lung involvement. If BOS is the *only* clinical manifestation in a patient without a prior established diagnosis of chronic GVHD, a lung biopsy is required to establish the diagnosis of chronic GVHD for the purposes of enrollment on general chronic GVHD trials.

Viral triggers are hypothesized to initiate BOS and repeat viral infections can accelerate the disease process by furthering inflammation and fibrosis. There may be an early inflammatory period where systemic steroids may be of use, though over the longer-term systemic steroids tend to cause more harm than good as via accessory muscle atrophy and infectious risk. If systemic steroids are used, it is recommended for 1 month maximum followed by relatively fast taper over a few weeks. There have not been any studies comparing second-line agents head-to-head, though reported response rate for new agents in clinical studies are outlined in Table 4 above. There is rationale for some of the more fibrosis-targeted therapies for this patient group.

Other supportive care is also of critical importance in this patient population. This includes:

- Infectious prophylaxis including coverage for encapsulated organisms, PJP, and a strong consideration for prophylaxis against aspergillus (eg. Posaconazole) if possible.
- Seasonal immunizations for influenza and COVID
- Management/treatment of concurrent exacerbating conditions including sinusitis and GERD/Prednisone-associated gastritis
- Pulmonary rehabilitation to improve muscle strength and endurance
- Supplemental oxygen if necessary for more severe cases

Patients with rapidly declining lung function should be referred early for consideration of lung transplantation.

iii. Atypical Manifestations of Chronic GVHD

There is growing recognition of atypical GVHD manifestations, which are cGVHD that differ from the classical manifestations of cGVHD (Table 1). Atypical GVHD manifestations can involve virtually all organ systems including the: central nervous system, peripheral nervous system, lungs, serositis, kidney, musculoskeletal system, and immune-mediated cytopenias (Figure 3)[14]. Atypical cGvHD affects a substantial number of patients, and it can manifest before or without NIH-defined cGvHD features. From a treatment standpoint, the atypical cGVHD manifestations are often managed with an analogous strategy to their occurrence in the non-allograft setting. As they fall outside the classic NIH defined entities, patient with atypical cGVHD have not been included recent clinical trials and thus the efficacy of newer agents in this setting is unknown.

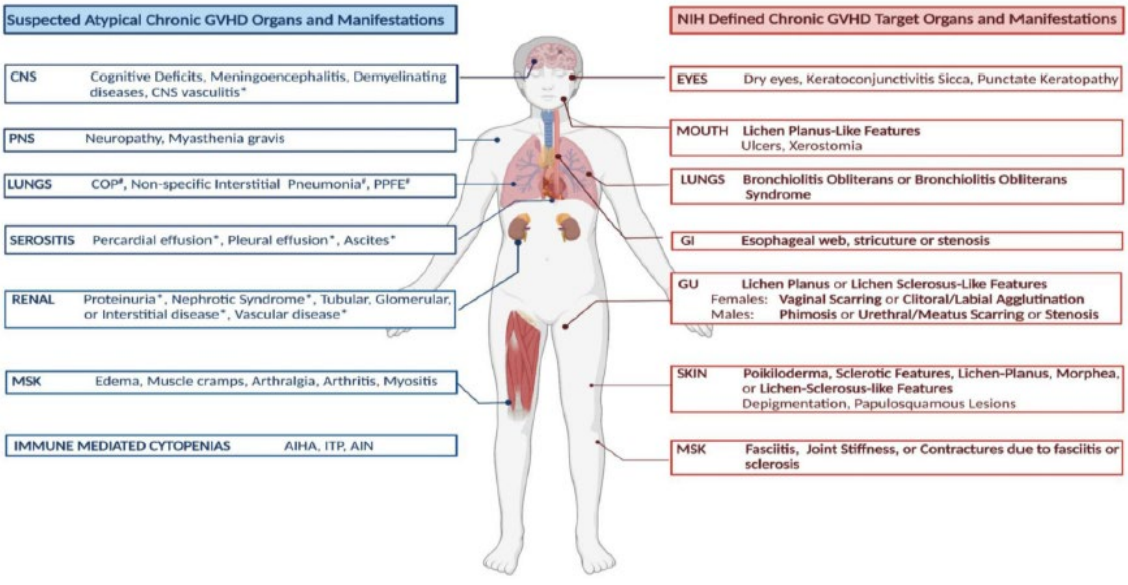

Figure 3. Comparison of Atypical versus NIH Defined Diagnostic and Distinctive Chronic GVHD Manifestations[14]

Topical Therapies for cGVHD

Topical therapies may be used for mild a) cGVHD not requiring systemic immunosuppression b) as adjunctive therapy c) for steroid sparing effects and/or d) to manage mild flaring following taper of immunosuppression.

Dosing of topical steroid therapies for various sites of application is outlined in the Table 6 below

Table 6: Topical Steroid Type and Dosing Recommendations

Organ site	Steroid dose/formulation
Skin	Betamethasone dipropionate 0.05%: Apply once daily to twice daily (High potency steroid) For longer term use over the face, consider lower potency steroid (hydrocortisone 2%) and/or steroid sparing agent with tacrolimus ointment 0.1% twice daily
Oral	Dexamethasone rinses Dexamethasone solution 0.5 mg/5 mL, 5 mL swish 3-5 minutes and spit, 2-4 times/day For focal troublesome ulcerations: clobetasol propionate gel 0.05% applied with gauze for 10-15 mins or nighttime application
Genital	clobetasol propionate 0.05% twice a day *Note vulvovaginal GVHD is an under-recognized site requiring early referral to Gynecology for assessment.

Chronic GVHD Treatment Algorithm

A general treatment algorithm for cGVHD management is presented below[3]. This algorithm was developed by the Cellular Therapy and Transplant Canada Chronic GVHD Working Group[3]. If reflects general approach based on currently available therapies in Canada and is expected to evolve with the use of combination treatment and new therapies. It is also recognized that patients with rapidly progressing cGVHD and atypical manifestations may require a more tailored approach.

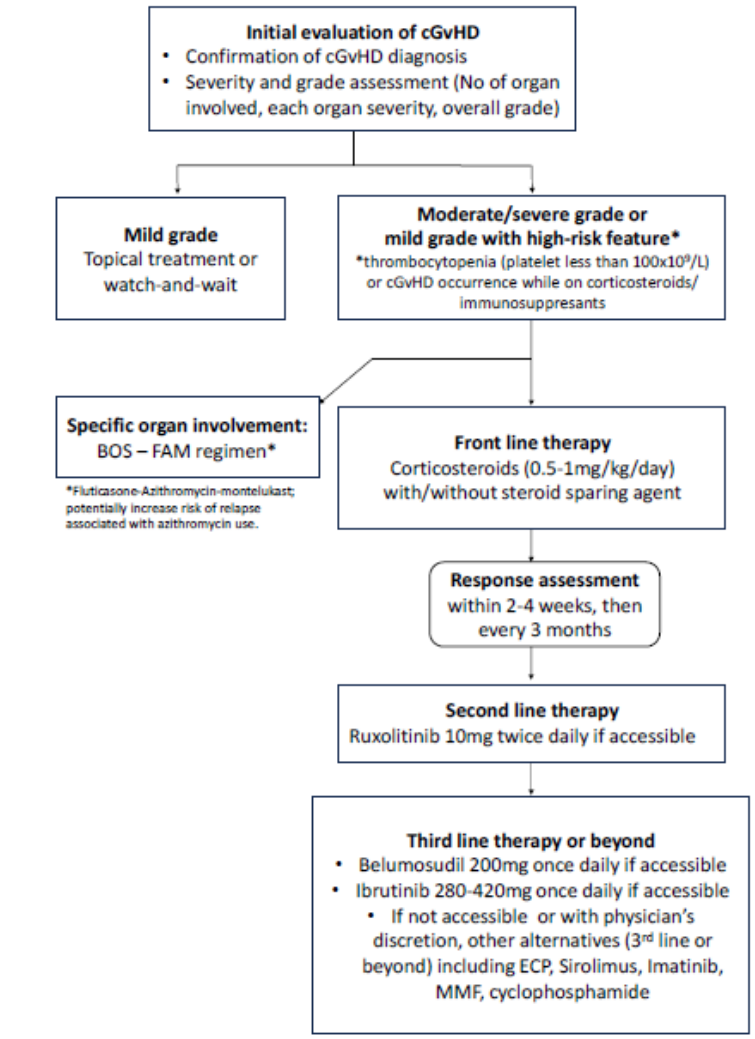

Figure 4: Chronic Graft vs Host Disease Treatment Algorithm

References

1) Lee SJ, Flowers ME. Recognizing and managing chronic graft-versus-host disease. Hematology Am Soc Hematol Educ Program. 2008:134-41. doi: 10.1182/asheducation-2008.1.134. PMID: 19074071.
2) Jagasia MH, Greinix HT, Arora M et al. . National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.e1.
3) Kim DDH, Popradi G, Lepic K et la. CTTC Chronic GVHD Guideline Working Group. Cell Therapy Transplant Canada (CTTC) Consensus-Based Guideline 2024 for Management and Treatment of Chronic Graft-Versus-Host Disease and Future Directions for Development. Curr Oncol. 2024 Mar 8;31(3):1426-1444
4) Zeiser R, Polverelli N, Ram R et a. Ruxolitinib for Glucocorticoid refractory chronic Graft vs Host Disease. *New England Journal of Medicine*.2021 **385**:3 228-238
5) Miklos, D.; Cutler, C.S.; Arora, M et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood 2017, 130, 2243–2250. [
6) Cutler C, Lee SJ, Arai Set al. Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study. Blood. 2021 Dec 2;138(22):2278-2289.
7) Ahmed A & White J. Review of local L/BMT Experience with Belomosudil. Program Quality Review Data
8) Wolff D, Cutler C, Lee SJ et al. Axatilimab in Recurrent or Refractory Chronic Graft-versus-Host Disease. N Engl J Med. 2024 Sep 19;391(11):1002-1014
9) Couriel, D.R.; Hosing, C.; Saliba, R.; Shpall, E.J.; Anderlini, P.; Rhodes, B.; Smith, V.; Khouri, I.; Giralt, S.; de Lima, M.; et al. Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. Blood 2006, 107, 3074–3080
10) Oarbeascoa, G.; Lozano, M.L.; Guerra, L.M et al. Retrospective Multicenter Study of Extracorporeal Photopheresis in Steroid-Refractory Acute and Chronic Graft-versus-Host Disease. Biol. Blood Marrow Transplant. 2020, 26, 651–658.
11) Flowers, M. Fred Hutchinson Cancer Centre Extra-corporeal Photopheresis Therapy Guidelines
12) Olivieri, A.; Locatelli, F.; Zecca et al. Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood 2009, 114, 709–718.
13) Chung S, Culos S, White J. Total Lymphoid Irradiation for Steroid-Refractory Chronic Graft-Versus-Host Disease: the British Columbia Experience. Program Quality Review
14) Cuvelier, GDE, Schoettler M, Buxbaum NP et al.; et al. Toward a Better Understanding of the Atypical Features of Chronic Graft-Versus-Host Disease: A Report from the 2020 National Institutes of Health Consensus Project Task Force. Transplant. Cell Ther. 2022, 28, 426–445.

Antimicrobial Prophylaxis in Chronic GVHD

Starting antimicrobial prophylaxis:

Patients with chronic GVHD are at risk of multiple different infectious complications as a result of their GVHD and the immunosuppression used to treat it.

Management should include:

1. TMP-SMX DS 1 PO daily for PJP and pneumococcal prophylaxis. For patients with sulfa allergy, dapsone is second line if TMP-SMX desensitization cannot be done. Dapsone cannot be used if the patient had a severe TMP-SMX reaction (ie. Steven-Johnson syndrome/toxic epidermal necrolysis, serum sickness, fever and rash). G6PD testing must be done before therapy initiation.
2. Most of the patients who have chronic GVHD are functionally hyposplenic and thus should get pneumococcal prophylaxis (ie. penicillin V 300 mg PO b.i.d. or TMP/SMX (400-80 mg) 1 tab PO daily (if penicillin allergic)).
3. Valacyclovir 500 mg PO b.i.d. for HSV/VZV prophylaxis.
4. Additionally, patients frequently have hypogammaglobulemia, so they should have quantitative immunoglobulins checked and receive IVIG 400 mg/kg q monthly or SCIg if the patient has received sinopulmonary infections and the serum IgG level is < 4.0 g/L. Reassess every six months.
5. Lamivudine for patients with isolated HBV cAb positivity, if not currently on therapy.
6. CMV PCR monitoring q weekly until two years post SCT then as per physician direction.
7. Antifungal prophylaxis for patients on > 1 mg/kg/day of steroid. This should be posaconazole if the patient has no history of invasive fungal infection but can be voriconazole if the patient has previously been treated with this agent.

Discontinuing antimicrobial prophylaxis:

Patients who remain on immunosuppression for chronic GVHD are at higher risk of late infectious complications than their unaffected counterparts. This is due both to the exogenous immunosuppression from continued medical therapy and the endogenous immunosuppression from having persistent cGVHD. Although these patients would ideally remain on prophylaxis as long as they were on immunosuppression, there are a subset of patients who want or need to have their drugs discontinued due to side effects, logistical issues with drug administration (e.g. pentamidine), or other patient specific factors. The following patients may be considered for early discontinuation of antimicrobial prophylaxis despite the ongoing need for immunosuppression.

Patients must meet all of the following criteria:

- Two years or more post-HSCT
- Stable GVHD
- Immunosuppression:
    - On single agent immunosuppression. If this is prednisone, the dose must be ≤ 15 mg/day
      PLUS
    - Stable immunosuppressive dose for a minimum of 6 months
      PLUS
    - No rituximab, ibrutinib, or TAI in the last 6 months
- No evidence relapsed or active malignancy
- CD4 count > 200 cells/mm3

Antimicrobial Agents To Be Discontinued:

1. PCP prophylaxis (TMP-SMX, pentamidine, atovaquone, dapsone)
2. HSV/VZV prophylaxis (valacyclovir, acyclovir)
3. Encapsulated organism prophylaxis (TMP-SMX, penicillin) - patients who have undergone splenectomy should take this for a minimum of two years after splenectomy*
4. IVIG/SCIg – patients who are eligible to come off prophylaxis should be evaluated for stopping IVIG/SCIg if not already done. Please see the IVIG/SCIg replacement section of the guidelines.
5. Lamivudine in patients with isolated HBcoreAb positive status. Any patient who discontinues lamivudine should be monitored by HBV DNA and HBV surface Ag q3months for at least one 1 year and preferably as long as they are on immunosuppression. Patients who have detectable HBV surface Ag and/or previously detectable HBV DNA should remain on treatment as long as they are on immunosuppression and until 6 months after stopping.
6. Antifungal therapy can be stopped when patients are on a daily steroid dose of <0.5 mg/kg/day.

*Patients with splenectomy should be counselled that the risk of overwhelming infection with encapsulated bacteria is lifelong. However, this risk is divided with the highest risk period occurring in the first two years after splenectomy (50% of episodes occur here). All patients – regardless of whether they are on antibiotic prophylaxis – should be counselled to urgently seek medical attention when they become unwell as these infections can rapidly progress and become fatal. As antibiotic resistance rates rise, this becomes more important for patients both on and off prophylaxis.

Immune reconstitution and CD4 count

CD4 recovery has been found to be associated with risk of opportunistic infection. Patients who are being considered for discontinuation of antimicrobial prophylaxis should be assessed by CD4 count in addition to other clinical parameters. CD4 measurements are preferably done on otherwise well patients taking a stable medication regimen as certain conditions (e.g. acute infection, rapid increases in steroid dosing) can result in decreased counts. Results also need to be interpreted carefully in the context of chronic liver disease or splenectomy which can lower or raise counts, respectively.

Recipients who have CD4 counts <200 cells/mm3 are recommended to remain on antimicrobial prophylaxis.

To determine a patient's CD4 counts, please send lymphocyte subsets counts to the VGH Immunology Lab. Blood should be drawn at VGH as the best results come if the sample is run within 24 hours of collection. To get this test, simultaneously draw a CBC and differential (lavender top tube) and lymphocyte subset count (order as CAAP on the requisition and use a dark green heparin tube for blood collection). The laboratory runs testing from Monday to Friday so samples can be drawn from Monday to Thursday in order to meet that 24 hour turnaround time.

NOTE: If only CD4 count is written on the requisition, it will be sent to St. Paul's hospital for CD4/CD8 counts and ratios only.

CMV

Recipients who require ongoing treatment for cGVHD remain at risk of CMV reactivation. However, CMV viral loads must be done on a weekly basis in order for pre-emptive monitoring to be effective. The doubling time for CMV in stem cell transplant recipients has been found to be 1-2 days. Less frequent monitoring allows patients to develop high viral loads between measurements.

Patients who are more than two years from transplant should be monitored for CMV weekly during periods of active cGVHD and/or increases in immunosuppression. If patients have four weeks of consecutive negative CMV PCRs, then monitoring can be discontinued. Prolonged monitoring up to three months can be considered for recipients of umbilical cord transplants or those with a prior history of CMV disease (GI, pneumonia) or frequent reactivations requiring treatment.

19-3. Chimerism Analysis and Ongoing Management Post-RICT

19.3.1 Chimerism analysis will be performed on blood samples on day +75 to determine rapidity of CSA taper. Patients showing >90% donor lymphoid chimerism (and not on steroids for prior acute GVHD) will taper CSA with rapidity of the taper dependent upon the underlying disease/disease status at the time of SCT. "Slow" taper (e.g. CLL in remission at the time of SCT) would usually be over 3 months. A "rapid" taper (e.g. AML with high-risk features) may be over 6 weeks, provided no GVHD develops.

19.3.2 Patients with <90% donor lymphoid chimerism on day +75 (and not on steroids for prior acute GVHD) will be rapidly tapered off CSA over 2-6 weeks, dependent upon the underlying disease and disease status at SCT. Peripheral blood lymphoid chimerism should be re-evaluated 4 weeks after CSA is discontinued. If the lymphoid chimerism is improving but still less than 90% donor, this test can be repeated at subsequent 2 month intervals until > 90% donor chimerism has been documented. For any patient with subsequent disease progression, lymphoid chimerism should be repeated at that time.

19.3.3 Patients with <50% donor lymphoid chimerism should be considered at high-risk for graft failure and <10% donor lymphoid chimerism is consistent with graft failure. If such individuals are severely pancytopenic (i.e no autologous recovery is evident), CSA should be rapidly tapered, a search for an alternative donor should be initiated and chimerism repeated in 1 month if appropriate.

19.3.4 Donor Lymphocyte Infusions (DLI)

19.3.4.1 Patients not converting to >90% donor lymphoid chimerism 4 weeks after CSA withdrawal may be considered for escalating doses of DLI, with reassessment of chimerism every 4 weeks until >90% donor lymphoid chimerism, or the development of acute or chronic GVHD, disease regression or graft failure. This decision will depend upon disease and patient-related risk factors. If the donor chimerism is <90% but improving on subsequent testing (as noted above), it may be reasonable to defer DLI to see if the patient achieves full donor chimerism without DLI.

19.3.4.2 DLI dose levels (± 10%) will be: 1 x 106, 5 x 106, 1 x 107, 5 x 107 and 1 x 108 CD3+ cells/kg actual recipient weight.

19.3.4.3 Timing of dose escalation will be dependent upon the patient and their disease/disease status but consecutive DLI doses will ideally be 4-6 weeks apart if mixed chimerism (or, in the absence of GVHD, if the underlying malignancy) persists. Patients with minimal residual disease (e.g. CML with no Ph+ but persistent BCR/ABL positivity) or patients with an increasing proportion of donor lymphoid chimerism may be observed for an additional 4-6 weeks (i.e. 8-12 weeks after previous DLI) without further escalation of DLI.

20-1. Hickman® Line

Hickman® Line or Tunneled Central Venous Catheter (T-CVC) Care

- Clinical Practice Documents/Guidelines (CPDs) for care of T-CVCs can be accessed through the Vancouver Coastal Health Intranet (VCHConnect) by clicking on ' PolicyNet – VA (VGH/UBC/GFS)' and then 'CVCs' under 'Frequently Accessed CPDs' in the left upper quadrant of the webpage. The Regional CPD, VCH-T-1500 deals with basic care and maintenance of a tunneled CVC. The Vancouver Acute CPD, T-400 deals with unblocking a T-CVC.
- The physician is responsible for removing a T-CVC except for the Tri-fusion catheters which are removed in Radiology.

LEUKEMIA/BMT MANUAL E-EDITION

CHAPTER 21. SCREENING AND PREVENTIVE PRACTICES FOR ALLO SCT PATIENTS

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21-1. Day +100 Evaluation

Required Investigations

Chemistry	Virology	Hematology
• Electrolytes • Creatinine • BUN	• HIV • CMV (on CMV negative patients) • HBsAg • Anti-HB surface & core Ab • Anti-HCV Ab	• CBC and differential • Reticulocytes • Lymphocyte subsets• • Group and Screen (BTS notification day 100 post HSCT)

Chemistry		Urine
Bili (T/D) Alk Phos ALT AST LDH Gamma GT Total Protein SPEP IgG, IgM, IgG	Albumin FSH/LH (females) Testosterone and LH/FSH for males <60 Testosterone and LH for males >60 Fasting lipid panel	• Routine urine • 24-hr urine protein quantitation

Consultations & Procedures

Prepare consultation and requisition forms for procedures listed below:

a. *Bone marrow aspirate & biopsy*
Appointment time and date:_____
** Give 24 hour urine containers**

b. *Pulmonary function test – Spirometry only (604-875-4830)*:
****There is a $50.00 cancellation fee for appointments missed or not cancelled at least 24 hours prior****
Appointment Date and Time:_____

c. *Bone density scan (all patients)*: Osteoporosis Clinic Dr Kendler (604-263-3644)
150-943 West Broadway, Vancouver BC
Appointment Date and Time:_____

d. *Dental Clinic*: Dr. M. Williams, BCCA Dental Clinic, 2nd Fl., Rm 2800, 604-877-6163
Appointment Date and Time:_____

e. *Endocrine Evaluation (FEMALES ONLY) and follow up for diabetic patients*:
Dr. B. Paty, Diamond Health Care Centre, local 55900
Appointment Date and Time:_____

f. *PM Dr's Clinic Appointment (CP6D)* ** **Once all other tests completed****
Appointment Date and Time:_____

21-2. Long-Term Follow-Up

√ - recommended for all patients
+ - recommended for abnormal testing in a previous time period or for new signs/symptoms

Recommended Screening/Prevention	six months	one year	annually
Liver			
Serum ferritin		√	+
Respiratory			
Pulmonary function testing †	q 3 monthly for 2 years		+
Musculoskeletal			
Bone mineral density	+	√	+
Kidney			
Urine protein screening		√	√
ACR		√	√
Endocrine			
TSH		√	√
Gonadal function assessment		+	+
Vascular			
CVS risk factor assessment		√	√
Lipids/Glucose		√	√
Echo		*	
Immune System			
Serum immunoglobulins		√	√
Immunizations	See Chapter 22		
Endocarditis prophylaxis with dental procedures **	for patients with chronic GVHD		
Oral Complications			
Dental assessment	√	√	√
Ocular			
Ocular fundus examination		√	+
Clinical screening for second cancers			
Second cancer vigilance counseling			√
Skin Exam****			√

	six months	one year	annually
Oral Cancer Screening	√q6mo		
Breast/skin/testes self-exam		√	
Mammogram	Annually at age 40 For patients who received TBI to commence 8 y post XRT but no later than age 40		
Pap smear	Annually as per BCCA high risk protocol		
Prostate exam	commencing at age 50 years		
Colonoscopy	commencing at age 50 years		

† Spirometry only at 'Walk In Spirometry Laboratory'- requisition at N:\Supportive Care\Forms. For patients receiving ongoing treatments for GVHD past the 2 year mark may require more frequent spirometry screening than annually.
* If patient received TBI or anthracyclines
** http://circ.ahajournals.org/content/116/15/1736.full.pdf
*** Specific recommendations for patients with Chronic GVHD are outlined in Chapter 19
**** where possible by a Dermatologist especially among high risk patients

21-3. Cardiovascular Risk Assessment following HSCT

Allogeneic HSCT patients are at a high risk of adverse cardiovascular outcome with risk increasing markedly at the 5 year mark following transplant. Premature cardiovascular events are a leading cause of death among HSCT survivors. Aggressive management of cardiovascular risk factors and metabolic syndrome is required in this patient population including lifestyle changes. HSCT survivors should be counselled to be physically active for 30 minutes 4 times per week and to consume a healthy diet.

In the absence of evidence for primary prevention of cardiovascular events specifically in HSCT recipients, the Leukemia/BMT Program LTFU Clinic uses the Framingham risk score to evaluate a patient's risk of cardiovascular disease. However, the thresholds for initiation of statin therapy for primary prevention are lower relative to the general population given the increased baseline risk in this group. Statin therapy is recommended for primary prevention in the following patients under the following circumstances (regardless of patient age):

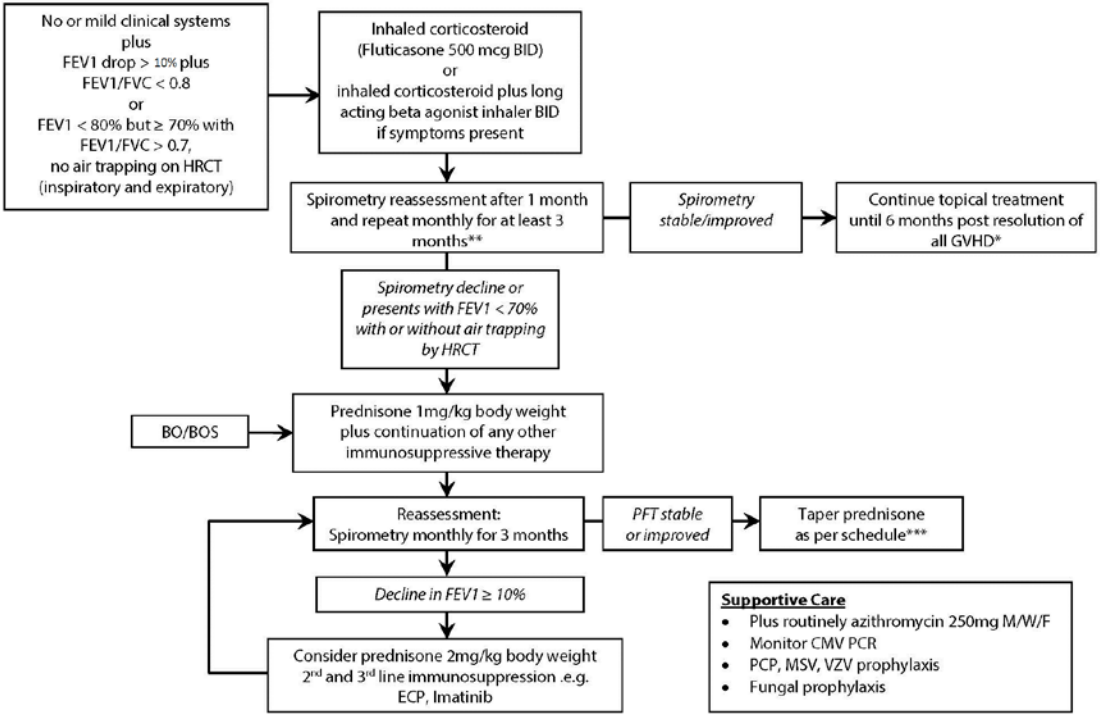
LDL-C $\geq$ 5.0 mmol/L

Framingham risk score 5-9% with LDL C $\geq$ 3.5 or any additional risk factor (hypertension, increased waist circumference, impaired fasting glucose, cigarette smoking)

Intermediate Framingham risk score (10-20% 10 year risk of cardiovascular disease) and LDL-C C ≥ 3.5 or non-HDL C ≥ 4.3

Fasting lipid profile is recommended annually. Therapy targets are an LDL-C of < 2.0 mmol/L or >50% reduction in LDL-C, or non-HDL < 2.6 Cardio-oncology referrals are recommended for patients with multiple risk factors or for whom the benefits of statin therapy are not clear. In addition, patients with LDL-C ≥ 5.0 should be referred to cardiology for evaluation of a genetic component to their dyslipidemia, for which they may warrant specialized lipid lowering therapies.

21-4. Lung Injury following allogeneic SCT- screening, follow-up and treatment algorithm



Therapeutic Algorithm for new onset airflow obstruction Following Allo-SCT

* Resolution of all reversible manifestations of GVHD without exacerbation after 6 months discontinuation of all systemic immunosuppressive treatment

** If spirometry stable after 3 months, repeat at 3 month intervals for 1 year, then if stable continue at 6 month intervals for 1 year and 6-12 month intervals thereafter

***Prednisone Taper Schedule

Week	Dose, mg/kg body weight
0	1.0
2	1.0/0.5* (to begin within 2 wk after objective improvement
4	1.0/0.25*
6	1.0 qod (continued until resolution of all clinical manifestations)
8	0.70 qod (to begin after resolution of all clinical manifestations)
10	0.55 qod
12	0.45 qod
14	0.35 qod
16	0.25 qod
18	0.20 qod
20	0.15 qod
22	0.10 qod

qod, every other day.
***Alternate-day administration**

References

1. Flowers MED, Martin PJ. How we treat chronic graft-versus-host disease. *Blood*.2015; 125:606-615.
2. Hildebrandt GC, Fazekas T, Lawitschka A, Bertz H, Greinix H, Halter J, Pavletic SZ, Holler E, Wolff D. Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD. Bone Marrow Transplantation. 2011; 46:1283-1295.
3. Chien JW, Martin PJ, Flowers ME, Nichols WG, Clark JG. Implication of early airflow decline after myeloablative allogeneic stem cell transplantation. Bone Marrow Transplantation. 2004; 33:759-764.
4. Thompson PA, Lim A, Panek-Hudson Y, Tacey M, Hijazi R, Ng AP, Ritchie D, Bajel A. Screening with spirometry is a useful predictor of later development of noninfection pulmonary syndromes in patients undergoing allogeneic stem cell transplantation. Biol Blood Marrow Transplant. 2014; 1-6.

21-5. Common patient questions post chemotherapy and BMT

Common Questions Asked By HSCT & CHEMO

Questions	Time after Transplant				
The general guidelines below may not apply to your case. You must discuss with you physician to asses if these rules apply to you.	All Patients <6 months Post-HSCT **OR** On chemo*	NOT on Immuno-suppression 6 mos – 1 yr	On Immuno-suppression ** 6 mos - 1 yr	On Immuno-suppression** > 1 year	NOT on Immuno-suppression > 1 year
Taking probiotics	No	No	No	No	Ok
Eating raw/undercooked seafood (e.g. sushi), unpasteurized milk/cheese, etc.	No	No	No	No	Ok
Work & School	No	Ok	No	Ok	Ok
Travel	No	Ok	No	Ok	Ok
Hot Tubs (Must not have venous catheter device)	No	Ok	No	No	Ok
Swimming (Avoid head submersion & diving, use sunscreen, must not have venous catheter device)	No	OK	No	Ok	Ok
Gardening; mowing the lawn; raking leaves (Wear gloves & a mask)	No	Ok	No	Ok	Ok
Having plants in the home (Not	Ok	Ok	Ok	Ok	Ok

handling)					
Making/kneading yeast breads	Ok	Ok	Ok	Ok	Ok
Carpentry or woodworking (Wear a mask)	No	OK	No	Ok	Ok
Animals, Birds, Reptiles, Fish, Other (not handling feces, litter boxes, cleaning utensils, or cages/tanks, etc.)					
➢ New pets in patient's household (Cats, dogs, fish are preferred)	No	Ok	No	Ok	Ok
➢ Cats/dogs/fish (No sleeping with pets, avoid bites/scratches)	Ok	Ok	Ok	Ok	Ok
➢ Domestic birds (parakeets, parrots, etc.) (Not with respiratory problems)	No	Ok	No	Ok	Ok
➢ Poultry & wild birds (pigeons, chickens, ducks, etc.) (Do not handle)	No	No	No	Ok	Ok
➢ Small cage rodents (gerbils, hamsters, guinea pigs, etc.), ferrets or reptiles (snakes, turtles, etc.) (Do not handle)	No	Ok	No	Ok	Ok
➢ Farm animals (pigs, horses, cows, etc.) (Stay out of	No	Ok	No	Ok	Ok

barns, no contact preferred)					
➢ Zoos & petting zoos (Do not handle animals)	No	Ok	No	Ok	Ok
➢ Public aquariums (Do not touch marine life in handling tubs)	Ok	Ok	Ok	Ok	Ok
➢ Animal trophy mounts in house	Ok	Ok	Ok	Ok	Ok
➢ Fishing (fresh & salt water) (OK to handle fish if wearing gloves; do not bait hooks)	No	Ok	Ok	Ok	Ok
➢ Hunting and sport shooting (Wear latex gloves when handling game; do not clean game; must not have catheter)	No	Ok	No	Ok	Ok
Horseback riding (Not caring for animal; stay out of barn)	No	Ok	No	Ok	Ok

*****Patients should avoid the following until ≥ 1 month after all therapy is complete
******Patients with active GVHD or recent increases in immunosuppression should limit their activities on this list.

Adapted from Fred Hutch.

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22-1. Immunization Following Stem Cell Transplant

Background

Although most adults undergoing stem cell transplant will have immunity against common viral pathogens from natural exposure or vaccination, it is known that such immunity may wane with high dose chemo/radiotherapy and/or immunosuppressive effects of drugs or disease.

Unfortunately, it is difficult to assess immunity after transplant. Although it is likely that patients undergoing autologous SCT will retain significantly more immunity than those undergoing allogeneic SCT, we have decided to make the practice universal to ensure good coverage of all patients. Similarly, the data around pathogen specific immunity post- CAR T-cell therapy (CART) is limited and the late infectious complications are not yet fully characterized. However, there are multiple reasons – including prolonged B cell aplasia – why immunity may be impaired and vaccination beneficial in this growing patient group.

The major classes of vaccines include those for diphtheria, polio, and tetanus; vaccines for the three encapsulated organisms to which immunocompromised or asplenic patients are susceptible (pneumococcus, Hemophilus influenza B, and meningococcus) and vaccination for hepatitis B (since many patients will unfortunately relapse and require further transfusion). Additionally, live attenuated viral vaccines may be indicated in patients who are more than two years post-transplant, have no graft versus host disease, and are off all immunosuppression.

Revaccination Policy

1. Vaccination should commence between three-six months post-transplant for all autologous, allogeneic, and CART recipients. The recently published international guidelines recommend NOT postponing vaccinations with non-live vaccines in allogeneic stem cell recipients with ongoing active or resolved cGVHD of any severity or grade. However, if patients receive prednisone > 0.5 mg/kg as part of a combination therapy or a three-agent immunosuppressive regimen is given, vaccination may be postponed until immunosuppression is reduced to a double combination or prednisone < 0.5 mg/kg bodyweight in order to achieve better vaccine response. The suggested prednisone dose is a compromise in order to have low immunosuppression at time of vaccination and to allow vaccination in almost all patients. However, immunosuppressive therapy should not lead to postponing vaccination for more than three months for patients on immunosuppression. The only exception to this is patients who have undergone autologous SCT for mantle cell lymphoma. These patients receive post-transplant rituximab for two years. In this case, vaccination, with the exception of the yearly influenza vaccine which should still be given, is recommended to start six months after the last infusion.
2. Live attenuated viral vaccines (measles, mumps, rubella, varicella) may be administered at 24 months post-transplant to all autologous, allogeneic and CART recipients who have no ongoing anticancer therapy, immunosuppression, IVIg or subcutaneous Ig, or active graft-versus-host disease (GVHD). Patients with multiple myeloma who are only on maintenance lenalidomide post-autologous HSCT may receive live vaccines if their disease is otherwise

in remission. Similarly, if recipients are only on low dose prednisone (prednisone equivalent of less than 20 mg/day or physiologic replacement therapy), they may be considered for revaccination as well. If two live vaccines (e.g., varicella and MMR) are to be given, they should be given simultaneously at different injection sites or separated by at least 30 days. In the setting of recent measles outbreaks, MMR vaccine for autologous and CART recipients can commence as early as 12 months post-transplant provided the above requirements (e.g. no ongoing immunosuppression, etc.) are met. If there are exceptional circumstances (e.g. travel to a country with an outbreak), MMR vaccination can be given between 12-24 months for allogeneic stem cell transplant recipients who meet the same criteria. If a patient is vaccinated earlier than 24 months for MMR, they may receive varicella vaccine at the same time.

3. Serology for measles or varicella are not recommended prior to revaccination. All post-transplant patients qualify for both MMR and varicella vaccine provided the criteria listed above are met. Two doses should be given separated by two months. Serology for measles and varicella should be checked 1 month after the second dose. If antibody to varicella is not detectable despite 2 vaccines, the client should be offered varicella zoster immune globulin on subsequent exposure to wild-type varicella or intravenous immunoglobulin if exposed to measles.
4. There is a recombinant inactive vaccine against shingles/herpes zoster (Shingrix). It is not covered by Public Health currently. All patients currently qualify for varicella vaccination at 24 months if they meet the criteria above, but this was not intended to prevent shingles, but primary chickenpox. Whether shingles vaccine will be required or where it fits into the revaccination strategy is yet to be determined (see further information in section 22-3).
5. Patients should receive influenza vaccine yearly and be revaccinated for COVID-19. Vaccination should be given before the influenza season starting at three months after SCT and continued yearly. If patients are between 3 – 6 months post-transplant or CART therapy at the time of their influenza vaccine, they should receive a booster one month later. Similar, revaccination for COVID-19 can begin at 3 months after SCT.
6. Patients who are asplenic should not assume that vaccination or antibiotics prophylaxis against the encapsulated organisms will provide 100% protection. All patients, regardless of whether they are on antibiotics prophylaxis, should be counselled to urgently seek medical attention when they become unwell as these infections can rapidly progress and be fatal. As antibiotic resistance rates rise, this becomes more important for patients both on and off prophylaxis. If they receive antibiotic prophylaxis, they should take it for a minimum two years post-splenectomy and be off immunosuppression before discontinuation. The risk of overwhelming infection with encapsulated bacteria is life-long. However, this risk appears to be divided with at least half of the infections occurring in the first two years after splenectomy.
7. If a patient has an exposure to a vaccine-preventable disease (e.g. tetanus, HBV), consideration should be given to whether the patient needs post-exposure prophylaxis (if available) despite revaccination. Immunocompromised patients may not reliably seroconvert or achieve protective antibody levels even with revaccination.

The L/BMT Program and the BC Centre for Disease Control have agreed on a common approach to vaccination for SCT recipients and there is a standard letter to patient, a re-immunization schedule, and blood requisition available in BMT Accuro.

22-2. Guideline for Use of Recombinant Inactive Shingles Vaccine (Shingrix)

Allogeneic transplant recipients who do not receive prophylaxis against herpes zoster will reactivate at rates as high as 20-25% at one year.[1] [2] With antiviral prophylaxis (acyclovir/valacyclovir), the incidence is reduced to 7.8%. Consistent with international guidelines, antiviral prophylaxis with valacyclovir is routinely given to VZV-seropositive allogeneic and autologous HSCT patients until 12 months post-transplant.

Shingrix ™ is an inactivated recombinant zoster vaccine (RZV) against Varicella Zoster Virus (VZV). RZV is designed to help induce antigen-specific immune responses in individuals *with pre-existing immunity* against VZV. Studies in immunocompromised patients include a randomised study of patients post autologous transplant where patients received either the Shingrix vaccine or placebo[3]. The incidence of shingles was 5.6% in the vaccinated group vs 15.9% in the placebo group at a median follow up of 21 months. The incidence of post herpetic neuralgia was reduced from 1.1% to 0.1%. The vaccine was well tolerated with localized pain, redness and swelling at the vaccination site being the most common adverse event. The efficacy of the vaccine in this trial was 68.17%.

In cancer patients undergoing chemotherapy[4], and in patients post autologous transplant[5], the recombinant zoster virus vaccine has been shown to be immunogenic with responses in humoral and cell mediated immunity again seen to persist up to one year post vaccination. Shingles can be a debilitating illness and limited data for both efficacy and safety of vaccination is available for immunocompromised patients. Currently, the guidelines for revaccination post-transplant recommend varicella vaccine for all patients at 24 months post-transplant provided they are eligible for live vaccines. This would be standard of care until further information is available about the efficacy of RZV or utility in the post-transplant setting. RZV can be offered to LBMT patients who are not eligible for live vaccination (e.g. still on immunosuppression), provided they fit the following criteria:

- The patient has positive serology for VZV at six months post-transplant, irrespective of age
- The patient is otherwise deemed fit to commence the standard revaccination schedule as per BC CDC
- The patient clearly understands that this vaccine is not currently standard post-transplant, and consequently, the patient will have to pay to receive it. The cost is approximately $300 for the two injections.
- The vaccine is given as two injections at least two months apart. We recommend it be given at 10 months and 12 months post-transplant to maximize the potential benefit that patients have coverage against VZV when the valacyclovir is routinely stopped.

[1] Blennow O. et al, BBMT 2014; 20(10): 1646-9

[2] Seo HM et al, Antiviral Res 2017. 140;106-115

[3] Clinicaltrials.gov :NCT01610414

[4] Vink, P et al, Cancer 2019, epub Feb1. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in patients with solid tumours, vaccinated before or during chemotherapy

[5] Stadtmauer EA et al, Blood 2014, 124:2921-2919. A phase ½ study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients

- Patients who receive RZV before 24 months post-transplant could still receive the live varicella vaccine at 24 months. The additional benefit is likely to be negligible, but it is unlikely to be harmful.
- The added benefit to giving RZV when patients remain on valacyclovir is unknown. It will not impair the development of an immune response – as it would with live varicella vaccine. There are reports of breakthrough VZV while on valacyclovir in the literature, although it has not been seen locally. Patients would still have to be willing to pay for the vaccine.

For patients who are VZV seronegative, there is only limited evidence that Shingrix can lead to seroconversion and it is unknown whether it protects against disseminated varicella infection. These patients should receive the live varicella vaccine as per the BC CDC guidelines at 24 months post-transplant provided they are in remission and off all immunosuppression. Until they are eligible for this vaccination, they should receive VarZIG if exposed to varicella or herpes zoster (ideally within 96 hours).

LEUKEMIA/BMT MANUAL E-EDITION

CHAPTER 23. MANAGEMENT OF THROMBOSIS AND ANTICOAGULATION

TABLE OF CONTENTS

23-1.Treatment of Acute Thromboembolism in Patients with Acute Leukemia or Undergoing Stem Cell/Bone Marrow Transplantation

Patients with hematological malignancies have a higher risk of venous thromboembolism (VTE) compared to the general population. A common presentation is catheter-related thrombosis, but other forms of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), also occur.

These complications require anticoagulant treatment to regain or preserve catheter function, reduce symptoms and prevent dangerous sequelae (e.g. fatal PE). However, because these patients also have prolonged periods of severe thrombocytopenia and other reasons for serious bleeding, anticoagulant therapy could potentially be harmful and must be administered with caution and closely monitored.

There are no clinical trials or prospective cohort evidence to guide optimal treatment in this special population. The following recommended approaches for treatment of VTE, including catheter-related thrombosis, is based largely on consensus among Leukemia BMT and VGH General Hematology/Thrombosis faculty and review of published guidelines.[1-4] These are recommendations that should not replace physician judgement and discretion in individual cases.

A. Anticoagulant of Choice

Evidence-based clinical practice guidelines recommend LMWH for both initial and long-term treatment for cancer-associated VTE. Although direct oral anticoagulants (DOACs) are considered to be acceptable alternatives in selected patients, insufficient evidence exists in patients with acute leukemia or stem cell/bone marrow transplant patients. Given the higher risk of bleeding and the frequency of drug-drug interactions with DOACs, LMWH remains the anticoagulant of choice for treatment and prevention of VTE in this patient population. Patients already on DOAC for non-valvular atrial fibrillation will continue on DOAC as long as there are no contraindications.

B. Duration of Anticoagulation

The optimal duration of anticoagulant therapy has not been determined. However, due to the underlying thrombotic risk associated with cancer and cancer therapy, experts recommend continuing anticoagulation while active disease is present or patients are undergoing cancer treatment.

Interruption of anticoagulant therapy may be more frequent in this population because of protracted periods of severe thrombocytopenia, need for invasive procedures, active bleeding, and other co-morbidities that might prohibit anticoagulation.

Consultation with General Hematology/Thrombosis is recommended to help determine when it is reasonable to stop anticoagulant therapy.

C. Acute Thrombosis (day 0 – 30 after diagnosis of VTE)

1. *Patient with larger clot burden (e.g., vena cava, segmental or larger PE, proximal leg or arm DVT) or in an organ-threatening location (e.g,. mesenteric or renal vein thrombosis):*

Platelet Transfusion*	Achieved Platelet Count	LMWH Dosage Recommended (CrCl > 30 mL/min)
Yes	**≥ 50 x 10^9**	Dalteparin 200 units/kg SC once daily
Yes	**20-50 x 10^9**	Dalteparin 100 units/kg SC once daily
Yes	**10-20 x 10^9**	Dalteparin 5000 units SC once daily
Yes	**< 10 x 10^9**	No anticoagulation. Filter may be considered.

*Transfuse platelets if count is < 50 x 10^9. Goal is to maintain platelet count ≥ 20 x 10^9 (if possible) to allow 50% dose anticoagulation.

2. *Patient with asymptomatic incidental PE or smaller clot burden (e.g., isolated subsegmental PE, distal calf or arm DVT, superficial vein thrombosis, catheter-related thrombosis):*

Platelet Transfusion*	Platelet Count	LMWH Dosage Recommended (CrCl > 30 mL/min)
No	**≥ 50 x 10^9**	Dalteparin 200 units/kg SC once daily
No	**20-50 x 10^9**	Dalteparin 100 units/kg SC once daily
No	**< 20 x 10^9**	No anticoagulation. DO NOT insert filter.

***Do not give** platelet transfusion if there are no other reasons for transfusion. Continue with routine prophylactic platelet transfusion threshold.

D. Chronic/Established Thrombosis (> day 30 after diagnosis of VTE)

Platelet Transfusion*	Platelet Count	LMWH Dosage Recommended (CrCl > 30 mL/min)
No	**≥ 50 x 10^9**	Dalteparin 200 units/kg SC once daily
No	**20-50 x 10^9**	Dalteparin 100 units/kg SC once daily
No	**< 20 x 10^9**	No anticoagulation. DO NOT insert filter.

***Do not give** platelet transfusion if there are no other reasons for transfusion. Continue with routine prophylactic platelet transfusion threshold.

E. In patients with **severe renal failure** (CrCl < 30 mL/min), consult General Hematology service to discuss anticoagulant options.

F. In patients with **catheter-related thrombosis**, only remove the catheter if one or more of the following occurs:
- Confirmed sepsis/bacteremia with no other source identified AND not responding to antibiotics
- Catheter breakage, leak or other mechanical problems
- Catheter occlusion (failure to aspirate or infuse) persistent 1 week after starting anticoagulation

G. In **patients who cannot receive anticoagulation**, serial imaging (1 and 2 weeks after initial diagnosis of VTE) should be done to detect silent clot extension. Consult General Hematology service if clot extension is demonstrated.

H. There are rare circumstances in which an **IVC filter** might be indicated. Consult General Hematology service if considering a filter insertion.

I. When to hold anticoagulation:
- Active bleeding not responsive to local measures (e.g. applying pressure for epistaxis)
- Planned invasive procedures or surgeries associated with moderate or high risk of major bleeding. See Table 2 for guidance. ***These recommendations should be considered in the specific clinical context and should not replace clinical judgement. Physician must consider the relative risks and benefits of withholding and resuming in each patient for the particular procedure.***

J. Pharmacare Special Authority:
- Call Pharmacare at 1-877-657-1188 #5 to obtain verbal authorization for 6 months of coverage for LMWH
- Fax completed Pharmacare form to 1-800-609-4884
- https://www2.gov.bc.ca/assets/gov/health/forms/5469fil.pdf

References:

1. Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy: An American College of Chest Physicians Clinical Practice Guideline Executive Summary. Chest 2022, doi: https://doi.org/10.1016/j.chest.2022.08.004.
2. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2020; 38:496-520.
3. Samuelson Bannow BT, Lee A, Khorana AA, Zwicker, JI, Noble S. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. J Thromb Haemost 2018; 16:1-4.
4. Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv 2021; 5:927-974.

23-2. Table 1. Guideline for the Interruption of Anticoagulation or Anti-Platelet Therapy Prior to Elective Procedures

Drug	Timing of last dose **before** procedure should be no later than		Timing of resumption **after** procedure should be no sooner than	
	Moderate Bleeding Risk	High Bleeding Risk	Moderate Bleeding Risk	High Bleeding Risk
ASA 81 mg	continue	continue	continue	continue
clopidogrel	continue	5 days	continue	24 hr
prasugrel	7 days	10 days	24 hr	24 hr
ticargrelor	3 days	5 days	24 hr	24 hr
warfarin	5 days*	5 days*	evening of procedure	evening of procedure
heparin IV	4 hr	4 hr	4 hr	12 hr
prophylactic-dose LMWH	12 hr	12 hr	24 hr	24 hr
therapeutic twice-daily dose LMWH	24 hr	24 hr	24 hr	24 – 36 hr
therapeutic once daily doseLMWH	36 hr†	36 hr†	24 hr	36 – 72 hr
fondaparinux 2.5 mg once daily	24 hr	24 hr	24 hr	36 – 72 hr
fondaparinux ≥5 mg once daily	48 hr	48 hr	24 hr	36 – 72 hr
apixaban 2.5 mg twice daily	Day -2	Day -3	24 hr‡	24 – 36 hr‡
apixaban 5 mg twice daily	Day -2	Day -3	24 hr‡	36 – 72 hr‡
edoxaban 30 mg once daily	Day -2	Day -3	24 hr‡	24 – 36 hr‡
edoxaban 60 mg once daily	Day -2	Day -3	24 hr‡	36 – 72 hr‡
rivaroxaban 10 mg once daily	Day -2	Day -3	24 hr‡	24 – 36 hr‡
rivaroxaban 15 or 20 mg once daily	Day -2	Day -3	24 hr‡	36 – 72 hr‡

* Consider bridging with LMWH for patients at very high risk for stroke or systemic embolism (mechanical heart valve, CHADS2 score 5 or 6.

† In patients at very high risk of thrombosis, can give half therapeutic dose of LMWH at 24 hr prior to procedure.

‡ Start therapeutic doses of direct oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban) ONLY AFTER hemostasis is achieved, usually no sooner than 36–48 hours after a major procedure. Anticoagulant effect is immediate and peaks at 2–3 hours after administration. Use prophylactic doses of LMWH for thromboprophylaxis (if indicated) before restarting full doses of direct oral anticoagulants.

CHAPTER 23. MANAGEMENT OF THROMBOSIS AND ANTICOAGULATION

These recommendations should be considered in the specific clinical context and should not replace clinical judgement. Physician must consider the relative risks and benefits of withholding and resuming in each patient for the particular procedure.

Table 2. Risk Stratification for Procedural Bleed Risk Based on ISTH Guidance (modified from Chest 2022 guideline)

High bleeding risk (30-day risk of major bleeding > 2%) Requires no residual anticoagulant effect at time of procedure (i.e. 4 – 5 drug half-life interruption)	Bone marrow harvest Major surgery with extensive tissue injury Cancer surgery (except for basal and squamous cell skin cancer excision) Major orthopedic surgery Reconstructive plastic surgery Major cardiac or vascular surgery Major thoracic surgery Major urological surgery, including prostatectomy Major gynecological surgery Major GI surgery Colonic polypectomy Biliary surgery or endoscopic retrograde cholangiopancreatography (ERCP) Variceal banding Major organ resection or biopsy Any neurological or spinal surgery Intraocular or retinal surgery Any neuraxial procedure (e.g. spinal anesthesia, epidural, nerve block)
Moderate bleeding risk (30-day risk of major bleeding 1 - 2%) Some residual anticoagulant effect allowed (i.e. 2 – 3 drug half-life interruption)	Tunneled central venous catheter insertion (e.g. Port, Hickman) Dialysis or apheresis catheter insertion Bone marrow biopsy and aspiration Lumbar puncture (including intrathecal chemotherapy) Excisional lymph node biopsy Thoracentesis or paracentesis without US guidance Bronchoscopy with or without biopsy Gastrointestinal endoscopic biopsy Abdominal hernia repair Abdominal hysterectomy Laparoscopic cholecystectomy Coronary angiography via femoral approach Complex dental or periodontal procedures

Low/Minimal bleeding risk (30-day risk of major bleeding ~0%) Procedure can be done safely under full anticoagulation (avoid peak anticoagulant effect)	Peripherally inserted central venous catheter (PICC) insertion Endoscopy without biopsy Minor dermatological procedures Cataract extraction and lens implantation Minor dental procedures (e.g. extraction, fillings) Pacemaker or defibrillator device insertion Coronary angiography via radial approach Lymph node needle biopsy Joint aspiration

These recommendations are modified from the Chest Guidelines 2022 in recognition that patients with hematological malignancies have additional risk factors for bleeding, such as anemia, thrombocytopenia and platelet dysfunction. Furthermore, given the repetitive schedule of some of the procedures, e.g., marrow biopsy and lumbar punctures, maintaining hemostasis is a top priority to minimize patient discomfort and anxiety.

Reference: Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy: An American College of Chest Physicians Clinical Practice Guideline Executive Summary. Chest 2022, doi: https://doi.org/10.1016/j.chest.2022.08.004.

CHAPTER 24. DICTATION – VGH SYSTEM

24-1. General VGH Dictation Instructions

Login Instructions

1. Dial 1-855-666-3240
2. Enter:
   - Unique ID (MSP billing number or assigned #) + # key
   - Facility + # key
   - Work Type + #
   - Patient MRN + # key

Facility

115 VGH
105 Richmond
114 UBCH
96 GPC
97 GPC

Standard Work Type

101 History & Physical
102 Transfer Summary
103 Progress Note
104 Consultation
105 Anesthetic Consultation
106 Delivery Note
107 Discharge Summary
108 Operative Report
109 Treatment Note
111 Outpatient Clinic Note
112 Televisit
114 Diagnostic Report
199 Standard Text Inserts/Canned Text

Dictation Keypad

1 Listen
2 Begin dictation, Pause or Resume dictation
3 Incremental rewind (few words)
4 Fast forward
5 Save and Disconnect
6 Prioritize
7 Rewind to beginning
8 Complete report and start new
9 Playback – patient MRN, work type, job ID
Job

Contact Information

Phone: 604-806-9696 – M-F 8:00-4:00
Fax: 604-806-8257
transcriptionalerts2@vch.ca

Discharge Summary Required Content

- Most Responsible Diagnosis
- Pre-Admit Diagnoses
- Post-Admit Diagnoses
- Secondary Diagnoses
- Code Status
- Operative Interventions
- Flagged Interventions
- Names of Relevant Specialists
- Allergies
- Medications on Discharge

Hints and Tips

- Identify yourself, patient name and work type at the beginning of dictation and spell difficult names
- Name the attending physician, Surgeon or Consultant
- State the site where the patient was seen
- Remember to copy relevant physicians
- Do not use cellular phones or speaker phones for dictating
- For priority reports, state reason for urgency
- Clearly state lab results, medication dosage (e.g. 15 or 50), new procedures, studies, tests or unfamiliar medical terms
- Dictate a separate report for any addendums
- An intermediate beep during dictation means system is in pause mode – press 2 to dictate

24-2. Fellow Clinic Template

FELLOWS CLINIC TEMPLATE

NEW PATIENT CONSULTS

1. Presenting complaints
2. System enquiry
3. Past medical history
4. Past surgical history
5. Current medications
6. Allergies
7. Social history
8. Family history
9. Examination:
   Vitals: Karnofsky/ECOG performance status
   Weight
   BP
   PR
   Skin
   Chest
   Cardiovascular
   Abdomen
   Musculoskeletal
10. Investigation results:
    Laboratory
    Pathology] if appropriate
    Radiological]
11. Impression
12. Recommendations

- Please dictate notes on the day you see the patient
- Please use Job ID 103 for follow ups and Job ID 104 for new patient consults
- **PLEASE MAKE SURE YOU COPY the relevant attending's ACTION LIST when you dictate**
- **Once the note is in your own action list please make sure to check and forward it to the attending's action list (the note will otherwise not be directed to the attending's action list)**

FELLOWS CLINIC TEMPLATE

FOLLOW-UP CLINIC NOTE

1. Diagnosis:

2. Transplant (if applicable):
   - Conditioning,
   - Donor type,
   - CMV status (recipient/donor),
   - Blood group (recipient/donor),
   - Date

3. Current Medications:

4. Allergies:

5. Interval history:

6. Examination findings:
   - ECOG
   - BP
   - HR
   - Weight
   - Oropharyngeal exam
   - CVS
   - RS
   - Abdo

   And, if applicable:
   - Skin
   - Hickman line
   - Joints
   - Fascia
   - Neuro

7. Laboratory data:

8. Impression

9. Recommendations:

FELLOWS CLINIC TEMPLATE

CGVHD CLINIC NOTE

DOB:

CA#
CLINIC DATE –

Cc –
CHRONIC GVHD CLINIC NOTE

HAEMATOPOIETIC STEM CELL TRANSPLANT HISTORY
DIAGNOSIS AT TRANSPLANT:
DATE OF DIAGNOSIS:
DATE OF TRANSPLANT:
PREPARATIVE REGIMEN:
TRANSPLANT TYPE:
DONOR SEX:
CMV: D/R ABO D/R
ACUTE GVHD PROPHYLAXIS:

EARLY TRANSPLANT HISTORY (INCLUDING ACUTE GVHD HISTORY)

CHRONIC GVHD HISTORY

CURRENT GVHD MEDICATIONS

OTHER MEDICATIONS

PHYSICAL EXAMINATION

VITAL SIGNS: EYES: MOUTH: SKIN: NAILS: HAIR: CHEST: CARDIOVASCULAR: MUSCULOSKELETAL: Prayer sign –7, Shoulder /7, elbow –/7; ankle movements/4.
GENITAL:

Chronic GVHD Status.

Skin Score
Mouth Score
Eye Score
GI tract Score
Liver Score
Lung Score
Musculoskeletal – score
Other

ONSET:
NIH GRADE:

INFECTION AND PROPHYLAXIS
Bacterial:
PCP:
Fungal:
Viral: recurrent CMV reactivation.

ENDOCRINE
Thyroid
Gonadal
Iron Status
Lipid Profile
Bone mineral density:

SECOND MALIGNANCY SCREENING:

RECOMMENDATIONS

24-3. T15 Discharge Summary Format

Follow the template below when dictating T15 Discharge Summaries.

Dictation Date:

Patient Name:

MRN:

DOB:

PHN:

Fellow:

Dictating for:

Date of Admission:

Date of Discharge:

cc: BC Cancer Agency
Family Dr. (provide name)
Referring Dr. (provide name)
Primary L/BMT Program Dr. (provide name)

MOST RESPONSIBLE DIAGNOSIS (Primary reason for the longest acute length of stay/care or treatment:

ADMISSION KPS PERFORMANCE STATUS:

(Use single value, no range)

PRE-ADMIT DIAGNOSES (Medical issues which existed prior to admission and affected the care/treatment and/or length of stay. Important to add if patient has an infection or colonization of MRSA/VRE/C. difficile):

POST-ADMIT DIAGNOSES (Medical issues which arose since the time of admission including complications and affected the care/treatment and/or length of stay, even if they have resolved by the time of discharge. Important to add if patient became infected or colonized with MRSA/VRE/C. difficile):

SECONDARY DIAGNOSES (other diagnoses that did not affect the care/treatment and/or length of stay but are important to communicate for continuity of care:

COMPLICATIONS:

A. Toxicities (For all patients)

   1. Transfusion Issues – only special blood products, poor increments, adverse reactions

2. Non-Hematologic Toxicity

a. Regimen related – specify grade per site using Bearman criteria

b. Non regimen related – e.g., drug-related renal dysfunction, infection-related toxicity

3. Infections – include date of positive cultures

Prophylaxis against invasive fungal infection with _____ commenced on _____

a. Presumed –
b. Bacterial –
c. Fungal – include date of positive CT scan, bronchoscopy and galactomannan testing
d. Viral –
e. Miscellaneous –

B. Other Problems (For all patients)

– e.g., psychiatric issues, non-GVHD skin rashes, arthritic issues

C. Graft-vs-Host Disease (Acute) (for allogeneic transplant patients only, non-allo: SKIP)

1. Prophylaxis – must include details of all MTX dose reductions and reasons for reduction

2. Maximum Stage/Dates of Onset:

a. Skin –
b. Gut –
c. Liver –

Overall Grade –

3. Biopsies

a.

4. Therapy and Response –

D. Graft-vs-Host Disease (Chronic) (for allogeneic transplant patients only, non-allo: SKIP)

1. Type – De Novo, Progressive, Quiescent
2. Sites involved with onset
3. Biopsies
4. Therapy – include special drugs

PROCEDURES:

A. Protocol(s) & Research Studies, if any –

B. Cytotoxic Therapy – Actual weight kg, ideal weight kg, corrected weight kg, height cm, BSA m^2, corrected BSA m^2.

1. State regimen dose and actual dose administered.

C. Transplantation Details (Include all information):

- Type of product (stem cell source):
- Donor information:
  - Type of donor:
  - Degree of match:
  - Sex of donor:
  - Patient's and donor's blood type:
  - Patient's and donor's CMV status:

D. Operative Interventions (Interventions done in the formal Operating Room/Procedure Room) and dates:

E. Other Interventions (Minor interventions performed outside of the formal Operating Room/Procedure Room that are important to communicate for continuity of care) and dates:

F. Flagged Interventions: If the following interventions were performed, they **must** be stated as they directly affect Patient-Focused Funding:

Central Lines – PICC/Portacath	Paracentesis
Chemotherapy (should be noted in B above)	Endoscopy (gastroscopy, sigmoidoscopy, colonoscopy, or bronchoscopy)
Dialysis	Pleurocentesis
Endoscopic/Percutaneous Biopsy	Tracheostomy
Feeding Tube	Radiotherapy
Heart Resuscitation	Total Parenteral Nutrition
Mechanical Ventilation	

G. Special Medications – e.g., G-CSF

CONSULTANTS: – List service and specify staff person, if possible

1.

CLINICAL NOTE

Hospital Course:

DISCHARGE MEDICATIONS:

1.

CONDITION ON DISCHARGE:

DISCHARGE KPS PERFORMANCE STATUS:

(Use single value, no range)

PENDING LABORATORY STUDIES:

FOLLOW-UP:

LEUKEMIA/BMT MANUAL E-EDITION

CHAPTER 25. ADMISSION TO & DISCHARGE FROM CP6

TABLE OF CONTENTS

25-1. T15 Discharge Procedure

1. Ensure ward pharmacist is aware of discharge- and patient has a discharge medication calendar: NB cyclosporine cannot be collected from community pharmacy on Sundays. Ensure the patient has an adequate supply especially if discharging over the weekend.

2. Dictate discharge summary- this is the responsibility of the doctor caring for the patient on the day of discharge. If your patient is being discharged on a weekend, this summary can be dictated on the day beforehand.

3. Complete CP6 discharge orders. Please be aware of the need to write orders for your patient for CP6 – the fluids/ antibiotics/ chemo needed orders need to be available for their first visit. If ordering continuing antibiotics, please indicate a date of discontinuation. Chemo orders should be noted on discharge orders with dates to be given and the original orders should be faxed/copied and sent to CP6.

4. Call clinical associate/ fellow who will take over patient on CP6 to provide verbal handover.

5. Encourage patient to review the later part of the Bone Marrow Transplant patient folder/ information pack. All of the later pages of this pack are written to orientate the patient who will be discharged from T15 and commence care on CP6.

6. Information to reinforce for patient: phone numbers for after hours / work hours advice, importance of compliance with medication, instructions not to take cyclosporine on morning of first CP6 review, to bring meds/ medication calendar with them to first clinic visit.

7. Fax the following to CP6 at 55419: CP6 discharge summary, medication calendar, chemotherapy protocol- photocopy if patient has ANY remaining therapy on the protocol and send to CP6.

25.2 CP6 Discharge Procedure

1. Pharmacy aware of discharge- discharge medication calendar: NB cyclosporine cannot be collected from community pharmacy on Sundays. Ensure the patient has an adequate supply especially if discharging over the weekend.

2. Ensure patient's primary physician is aware of discharge plan in advance.

3. Book appointment with primary physician in pm clinic OR in CP6 where the patient will be seen by the primary physician so that a full discharge summary can be dictated. This needs to happen before the patient is discharged home. (Email primary physician if clinic spots are full.)

4. Complete written discharge summary- this is the responsibility of the doctor caring for the patient on the day of discharge. Ideally however, if your patient is being discharged in the near future, the discharge summary could be filled out in advance.

5. Call family doctor who will be resuming care of the patient in the local community to inform of discharge and to give instructions re: e.g., management of fevers/ who to contact in an emergency etc.

6. Information to reinforce for patient: phone numbers for after hours / work hours advice, importance of compliance with medication, instructions not to take cyclosporine on morning of blood tests, to bring meds/ medication calendar with them to first clinic visit.

7. Fax the following to the Primary Physician: at 54763 AND send a copy with the patient OR by fax to the family doctor: CP6 discharge summary, Medication calendar, date of next clinic follow up.

8. Make sure the patient is aware of who to call in the event of a fever/ new symptom.

LEUKEMIA/BMT MANUAL E-EDITION

CHAPTER 26. RESEARCH PROJECTS

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26-1. Steps to a Successful Research Project

1. Keep in mind that research projects can take 6 months to 1 year to complete from start to finish, depending on the amount of missing data, the number of variables and the complexity of the analysis required. If you are planning to conduct a research project, begin as soon as possible. (See Chapter 26-3 for Research Project Policies).

2. Meet with the Senior Staff Member overseeing your project to determine an appropriate research topic and patient cohort to study.

3. Request from Janet Nitta, Senior Data Coordinator, a preliminary list of patients who meet the selection criteria to determine feasibility. Do NOT start any data collection at this point.

4. Meet with Senior Staff Member, Janet Nitta, and possibly the statistician, to discuss the hypothesis and details of the research project.

5. Obtain authorization from the Director of the L/BMT Program to proceed with the project.

6. Obtain approval from the Research Ethics Board to proceed with the project. Consult with the Senior Staff Member for guidance.

7. Once authorization from the Director of the L/BMT Program is obtained, Janet Nitta or another data coordinator will retrieve the required patient cohort and requested variables from the database.

8. If any data is missing, an excel file of all retrieved data will be forwarded to the fellow to fill in any blanks.

9. The fellow will review charts and/or PCIS and/or CAIS and/or Accuro to fill in any blanks, following specific guidelines for data entry.

10. Once the excel data file is complete, the fellow will send the file back to the data coordinator.

11. The data coordinator will review the file and format for readability into SPSS.

12. The data coordinator will delete the names of the patients and forward the data file to the statistician for statistical analysis, if required.

13. The statistician will complete the statistical analysis and forward the results to the data coordinator, the fellow and the Senior Staff Member.

26-2. Excel Data Entry Guidelines

Based on your data analysis request and patient selection criteria, the data coordinator will retrieve the patient data and copy the variables you require into an excel file. Please use the following guidelines when entering data from chart reviews:

1. There should only be 1 row per patient.

2. If you need to change the order of the rows, click on cell in extreme top left corner, then click Data, Sort. Always inform the data coordinator if you have changed the sort order.

3. Use the date format DD-MMM-YYYY.

4. If you find it necessary to exclude or add any patients to the excel file, inform the data coordinator of any exclusions or additions.

5. When entering data into a blank cell within a column of data retrieved from BMTserve by the data coordinator, use red text. This will alert the data coordinator that this data was not previously in BMTserve and needs to be entered once your data collection is complete.

6. If you notice a discrepancy between data retrieved from BMTserve and information you find in the chart, do not over-write the data from BMTserve. Instead, right-click on the cell, and click "Insert Comment". Insert a comment noting the information found on the chart.

7. Wherever possible, when you are adding new columns of data, use codes instead of free-form text. For example, 1 = low grade, 2 = intermediate grade, 3 = high grade. In this case, only the numbers need to be entered. Insert a comment in the cell at the top of the column to explain the codes used. It is also recommended that you use a separate sheet of the excel file to prepare a list of all the codes used and their meanings.

8. When entering text, maintain consistency in wording, spelling, and use of spaces. For example, SPSS (the statistical analysis software) does not consider IIA to be the same as II A.

9. After you have completed data entry on the first 5 to 10 patients, send the excel file back to the data coordinator for review before proceeding. She will inform the fellow if any changes in data entry are required and send the excel file back to the fellow to continue with the project.

10. Provide the data coordinator with a list of any charts you are unable to locate. She can determine whether any of the charts are in off-site storage or possibly in use by other researchers or staff.

26-3. Research Project Policies

The following policies were established to allow sufficient time to conduct research thoroughly and to facilitate the completion and publication of research projects in a timely manner.

1. A fellow can embark on a research project only if the fellowship's duration is one year or longer. A case report may be written if the duration is less than one year.

2. All fellows' research projects must be approved by the Fellowship Director with final approval by the Director of the L/BMT Program.

3. Any requests for data retrieval for a research project must be submitted within the first two months of the fellowship.

4. Requests for data retrieval for ASH abstracts should be submitted by March 1.

CHAPTER 27. CAR T-CELL THERAPY AND ASSOCIATED TOXICITIES

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27-1. Introduction

CAR T-cell therapy involves the collection and viral transduction of T-cells with chimeric antigen receptors (CARs), highly specific receptors to a target antigen. Patients treated with CAR T-cell therapy receive lymphodepleting chemotherapy (LDC) which often involves a product and indication specific combination of cyclophosphamide and fludarabine. In specific cases Bendamustine can be used as an alternative. LDC serves to create an immunologic niche in which CAR T-cells can expand. CAR T-cell are infused no sooner than 48 hours after completion of LDC. Upon recognition of their target antigen, CAR T-cells become activated leading to tumor directed killing but also cytokine release that results in complications outlined below.

27-2. Indications

Indications for CAR T-cell therapy are rapidly changing. Current indications include

Tisagenlecleucel (Kymriah) – autologous, antiCD19, 4-1BB costimulatory domain

- Relapsed/refractory B-ALL 25 years of age or younger
- Large B-cell lymphoma (transformed or de novo) relapsed after or refractory to ≥2 lines of systemic chemotherapy for aggressive disease including a CD20 monoclonal antibody and anthracycline or etoposide based regimen
- Follicular lymphoma relapsed or refractory to at least 2 lines of therapy[&]

Axicabtagene ciloleucel (Yescarta) – autologous, antiCD19, CD28 costimulatory domain

- Large B-cell lymphomas (transformed or de novo) and primary mediastinal B-cell lymphoma
    - relapsed after or refractory to 2 or more lines of systemic chemotherapy for aggressive disease including a CD20 monoclonal antibody and anthracycline or etoposide-based regimen
    - refractory to or relapsed within 12 months of completing front line chemotherapy containing a CD20 monoclonal antibody and anthracycline or etoposide
- Follicular lymphoma or marginal zone lymphoma relapsed or refractory to at least 2 lines of therapy

Brexucabtagene autoleucel (Tecartus) – autologous, antiCD19, CD28 costimulatory domain

- Mantle cell lymphoma relapsed after or refractory to 2 or more lines of systemic chemotherapy including a BTKi, CD20 monoclonal antibody and bendamustine or anthracycline based therapy
- Relapsed/refractory B-ALL 18 yrs or older

Lisocabtagene maraleucel (Breyanzi)[&] – autologous, antiCD19, 4-1BB costimulatory domain

- Large B-cell lymphomas (transformed or de novo) and primary mediastinal B-cell lymphoma
    - relapsed after or refractory to 2 or more lines of systemic chemotherapy for aggressive disease including a CD20 monoclonal antibody and anthracycline or etoposide-based regimen
    - refractory to or relapsed within 12 months of completing front line chemotherapy containing a CD20 monoclonal antibody and anthracycline or etoposide

Ciltacabtagene autoleucel (Carvykti)[&] – autologous, antiBCMA, 4-1BB costimulatory domain

- Multiple Myeloma treated with 1-3 prior lines of therapy

[&] Not currently funded in BC

Definition of relapsed and refractory disease for purposes of CAR T-cell therapy

Lymphoma

- Progressive disease at any time on therapy
- Stable disease after 3 or more cycles of chemotherapy
- Partial response with biopsy proven residual disease as best response after at least 6 cycles of chemotherapy for aggressive lymphoma only

B-ALL

Philadelphia (Ph) chromosome negative
- o Primary refractory disease
- o First relapse if remission is ≤ 12 months
- o Relapsed/refractory after 2 or more lines of systemic therapy
- o Relapse/refractory after alloSCT

Philadelphia (Ph) chromosome positive
- o Relapse/refractory and intolerant of TKIs
- o Relapse/refractory despite 2 different TKIs

Notable disease / treatment-based criteria

Lymphoma

- Exposure to CD20 directed bispecific antibodies is not an exclusion
- Patients exposed to CD19 directed therapy must demonstrate persistent CD19 status
- Patients with indolent lymphomas who are responding to therapy
- CNS involvement is not an exclusion criteria however untreated or progressive CNS disease can compromise outcomes and CAR T-cell therapy in these patients may be inappropriate
- Primary CNS lymphoma, Burkitt lymphoma, CLL/SLL or Richter transformation are not eligible for SOC CART

B-ALL

- Patients post Blinatumomab must demonstrate persistent CD19 positivity
- CNS-1 and CNS-2 disease is permitted but CNS-3 disease must be treated prior to administration
- Patients post AlloSCT must not have GVHD requiring immunosuppression

Disease specific inclusion / exclusion criteria are available on the BC Cancer website

27-3. Patient Workup

Mandatory investigations

- Infectious disease screening within 30 days of T-cell collection
- RVG or ECHO
- Renal and hepatic indices (Cr, Urea, AST, ALT, ALP, GGT and T bilirubin)
- Clinical frailty score
- Performance status (ECOG)
- CD19+ status ONLY for patient who have been exposed to anti-CD19 directed therapy
- MRI
    - In those with suspected or known CNS disease MRI with contrast (gadolinium) is indicated
    - In those without suspected or documented CNS disease MRI "fast stroke protocol" can be done for a baseline. This study is available at VGH and takes 1/3 the time of a contrast MRI.

Discretional investigations

- Lumbar puncture recommended where CNS IPI score is above 4
- Bone marrow biopsy recommended when never previously performed, where concurrent low grade lymphoma is present or where unexplained cytopenias are present
- PFT recommended when suspicion of lung disease is present

Repeat biopsy

- Repeat biopsy to confirm disease pathology and relapse/refractoriness is strongly recommended whenever feasible to ensure pathology meets the funded indications. In cases where repeat biopsy is not feasible this can be discussed with the treating physician.

27-4. Eligibility Criteria

Patient should be free from severe end organ dysfunction, active untreated infection, and clinically significant frailty. **Recommended** criteria include

- **No active grade 2-4 GVHD** and off immunosuppressive therapy as per washout recommendations
- **No active uncontrolled infection**
    - *Patient with well controlled HIV may be eligible for certain products on a case-by-case basis though certain products remain contraindicated as per manufacturer labeling*
- **No concurrent active malignancy**
- **Cardiac:** LVEF ≥40% with no severe coronary artery or valvular disease
- **Pulmonary:** no severe lung disease or need for supplemental oxygen
- **Renal**: Creatinine clearance ≥45ml/min.
    - *Patients with renal dysfunction may be eligible for lymphodepletion with bendamustine.*
- **Hepatic**: No severe fibrosis or cirrhosis, ALT or AST ≤3x ULN and Total bilirubin ≤2x ULN
- **Clinical frailty score:** <6 the Clinical Frailty Scale can be found here
- **ECOG:** 0-2

27-5. Washout Recommendations

These recommendations serve as guidelines and may require adjustments on a case-by-case basis

Minimum washout recommendations prior to CAR T-cell collection (holding therapy)

Stop date	agent
12 weeks	Allogeneic cell therapy
8 weeks	T-cell lytic agents (ie Alemtuzumab) Clofarabine CNS radiation
6 weeks	Check point inhibitors[α]
4 weeks	DLI Pegylated asparaginase PD1-inhibitor *(4wks +)*
2 weeks	**Systemic chemotherapy including monoclonal Abs or antibody drug conjugates** (eg. Pola, Ritux) **Radiation** Maintenance methotrexate Vincristine GVHD therapy Immunomodulatory drugs Long acting growth factors
1 week	**Corticosteroids >5mg/d prednisone** IT chemotherapy
5 days	Short active growth factors
3 days	Hydroxyurea Venetoclax
2 days	**Bruton tyrosine kinase inhibitors**

*CART patients should receive **irradiated blood products** for 7 days prior to collection and 6 months after administration*

Administration of bendamustine any time prior to CAR T-cell therapy impacts quality or CAR T-cells and patient's response. *Do not administer bendamustine as holding therapy prior to leukapheresis.*

Use of checkpoint as bridging is not recommended

Minimum washout recommendations prior to initiation of lymphodepletion (bridging therapy)

Stop date	Agent
8 weeks	T-cell lytic agents (ie Alemtuzumab) CNS radiation
6 weeks	DLI Live vaccines
4 weeks	Pegylated –asparaginase
2 weeks	**Intensive, salvage chemotherapy** GVHD therapy (including CNi, MTRX, MMF) Maintenance chemotherapy Monoclonal antibodies Small molecules
1 week	**Radiation up to 30Gy[%]** Vincristine 6-mercaptopurine 6-thioguanine anti-TNF, anti IL-6 or antil-IL6r Methotrexate <25mg/m2 Ara c <100mg/m2 Non-pegylated asparaginase **IT chemotherapy**
3 days	**Bridging corticosteroids >20mg/d prednisone** Venetoclax
0 days	Hydroxyurea **Bruton Tyrosine kinase inhibitors***

**Some clinicians may continue BTKi though LD chemo and for a few days post CART to prevent disease rebound.*

[%] *A washout between radiation and LD chemo is recommended to allow for tumour shrinkage and prevent overlapping toxicity. However, this may not always be feasible and can be shortened based on clinician discretion.*

27-6. Infusion reactions

Patient should receive diphenhydramine 25-50 mg and acetaminophen 650 mg prior to CAR T-cell administration to avoid infusion reactions. Steroids can be administered for CRS/ICANS prophylaxis in select patients (See sections 8 and 9) but should not be used as routine, pre-infusion premedication.

27-7. Tumor lysis syndrome (TLS)

Tumor lysis syndrome is uncommon during CAR T-cell therapy. It occurs most often after cellular infusion. All patients should receive adequate hydration and prophylactic allopurinol (300 mg PO daily) from initiation of lymphodepleting chemotherapy. Patients with baseline elevations in uric acid or high tumor burden can be monitored with TLS labs during their inpatient stay.

27-8. Cytokine release syndrome (CRS)

Cytokine release syndrome occurs in most patients treated with CAR T-cell therapy as activated T-cells secrete various cytokines creating a hyperinflammatory state. High disease burden, elevated LDH, CRP and ferritin as well as primary refractory disease is associated with CRS. Clinical features include fever, tachycardia, hypotension, myalgias or arthralgias. Rising ferritin and CRP can herald the onset of CRS. Severe CRS is most common with Yescarta and Tecartus and treatment of aggressive lymphomas or B-ALL. It is less common with Breyanzi and treatment of indolent lymphomas. CRS usually develops on day 1-3 and lasts about 5 days. **It is uncommon for CRS to occur more than 2-3 weeks after CART administration. Fever >3 weeks after CART should prompt investigation for non-CRS related causes such as infection, relapse or IEC-HS (see section 27-13).**

Diagnostic workup

- CBC with differential, LFTs, Electrolytes, Creatinine, Ferritin, CRP, INR/PTT/Fibrinogen
- Blood and urine cultures,
    - Consider nasal swab or equivalent and Stool culture / C. difficile Toxin assay
    - Consider CMV and EBV titres
- Baseline chest x-ray and further symptom directed imaging (*CT chest, CT abdomen, etc.)*

Prevention of CRS

The use of dexamethasone 10 mg daily on Day 0, 1 and 2 has been demonstrated to reduce the incidence of severe CRS in Cohort 6 or the ZUMA-1 trial and can be considered in high-risk patients receiving Yescarta or Tecartus (high burden of disease or comorbidities that suggest poor tolerance of high-grade CRS). Anakinra has demonstrated efficacy in prevention of high grade ICANS but is not on formulary for this indication.

CRS Grading & Management – Abbreviated ASTCT Consensus Grading

	Grade 1	Grade 2	Grade 3	Grade 4
Fever	≥38°C (not attributable to any other cause). In patients who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia			
With				
Hypotension*	None	Responsive to IV fluids	Requiring a vasopressor	Requiring multiple vasopressors
And/Or				
Hypoxia		Requiring supplemental oxygen ≤ 6 L/min	Requiring supplemental oxygen > 6 L/min	Requiring CPAP, BiPAP or intubation and ventilation

**systolic blood pressure (SBP) ≤ 100 mmHg or a decrease of ≥ 20mmHg SBP from baseline*

Initial management of CRS

CRS closely resembles infection, and it is critical to treat as such until infection has been ruled out. CRS therapy can be initiated at the same time as antibiotics.

The goal of treating CRS is to improve toxicity to grade 1 or less. Tocilizumab 8 mg/kg IV (up to 800 mg per dose) is the first choice for CRS. When refractory to 2-3 doses of tocilizumab, escalating doses of steroids can be used until CRS resolves **to grade 1 or less**.

Tocilizumab is an IL-6 receptor antagonist and does not cross the blood brain barrier. It transiently increases serum IL-6 levels and can worsen ICANS. Therefore, tocilizumab is not recommended for the prevention of CRS and should be used judiciously in grade 1 CRS (see below)

Grade 1	Grade 2	Grade 3	Grade 4
Supportive care with analgesia, antipyretics and supplemental oxygen Fluid replacement Treatment of febrile neutropenia / possible infection			
MONITOR If fever persists for 24-72hr without other cause consider Tocilizumab IV x 1	**Tocilizumab** X 1 dose. If hypotension/hypoxia do not resolve, repeat q8h If hypotension/hypoxia do not resolve after **2-3 tocilizumab doses** add **dexamethasone 10 mg IV X 1** If hypotension/hypoxia do not resolve stop ? tocilizumab and continue **dexamethasone 10 mg IV q6h (can escalate up to 20 mg)**	If not previously given start **tocilizumab q8hr** for up to 3 doses **AND dexamethasone 10 mg IV q6h** If no improvement in 24 hours or clinical deterioration escalate **dexamethasone to 20 mg IV q6h**	If not previously given start **tocilizumab** q8hr for up to 3 doses AND **Dexamethasone 20 mg IV q6h OR** **Methylprednisolone 1 g daily X 3 days**
In patients with grade 3+ CRS that has not improved in 24 hours consider the addition of anakinra			

Management of Refractory CRS

There are no standard management guidelines for refractory CRS. Patients with grade 3 or 4 CRS who have not improved after 24 hours and 3 doses of tocilizumab **with** the addition of steroids may benefit from **anakinra, an IL-1 receptor antagonist.** Tocilizumab can be stopped in these patients.

- Anakinra 100 mg IV q12h (can be escalated to q6h)
  - *Consider 50% dose reduction in patients with CrCl <30ml/min*
  - ***In severe CRS higher initial doses of anakinra (>200 mg per day or 100mg q6 hr) are associated with reduced TRM***

There is no standard treatment for patient's refractory to anakinra. Use of anti-cytokine therapy or ablative strategies such as ATG can be used in severe, protracted and life-threatening cases. ATG is non-formulary for this indication.

Discontinuation of CRS directed therapy

Discontinuing and tapering therapy is a balance of risks of interventions (ie steroids) and severity of CRS. Treatments should be stopped or tapered when CRS resolves to grade 1 or less. **Patient must have resolution of CRS related hypotension or hypoxia to taper therapy but fever does not need to be completely resolved**.

Tapering recommendations

- Tocilizumab – discontinue
- Steroids – discontinue if ≤10 mg/day dexamethasone. Taper over 2-7 days if >10 mg/day dexamethasone.
  - *Steroids should be tapered first before anakinra*
- Anakinra – taper over 7 days

27-9. Immune effector cell-associated neurotoxicity syndrome (ICANS)

ICANS is a known complication of CAR-T cell therapy and can present with dysgraphia, confusion, decreased level of consciousness or seizure. High disease burden, elevated LDH, CRP and ferritin is associated with high grade ICANS. High grade ICANS is more common with Yescarta, Tecartus and treatment of aggressive lymphomas or B-ALL. It is less common with Breyanzi and treatment of indolent lymphomas. ICANS usually occurs around day 5-7 and last 7 days. **It is uncommon for ICANS to occur greater than 21 days post CART. Late onset neurologic symptoms should prompt investigation for other causes such as infection, CNS relapse or non-ICANS neurotoxicity (**more often seen with anti-BCMA CART)**.**

Prevention of ICANS

The use of dexamethasone 10 mg daily on Days 0, 1 and 2 has been demonstrated to reduce the incidence of severe ICANS in Cohort 6 of the ZUMA-1 trial and can be considered in high risk patients (high burden of disease or suspected poor tolerance of ICANS). Anakinra has been shown in smaller trials to reduce the risk of severe ICANS but is not available on formulary for this indication at this time.

Seizure prophylaxis

Patients treated with Yescarta or Tecartus should receive seizure prophylaxis with levetiracetam 500 mg PO BID for 30 days. Prophylactic anti-epileptics can be considered in patients with history of seizure or brain lesions.

Grading of ICANS – ASTCT Consensus Grading

Grading of ICANS involves a combination of patients ICE (immune-effector cell-associated encephalopathy) score and assessment of neurologic signs. Patients with features in 2 grades should be assigned the higher grade of toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0, unable to perform
Level of consciousness	Awake	Awakes to voice	Awakes to touch	Unrousable or requires vigorous stimuli
Seizure			Any seizure lasting <5min	Prolonged (>5min) or repetitive seizure without return to clinical baseline
Motor findings				Dense focal motor weakness
Raised ICP or cerebral edema			Focal cerebral edema on imaging	Diffuse cerebral edema on imaging or clinical signs of raised ICP (papilledema, Cushing triad, posturing, cranial nerve VI palsy)

ICE Scoring (10)

Orientation (4)
- Year (1), month (1), city (1), hospital (1)

Naming(3)
- Names 3 objects (3)

Follows a command (1)

Writing (1)
- Writes a legible sentence (1)

Attention (1)
- Counts back from 100 by 10s (1)

Diagnostic workup

- CBC with differential, LFTs, Electrolytes, Creatinine, Ferritin, CRP, INR/PTT/Fibrinogen
- Blood and urine cultures
    - *Consider respiratory viral panel, stool culture or C. difficile toxin assay if symptoms present*
- CNS imaging (preferably MRI brain but CT can be preformed if not feasible)
    - *Consider MRI Spine if focal deficits exist OR grade 3-4 disease to evaluate for cerebral edema*
- EEG
- Neurology consultation
- Consider Lumbar puncture with cultures and opening pressure

Initial management of ICANS

Initial management of ICANS involves **corticosteroids and supportive care**. **Tocilizumab should only be added if concurrent CRS** is present as tocilizumab does not cross the blood brain barrier and transiently increases serum IL6 levels which can worsen ICANS. **Treatment aims to improve ICANS to grade 1 or less.**

Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Consider dexamethasone 10 mg IV once and reassess in 6 hours Dexamethasone 10 mg IV X 1 can be repeated on an as needed bases up to every 6 hours for more severe grade 1 presentations. However, most patients with grade 1 ICANS simply require supportive management and time.	Dexamethasone 10 mg IV q6h If persistent grade 2 at 24 hr escalate to 20 mg IV q6h If no improvement after 24 hr of dexamethasone 20 mg IV q6h, manage as refractory ICANS	Dexamethasone 20 mg IV q6h If **focal cerebral edema** present give methylprednisolone 1 g X 3 days, then resume Dexamethasone 20 mg IV q6h If no improvement after 24 hr of methylprednisolone or dexamethasone 20 mg IV q6h, manage as refractory ICANS	Methylprednisolone 1g IV x 3 days, then taper If no improvement after 24 hr of methylprednisolone, manage as refractory ICANS

Supportive care measures

- NPO status, medication with sips
- Initiation of levetiracetam 750 mg PO/NG BID if not currently taking
- Close monitoring with repeat CARTOX scoring twice daily
- Low dose lorazepam (0.5 mg IV q8h) or haloperidol (0.5 mg IV q6h) can be used for agitated patients after EEG completion
- Control hypertension, glucose levels, electrolytes, uremia and other possible aetiologies of confusion
- Treatment of concurrent or suspected infection

Initial management of seizures

- Lorazepam 1-2 mg IV repeated up to 4 mg total per episode.
- Levetiracetam
    - Focal or generalized seizure lasting <5 minutes: 750 mg PO/NG BID
    - Status epilepticus: 1g IV x 1 dose, then reassess
- Consultation with neurology and / or ICU if status epilepticus is present

Management of refractory ICANs

Management guidelines and definition of refractory ICANS is lacking. Patient with grade 2-4 ICANS without improvement on high dose steroids (>dexamethasone 20 mg IV q6h) or with rapid clinical deterioration should be treated **anakinra, and IL1 receptor antagonist which does cross the blood brain barrier**.

- Anakinra 100 mg IV q12h (can be escalated to q6h)
    - *Consider 50% dose reduction in patients with CrCl <30ml/min*
    - ***In severe CRS higher initial doses of anakinra (>200 mg per day or 100 mg q6h) are associated with reduced TRM***
    - *The median duration of therapy with anakinra is 7 days*

There is no standard treatment for patient's refractory to anakinra. **Most centres recommend either dasatinib 100mg po daily OR cyclophosphamide 1gr IV once** . Both of these agents can treat ICANS and may preserve CART persistence. Other strategies include additional anti-cytokine therapy (siltuximab), intrathecal therapy or ablative strategies (ATG).

Discontinuation of therapy for ICANS

Grade 2 ICANS: Steroids should be continued at treatment doses until ICANS is grade 1 or less. After this time tapering of high dose (>10 mg/day dexamethasone) over 2-5 days and cessation of low dose steroids (≤10 mg/day dexamethasone) can commence.

Grade 3-4 ICANS: Tapering can begin after 24-48 hours of clinical improvement. **Steroids should be tapered first then anakinra taper can commence.** Anakinra should be tapered over 7 days.

27-10. Non-ICANS neurotoxicity

Movement and neurocognitive toxicity (MNT)

Occurs in up to 5% of patients receiving anti-BCMA cart and generally presents with parkinsonisns and neurocognitive decline. It generally occurs 4-8 weeks after CART administration. Systemic steroids are the first line of therapy followed by cyclophosphamide. Symptoms generally do not improve and therapy seeks to stabilize function.

Cranial and peripheral nerve palsies

Seen after anti-BCMA CART. Generally response to short course of oral steroids. Guillain Barre syndrome is also described post anti-BCMA CART and is treated with steroids and IVIg.

Ischemic stroke

Can be seen in up to 3% of patients treated with CART. This is most often seen in patients receiving CD19 CART who have severe ICANS. Management is per standard stroke guidelines.

Tumour Inflammation-Associated Neurotoxicity (TIAN)

TAIN is seen in patients with pre-existing CNS involvement. Infiltration from CAR T-cell and associated inflammation can exacerbate existing CNS symptoms, cause edema and even CSF outflow obstruction. Treatment may involve steroids, CSF diversion or hyperosmolar therapy depending on the severity and location.

27-11. Immune Effector Cell-Associated Hematotoxicity (ICAHT)

Cytopenias, also known as immune effector cell-associated hematotoxicity (ICAHT), are **expected** within the first month following CART-cell therapy. Neutropenia and thrombocytopenia are extremely common. However, 30% of patients treated with CAR T-cell therapy experience cytopenias beyond day 30. Risk factors include high disease burden (particularly marrow-based disease), number of prior therapies, previous HSCT, pre-existing cytopenias, baseline elevations in ferritin/CRP and CRS.

Irradiated blood products and CAR T-cell recipients

Patients treated with autologous CAR T-cell therapy require irradiated blood products **7 days before collection and 6 months after administration of CART.**

Risk Stratification; Pre-lymphodepletion CAR-HEMATOTOX Score validated with labs <72hr pre lymphodepletion

	0 Point	1 Point	2 Point
Platelet Count	>175 10^9 L	75-175 10^9 L	<75 10^9 L
Neutrophil count	>1.2 10^9 L	≤ 1.2 10^9 L	
Hemoglobin	>90 g/L	≤ 90 g/L	
C-reactive protein	<30 mg/L	≥ 30 mg/L	
Ferritin	<650 ug/L	650-2000 ug/L	>2000 ug/L

Low risk (0-1)
- Duration of severe neutropenia 3-6 days
- Risk of severe infection 5-8%
- Aplasia ≤3%

High risk (2+)
- Duration of severe neutropenia 9-14 days
- Risk of severe infection 30-40%
- Aplasia 32-47%

Treatment of Cytopenias

- Transfusion support (*irradiated products – see below)*
- In patients with ANC<0.5 after day +10 give GCSF 5 µg/kg once daily until ANC >0.5 then taper
  - Please submit a BC Pharmacare Special Authority Request for exceptional drug coverage if the patient does not already have Pharmacare Special Authority approval.
- TPO agonists can be considered in patients with persistent cytopenias beyond day 30 despite at least 5 consecutive days of GCSF once other causes (such as relapse) have been ruled out

Investigations or persistent or refractory cytopenias

If patients do not respond to GCSF OR have other signs / symptoms additional investigations may be needed. **Not all patients require all the following investigations**. Physician assessment and discretion should guide investigations.

- Drug effect: assess for myelosuppressive medications
- Infectious cause: blood cultures, NP swab
- IEC-HS (see 27-13): ferritin, triglyceride, LFTs, INR / PTT, CRP
- Hematinic deficiency: Vit B12 level, Iron studies, TSH
- Relapse: imaging
- Secondary malignancy: Bone marrow biopsy
- Rare infections cause: Parvo B19 PCR, EBV PCR, Adenovirus PCR, CMV PCR

27-12. Infection

Patients treated with CAR T-cell therapy are at increased risk of infection both from the procedure itself, B-cell aplasia, underlying disease and multiple prior lines of therapy.

	When	Medication	Duration
HSV / VZV	Seropositive patients	Valacyclovir 500 mg PO BID Acyclovir 800 mg PO BID	Start Day +1 and continue until 1 year post infusion*
PJP	All patients	Co-trimoxazole DS 1 tab PO BID Mon & Thurs *If toxi IgG positive use 1 SS tab PO Daily* Alternatives: o Dapsone[¥] 100 mg PO daily o Pentamidine 300 mg IV q21-28 days o Atovaquone[t] 1500 mg PO daily	Start by Day +28 and continue until 1 year after infusion*
HBV	HBcAb or HBsAg positive patients	Entecavir 0.5 mg PO daily Tenofovir disoproxil fumarate 300 mg PO daily	18 months post CAR T-cell infusion
Fungal	Patients with persistent ANC < 0.5	Fluconazole 400 mg PO daily	ANC > 0.5 for 24 hours
Bacterial	Patients with persistent ANC < 0.5	Ciprofloxacin 500 mg PO BID	ANC >0.5 for 24 hours

LD = lymphodepletion.

*VZV/HSV and PJP prophylaxis can be continued at the discretion of the provider dependent on patient risk taking into account patient history, vaccination status, use chemotherapy / steroids for relapse.

[t] Optimal alternative in Toxoplasmosis IgG positive patients. *Not covered by Pharmacare.* Take with high fat meal to optimize absorption.

[¥] Contraindicated with patients with G6PD deficiency. Screen for G6PD prior to initiation. Use with caution in patients with sulfa allergy

See Section 27-10 regarding G-CSF administration

Intravenous Immunoglobulin

Prophylactic IVIg administered in accordance with provincial guidelines is indicated in patients with IgG levels <5.0g/L AND

1. One life threatening bacterial infection in the past 12 months or
2. Two serious bacterial infections in the past 6 months

The use of IVIg in patients without history of infections is not recommended or evidence-based.

IVIg should be administered at an initial dose of 0.4g/Kg (adjusted body weight) given IV monthly to target a trough IgG level of 7-10g/L. The lowest possible maintenance dose to achieve this trough should be utilized and use should be assessed every 6 months.

Patients treated with IVIg should have live vaccines delayed until 8 months after their last dose.

Re-vaccination

Vaccination strategy post CAR T-cell therapy is similar to that of patients undergoing HSCT. Recommendations can be found on the BCCDC website.

27-13. Immune effector cell-associated hemophagocytic lymphohistiocytosis (HLH)-like syndrome (IEC-HS)

HLH is a hyper-inflammatory syndrome related to pathologic T-cell activation and NK cell dysregulation. IEC-HS refers to HLH seen in patients following CAR T-cell therapy. It is most frequently observed in those receiving CD22 targeting, 4-1BB constructs and is associated with robust T-cell expansion but, as compared to standard HLH, NK cell cytotoxicity appears to be preserved. IEC-HS is primarily seen in patients who first develop CRS then IEC-HS. In the largest case series to date, median time from infusion to CRS was 8 days and from infusion to IEC-HS was 14 days. Patients with IEC-HS have roughly a 10-fold higher peak ferritin than those with CRS (in the 200,000 range) as well as more pronounced transaminitis and hyperbilirubinemia. Hemophagocytosis can be seen on bone marrow biopsy. **In patients who have CRS that initially resolved then develop rising ferritin, fever, cytopenias, LFT abnormalities or coagulopathy consider IEC-HS and discuss treatment with a CART physician.**

27-14. Outpatient management of patients receiving CAR T-cell therapy

Prior to discharge from the BMT day program (ie day +28), any patient treated with CART who have signs or symptoms of CRS or ICANS should be admitted and managed as outlined above. Patients who call in with symptoms should be directed to come to VGH only. **They should not go to a local hospital.**

Patients may have a “pill in pocket” approach where they have a 10 mg tablet of dexamethasone on hand. In patients with symptoms of ICANS they can be instructed to take this medication enroute to the hospital.

Resources

- ASTCT App
- CARTOX App
- EU CAR-T Handbook

References

Kröger N, *et al.* editors. The EBMT/EHA CAR-T Cell Handbook. 2nd ed. Cham, Switzerland: Springer; 2025.

Lee, DW. *et al.* ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biology of Blood and Marrow Transplantation (2019) 25 (4): 625-638.

Hayden, PJ. *et al.* Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Annals of Oncology (2022) 33(3): 259-275.

MD Anderson; IEC Therapy Toxicity Assessment and Management. 2023.

Rajeski, K. *et al*. Immune effector cell–associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations. *Blood* (2023) 142 (10): 865–877.

Baird, JH. *et al.* Immune reconstitution and infectious complications following axicabtagene ciloleucel therapy for large B-cell lymphoma. *Blood Adv* (2021) 5 (1): 143–155.

Gazeau, N. Anakinra for Refractory Cytokine Release Syndrome or Immune Effector Cell-Associated Neurotoxicity Syndrome after Chimeric Antigen Receptor T Cell Therapy. *Transplantation and Cellular Therapy* (2023) 29 (7): 430-437.

Santomasso, BD. *et al.* Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline. *J Clin Oncol* (2021) 39(35): 3978 – 92.

BC transfusion Medicine Advisory Group; Secondary immunodeficiency – Indications for Ig Use. 2017.

Lichtenstein, DA. *et al.* Characterization of HLH-like manifestations as a CRS variant in patients receiving CD22 CAR T cells. *Blood* (2021) 138 (24): 2469–2484.

Kansagra, AJ. *et al.* Clinical Utilization of Chimeric Antigen Receptor T Cells in B Cell Acute Lymphoblastic Leukemia: An Expert Opinion from the European Society for Blood and Marrow Transplantation and the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant (2019) 25 (3):e76-e85.

Hayden, PJ. *et al.* Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). *Annals of Oncology* (2022) 33 (3) 259-275.

Oluwole, O. *et al.* Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. *BJHaem* (2021) 194 (4) 690-700.

Rockwood K, Theou O. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. *Can Geriatr J*. 2020: 23 (3): 210-215.

LEUKEMIA/BMT MANUAL E-EDITION

CHAPTER 28 MOLECULAR DIAGNOSTICS AND MONITORING

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MOLECULAR DIAGNOSTICS AND MONITORING

28-1. Introduction

All hematologic malignancies at diagnosis have genetic testing performed that can include cytogenetics, optical genome mapping, myeloid gene panel or targeted gene mutation testing (FLT3, BCRABL, NPM1, JAK2 etc). The specific testing performed depends on the specific disease being evaluated (acute leukemia, MDS, MPD, CML etc).

There are also certain subsets of acute and chronic leukemia that can be followed by molecular monitoring for minimal residual disease (MRD). Our current recommendation is as follows:

28-2. Acute Myeloid Leukemia

1. Core binding factor acute myeloid leukemia [t(8;21), inv (16)] should be monitored by molecular MRD at diagnosis, following 2 cycles of intensive chemotherapy, at the end of consolidation and then monthly for 2 years after completion of all chemotherapy or for 2 years following stem cell transplant.
2. NPM1-A, NPM1-B, NPM1-D, NPM1-J, NPM1-R mutated acute myeloid leukemia should be monitored by molecular MRD at diagnosis, following 2 cycles of intensive chemotherapy, at the end of consolidation and then monthly for 2 years after completion of all chemotherapy or for 2 years following stem cell transplant.
3. Acute promyelocytic leukemia with PMLRARA mutation should be monitored by molecular MRD every 3 mos for 3 years following completion of all chemotherapy

28-3 Acute Lymphoid Leukemia

1. Philadelphia positive acute lymphoid leukemia should be monitored by molecular MRD for BCR-ABL every 3 months following completion of all therapy

28-4 Chronic Myeloid Leukemia

1. Chronic myeloid leukemia in chronic phase (without prior resistance) should be monitored by molecular MRD for BCR-ABL every 3 mos while on TKI and once MMR achieved and stable can be reduced to every 6 mos. If there is a history of prior resistance to TKI, then monitoring frequency should be every 3 mos.
2. Advanced phase CML (AP or BP) should be monitored every 3 mos if clinically stable, but may require more frequent monitoring in special circumstances (rapidly rising transcripts etc).

There are also certain diseases (example, Philadelphia negative B ALL) that can be followed by flow cytometry for MRD assessment. The specific time points for this are listed in the disease specific treatment algorithm and chemotherapy flow sheets.

Please refer to the table below for the specimen type required for each test. It is advisable that these tests be obtained on Monday-Wednesday to ensure they reach the Cancer Genetics Laboratory within the 48 hour time limit

MOLECULAR (DNA, RNA)				EXTRACTION	PB EDTA	BM EDTA	MAA PB / BM
MYELOID	**Acute Myeloid Leukemia**	*New Diagnosis (all required)*	Myeloid Panel AND Rapid Mutation Panel	DNA		0.5ml	✓
			MRD Baseline - BM	RNA		0.5ml	✓
			MRD Baseline - PB	RNA	20ml		✓
		MRD Monitoring	*t(8;21)* *inv(16)/t(16;16)* *NPM1*	RNA	20ml	0.5ml	✓
		Relapsed/Refractory	*FLT3* ITD & TKD	DNA	6ml	0.5ml	
	Acute Promyelocytic Leukemia		MRD Baseline / Monitor	RNA	20ml	0.5ml	✓
	Chronic Myelogenous Leukemia		MRD Baseline / Monitor Kinase Domain	RNA	20ml	0.5ml	✓
	Mast Cell Disease		*KIT* D816V/F	DNA	6ml	0.5ml	✓
	Myelodysplastic Syndrome		Myeloid Panel	DNA		0.5ml	
	Myeloproliferative Neoplasm		Single-gene testing query *JAK2* V617F MPN	DNA	6ml	0.5ml	✓
VEXAS		*UBA1* mutation screen	DNA	6ml	0.5ml		
OTHER	**Chimerism**		Pre-transplant assessment	DNA	6ml		
			Post-transplant assessment (sample processed at Stem Cell Lab)	DNA	**20 mL NaHep @Stem Cell Lab**		

MOLECULAR (DNA, RNA, ctDNA)			EXTRACTION	PB	BM	MAA	FFPE		
				EDTA	EDTA	PB / BM	H&E (circl	BLOCK / SLID	TUMOUR CON
LYMPHOID	**Acute Lymphoblastic Leukemia**	MRD Baseline MRD Monitor Kinase Domain	RNA	20ml	0.5ml	✓			
LYMPHOID	**Chronic Lymphocytic Leukemia**	CLL NGS Prognostic (CVM) Panel	DNA	6ml	0.5ml	✓		✓	
LYMPHOID	**Lymphoplasmacytic Lymphoma**	*MYD88*	DNA			✓		✓ **BM**	✓
LYMPHOID	**Non-Hodgkin's Lymphoma**	B/T cell clonality	DNA	6ml	0.5ml			✓	
OTHER	**Chimerism**	Pre-transplant assessment	DNA	6ml					
OTHER	**Chimerism**	Post-transplant assessment (sample processed at Stem Cell Lab)	DNA	**20ml NaHep @Stem Cell Lab**					

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