

Management of Children with Idiopathic Severe Aplastic Anemia

Version: 3

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Approved by Haematology/Oncology Quality Utilization and Patient Care Committee: February 1, 2021

1.0 Introduction

Aplastic anemia (AA) is characterized by an “empty” bone marrow, whereby hematopoietic precursor cells are replaced by fat leading to pancytopenia and results from either an inherited or an acquired (immune/idiopathic) cause (Scheinberg, et al, 2011).

1.1 Target Users: this guideline will be used by Haematology/Oncology physicians, fellows, and nurses, as well as all health care professionals caring for patients with aplastic anemia across the hospital.

2.0 Definitions

AA is defined as hemoglobin ≤ 100 g/L, platelet count $\leq 50 \times 10^9/L$, granulocytes $\leq 1.5 \times 10^9/L$, and a bone marrow biopsy demonstrating decreased cellularity in the absence of significant fibrosis or neoplastic infiltration (International Agranulocytosis and Aplastic Anemia Study, 1987; Davis, et al., 2007).

Acquired Aplastic Anemia (AA)	Classified into idiopathic aplastic anemia and secondary aplastic anemia
Idiopathic Aplastic Anemia	AA not attributed to a definable cause, presumed immune dysregulation
Secondary Aplastic Anemia	AA attributed to a definable cause e.g. drugs, toxins, infection, auto-immune disorders, paroxysmal nocturnal hemoglobinuria, or hepatitis-associated
Inherited Aplastic Anemia	AA secondary to an inherited bone marrow failure syndrome such as Fanconi anemia, Dyskeratosis congenita, Shwachman Diamond syndrome etc.
Severe Aplastic Anemia (SAA)	BM cellularity $<25\%$ or $25-50\%$ with $<30\%$ residual hematopoietic cells plus: <ul style="list-style-type: none"> • 2 out of 3 of the following: <ul style="list-style-type: none"> • Neutrophil count $<0.5 \times 10^9/L$ • Platelet count $<20 \times 10^9/L$ • Anemia with reticulocyte count $<40 \times 10^9/L$
Very Severe Aplastic Anemia (VSAA)	Same as SAA but neutrophils $<0.2 \times 10^9/L$
Moderate/Non-Severe Aplastic Anemia	Criteria for SAA are not met
Complete Response	After receipt of AA-directed therapy, blood counts normal for age and gender, or no transfusion support and hemoglobin normal for age and gender, absolute neutrophil count $> 1.5 \times 10^9/L$, and platelet count $> 150 \times 10^9/L$
Partial Response	After receipt of AA-directed therapy, no transfusion support required, no longer meets criteria for severe aplastic anemia
No Response	Despite receipt of AA-directed therapy, continues to meet criteria for severe

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	aplastic anemia
G-CSF	Granulocyte colony stimulating factor; filgrastim
ATG	Anti-thymocyte globulin
ATGAM®	Anti-thymocyte globulin – equine
Thymoglobulin®	Anti-thymocyte globulin – rabbit

3.0 Clinical Practice Recommendations (Grade C)

3.1 Work-up

3.1.1 Laboratory:

1. CBC, differential, smear, reticulocyte count
2. Haemoglobin analysis/hemoglobin variant quantification
3. Bone marrow aspirate (including morphology, iron staining for ringed sideroblasts and cytogenetics for standard karyotype) and trephine biopsy (for cellularity, collagen and reticulin fibrosis)
4. Liver enzymes and function – ALT, alkaline phosphatase, bilirubin (conjugated & unconjugated), GGT, albumin, total protein, INR/PTT/fibrinogen
5. Electrolytes - Na, K, calcium, phosphate, magnesium, glucose
6. Renal function tests – creatinine
7. Direct Antiglobulin Test (DAT), haptoglobin, LDH, ESR, urate
8. Nutritional studies – iron, ferritin, transferrin, red cell folate, serum vitamin B12, vitamin A, vitamin D, vitamin E
9. Pancreatic function – serum pancreatic amylase, amylase, lipase, and fecal elastase. Trypsin if evidence of pancreatic dysfunction.
10. Viral studies – hepatitis A, B, and C, EBV, CMV (IgM and IgG), HSV, VZV and Parvovirus serology, PCR for EBV, CMV, HSV, HHV6, HHV7, and VZV.
11. Anti-nuclear antibody (ANA), anti-double stranded DNA, rheumatoid factor (RF)
12. Complement C3 & C4, CRP, CH50
13. Immunoglobulins (IgG, IgA, IgM)
14. G6PD assay (as screening pre-Dapsone for PJP prophylaxis)
15. Type and Screen
16. HIV testing

3.1.2 Other testing:

- **Telomere length measurements** to screen for Dyskeratosis Congenita. This test is sent out-of-province and completed through the DNA resource center. The following forms are required:
 - DNA Resource Center Service Request Form
 - DNA Resource Center Parent/Guardian or Adult Patient/Capable Minor Consent Form for DNA Testing or Blood or Tissue Storage
 - Ministry of Health Prior Approval Application for Full Payment of Insured Out-of-Country Health Services – Request for Diagnostic Laboratory Testing Form
 - Repeat Diagnostics Telomere Length Measurement requisition.
 - EPIC order for external fresh blood send out.

All forms must be completed and faxed to the DNA Resource Center at 416-813-5557. A fresh sample of blood must be sent to the SickKids Molecular Genetics Laboratory, Roy C. Hill Wing, Room 3421 by 3 pm, Monday through Thursday. Forms can be found in [Sharepoint](#) or obtained from the Marrow Failure and Myelodysplasia team.

- **Peripheral blood to test exon 2 of SBDS gene** to exclude Shwachman-Diamond Syndrome – Molecular Diagnostics at SickKids. The following forms are required:

- <https://www.sickkids.ca/contentassets/daff5ed3ca748d4b0186c397bfe95a0/genome-diagnostics-billing-requisition.pdf>
- EPIC order for Shwachman-Diamond Syndrome
- **Peripheral blood for chromosomal breakage analysis** to exclude Fanconi Anemia – Cytogenetics at SickKids. The following forms are required:
 - [http://notesdb03.sickkids.ca/dplm/labguide.nsf/696f2a8995f98d7c85256c9100538c54/ff32e8c751c4e7d085256cba00782580/\\$FILE/66666803.pdf/Constitutional-AnalysisReq-INT_06.pdf](http://notesdb03.sickkids.ca/dplm/labguide.nsf/696f2a8995f98d7c85256c9100538c54/ff32e8c751c4e7d085256cba00782580/$FILE/66666803.pdf/Constitutional-AnalysisReq-INT_06.pdf)
 - EPIC order for Fanconi Anemia Chromosome Breakage test
- **Flow cytometry for CD55/CD59/Fluorescent aerolysin (FLAER)** markers on red blood cells, granulocytes, and monocytes to exclude Paroxysmal Nocturnal Hemoglobinuria – Flow cytometry lab at SickKids (sent out by SickKids lab to Toronto General Hospital): Ordered through EPIC under PNH Markers.
- **Diagnostic Imaging:**
 - Chest X-ray as a screen for congenital anomalies that may be related to an inherited bone marrow failure syndrome (after Fanconi Anemia and other DNA damage and genomic instability disorders are ruled out)
 - Abdominal ultrasound as screen for congenital anomalies that may be related to an inherited bone marrow failure syndrome
 - Forearm x-ray as indicated (after Fanconi Anemia and other DNA damage and genomic instability disorders are ruled out)

Other Bloodwork:

- **Peripheral blood for DNA banking for possible future testing** (if discussed and agreed upon by patient and/or family). The following form is required:
 - <http://my.sickkids.ca/care/DPLM/DNA-resource-centre/Documents/1a-DRC%20DNA%20banking%20form%20Final.pdf>
- **Urgent HLA-typing (patient and immediate family) and urgent referral to the Bone Marrow Transplant Team.**
 - Typing of patient can be arranged through notification of a BMT Nurse Coordinator or Staff Physician.
 - Typing of immediate family members (ie. fully biological parents and siblings) requires a referral to be sent to the Bone Marrow Transplant team for HLA-typing via EPIC.
 - Please download, print, and complete the "Request for HLA-Typing and Identification of Potential Related Donors" form from [SharePoint](#). The completed form with family member signatures must accompany the EPIC referral.
 - Request CBC, differential, retic, smear and haemoglobin electrophoresis on all family members being HLA-typed.
 - Urgent consult not necessary in moderate aplastic anemia or in less severe cases.

Research:

- When appropriate during work-up, please contact the Marrow Failure research coordinator to discuss with the family and facilitate the collection of a bone marrow sample for research if consent obtained.

3.2 Treatment

3.2.1 Supportive measures (Grade C)

Transfusion Support

The overall goal should be to minimize the number of transfusions to decrease the risk of allo-immunization through HLA and non-HLA antibodies and to decrease the risk of iron overload secondary to frequent red blood cell transfusions (Marsh, et al., 2009).

Anemia

- Transfuse as needed for clinical symptoms related to anemia and/or to maintain hemoglobin levels >60-65 g/L.
- Patients with low T lymphocyte counts or on ATG therapy must receive irradiated red cells and platelets.
- In cases of allo-immunization, appropriately matched blood products are required.
- Monitoring of ferritin levels and liver enzymes is recommended to detect possibility of iron overload. Ferriscan (liver MRI) to measure liver iron concentrations and assess need for iron chelation therapy may be necessary in rare cases of significant iron overload more accurately.

Thrombocytopenia

- Transfuse as needed for clinical indications of bleeding and/or to maintain platelet counts >10 x 10⁹/L when patient is well and >20 x 10⁹/L when febrile.
- Patients with low T lymphocyte counts or on ATG therapy must receive irradiated red cells and platelets.
- Recipients of allogeneic hematopoietic stem cell transplant will receive CMV seronegative red cells and platelets post-transplant if they are CMV seronegative pre-transplant.
- In cases of allo-immunization, appropriately matched blood products are required.

Management of Fever and Neutropenia

- In the event of a fever, refer to the SickKids Formulary Antimicrobial Guidelines for: [Management of Haematology/Oncology & Hematopoietic Progenitor Cell Transplant Patients \(HPCT\) with Fever](#) (Grades A & B)
- Consider filgrastim (G-CSF) for patients with SAA with recurrent infections or severe infection. See section 3.4.2: Use of filgrastim for dosing guidelines (Grade C)
- Consider granulocyte transfusions if documented fungal/bacterial infection and profound neutropenia in clinically unwell children.

3.2.2 Treatment of Patients with a Matched Sibling Donor for Hematopoietic Stem Cell Transplant (Grade B)

A matched sibling donor hematopoietic stem cell transplant is the first line of therapy for patients with acquired severe and very severe aplastic anemia resulting in approximately 90% cure rate. HLA-typing of the patient and all immediately related fully biological family members (parents and siblings) is carried out as part of the initial work-up for SAA. An urgent referral to the Bone Marrow Transplant Team must be made through EPIC at the time of diagnosis of SAA. If HLA- typing identifies a suitable HLA matched donor within the family, then a member of the BMT team will contact the potential donor (or substitute decision maker) to affirm their willingness to proceed and to obtain consent to disclose the match to the patient's treating team. Once affirmation and consent are obtained the patient's treating team will be contacted and asked for an update to facilitate planning for urgent transplantation.

3.2.3 Treatment of Patients without a Matched Sibling Donor for Hematopoietic Stem Cell Transplant: Immunosuppressive Therapy (1st course) (Grade C)

When no suitable matched sibling donor for hematopoietic stem cell transplant is available, a search will automatically be initiated within BMT for an alternative hematopoietic stem cell donor. Immunosuppressive therapy (IST) should be initiated as soon as possible. This requires an admission to the Haematology/Oncology inpatient unit (8A).

Prior to Admission to 8A:

1. Dictate admission note that summarizes patient's present history of illness and outlines the details of immunosuppressive therapy. Enter pre-admission orders into EPIC in the

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Admission Pending encounter using the **SK SOC IST SAA therapy (ATGAM and cyclosporine)** treatment plan.

2.

Baseline Blood Work to be done within 24 hours of Admission to 8A

1. CBC, differential, reticulocyte count, and smear
2. Liver enzymes - ALT, Alk Phosph, Bilirubin (unconjugated & conjugated), GGT, LDH
3. INR/PTT/fibrinogen, albumin, protein
4. Renal function test - creatinine
5. Na, K, Mg, Ca, Phosphate, glucose
6. Type & screen

Medications for Immunosuppressive Therapy - 1st Course

IST Regime	Dose	Notes
Anti-thymocyte Globulin (ATG) (ATGAM® = equine ATG)	40 mg/kg/dose IV over 6 hours daily x 4 days	To be infused over a minimum of 6 hours; infusion may be prolonged up to a maximum of 12 hours
predniSOLONE/ predniSONE	1 mg/kg/dose (max 40 mg/dose) PO two times daily x 7 days	<ul style="list-style-type: none"> Start 3 hours before ATGAM Taper slowly over 3 weeks once ATGAM therapy completed
cycloSPORINE (CSA)	6 mg/kg/dose (max 250 mg/dose before TDM) PO q12h	<ul style="list-style-type: none"> Trough CSA concentration to be drawn on day 3 of therapy prior to a.m. dose. Adjust dose to maintain whole blood serum concentrations between 150-200 mcg/L Available as 100 mg/mL liquid, & 10, 25, 50 or 100 mg capsules
Pre-medication	Dose	Notes
acetaminophen	10-15 mg/kg/dose (max 1000 mg/dose) PO pre-ATGAM and then q6h PRN	Dose limit of 75 mg/kg/day or 4 g/day, whichever is less
Cetirizine	Administer PO at least 1 hour pre-and then once daily until last dose is complete <ul style="list-style-type: none"> age based dosing (Refer to e-formulary) use upper end of dosing range may give second dose of cetirizine daily if allergic symptoms if <6 months or not able to tolerate cetirizine use diphenhydramine 0.5-1 mg/kg IV q6h during infusion 	
meperidine	1 mg/kg/dose (max 50 mg/dose) IV q6h PRN for rigors	

Supportive care management:

Complication	Treatment	Notes
Anemia	Transfuse with PRBC to maintain Hgb > 65 g/L of anemia-related symptoms	See section 3.2.1 Supportive Measures
Thrombocytopenia	Transfuse with platelets to maintain platelets > 20 x 10 ⁹ /L	See section 3.2.1 Supportive Measures. During ATG treatment and until one day after, platelets should be maintained over 20 x 10 ⁹ /L, to prevent acute drop in counts to very low levels and bleeding.

Management of possible complications secondary to medications

Causal Medication	Complication	Treatment/Management
cycloSPORINE (CSA)	Hypomagnesemia	Provide patient/family with magnesium diet information: http://www.aboutkidshealth.ca/En/HealthAZ/TestsAndTreatments/SpecialDiet/Pages/High-Magnesium-Diet.aspx Supplement with oral magnesium (magnesium hydroxide or glucophenolate) as per SickKids formulary *Note: Give with food to reduce risk of diarrhea; follow symptoms closely and adjust dose accordingly.
	Hypertension	If SBP and or DBP >90th %ile for age and height on 2 separate occasions 15 minutes apart, and on >2 consecutive days or clinic visits, start amlodipine dosed as per the SickKids formulary.
	Nephrotoxicity	If serum creatinine is elevated to 1.5 x baseline, increase fluid intake to 1.5 x maintenance, and consider reducing cyclosporine target trough concentration after discussion with marrow failure and myelodysplasia team, as well as a pharmacist.
	Gingival Hypertrophy	Supportive care such as soft bristle toothbrush. If extensive and/or severe, may require a consult with Dentistry with possible intervention. If severe, consider switching to tacrolimus (at the discretion of the Marrow Failure and Myelodysplasia Team.
ATG	Serum Sickness	See section 3.03 Management of Serum Sickness Post-ATG

	Anaphylaxis	<ul style="list-style-type: none"> Stop ATG infusion immediately and call MD/NP Refer to the SickKids Policies & Procedures for Administration of Intravenous Medications, Anaphylaxis Treatment Kit, Adverse Drug Reaction Reporting Programme
predniSOLONE/ predniSONE	Gastritis/Heartburn	Initiate famotidine if symptomatic while receiving prednisone Refer to Sick Kids guideline: Treatment of Gastric Acid-Related Symptoms in Paediatric Haematology/Oncology & HPCT Patients
	Hypertension	See cycloSPORINE above.

3.2.4 Treatment of Patients with No Response to First Course of Immunosuppressive Therapy: Unrelated HLA Matched or Haploidentical Hematopoietic Stem Cell Transplant (Grade C)

If there is no response at 3-6 months post-initial immunosuppressive therapy, then consideration should be made for a bone marrow transplant from an unrelated HLA matched or haploidentical- hematopoietic stem cell donor. A thorough discussion must occur with the Bone Marrow Transplant team regarding potential donors and the approach to therapy that will yield the best possible outcome.

3.2.5 Treatment of Patients with No Response to First Course of Immunosuppressive Therapy and not suitable for hematopoietic stem cell transplantation (no suitable hematopoietic stem cell donor or other): Immunosuppressive Therapy (2nd course) (Grade C)

If no response is achieved at 3-6 months post-initial immunosuppressive therapy and there is no suitable hematopoietic stem cell donor, then a second course of immunosuppressive therapy may be considered. A bone marrow aspiration and biopsy with cytogenetic analysis for standard karyotype should be completed to ensure that there has been no clonal evolution and that there are no malignant infiltrates.

For the second course of immunosuppressive therapy, rabbit ATG (Thymoglobulin®) is used instead of equine ATG (ATGAM®) to reduce the risk of sensitization related to re-exposure to equine ATG (ATGAM®) and for possible benefit from a different ATG source. In addition, prolonged immunosuppression with tacrolimus, instead of cycloSPORINE, may be considered for possible benefit from a different source or oral immunosuppression, and decreased side effects such as gingival hypertrophy and hypertrichosis seen with cycloSPORINE.

This requires an admission to the Haematology/Oncology inpatient unit (8A).

Prior to Admission to 8A:

1. Dictate admission note that summarizes patient's present history of illness and outlines the details of immunosuppressive therapy.
2. Enter pre-admission orders into EPIC in the Admission Pending encounter using the **appropriate treatment plan**.

Baseline Blood Work to be done within 24 hours of Admission to 8A

1. CBC, differential, reticulocyte count, and smear
2. Liver enzymes - ALT, Alk Phosph, Bilis (unconjugated & conjugated), GGT
3. INR/PTT/fibrinogen, albumin, protein
4. Renal function test - creatinine
5. Na, K, Mg, Ca, Phos, urate, LDH
6. Type & Screen

Medications for Immunosuppressive Therapy - 2nd Course

IST Regime	Dose	Notes
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Anti-thymocyte Globulin (ATG) (Thymoglobulin® = rabbit ATG)	2.5 mg/kg/dose IV over 6 hours daily x 5 days	
predniSOLONE/ predniSONE	1 mg/kg/dose (max 40 mg/dose) PO two times daily x 7 days	<ul style="list-style-type: none"> Start 3 hours before Thymoglobulin Taper slowly over 3 weeks once Thymoglobulin therapy completed
cycloSPORINE (CsA)	6 mg/kg/dose (max 250 mg/dose) PO q12h	<ul style="list-style-type: none"> If patient already on CsA prior to initiation of 2nd course of IST, continue on same dose of CsA to maintain therapeutic levels Trough CsA concentration to be drawn on day 3 of therapy prior to a.m. dose only if initiating CsA Adjust dose to maintain whole blood serum concentrations between 150-200 mcg/L
Tacrolimus	0.1 mg/kg/dose PO q12h	<ul style="list-style-type: none"> Trough Tacrolimus concentration to be drawn on day 3 of therapy prior to a.m. dose Adjust dose to maintain whole blood serum concentrations between 8-12 mcg/L. Sometimes target levels are lower due to renal functions or other organ concerns.

Pre-medication	Dose	Notes
acetaminophen	10-15 mg/kg/dose (max 1000 mg/dose) PO pre-Thymoglobulin and then q6h PRN	Dose limit of 75 mg/kg/day or 4 g/day, whichever is less
Cetirizine	Administer PO at least 1 hour pre-and then once daily until last dose is complete <ul style="list-style-type: none"> age based dosing (Refer to e-formulary) use upper end of dosing range may give second dose of cetirizine daily if allergic symptoms if <6 months or not able to tolerate cetirizine use diphenhydramine 0.5-1 mg/kg IV q6h during infusion	
meperidine	1 mg/kg/dose (max 50 mg/dose) IV q6h PRN for rigors	

3.3 Management of Serum Sickness Post-ATG (Grade C)

Serum sickness post ATG is a type III hypersensitivity (immune complex-mediated) reaction that results due to the injection of foreign protein into a patient.

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Signs and symptoms of serum sickness (% of patients): fever (100%), malaise (93%), cutaneous eruptions (especially urticaria) (77%), arthralgias/arthritis (67%), GI complaints (abdominal pain, nausea, vomiting, diarrhea) (57%), headache (37%), myalgia (37%), blurred vision (37%), dyspnea/wheezing (20%) and lymphadenopathy (17%) starting usually 1-2 weeks post-ATG administration. Clinical recovery can take between 1-4 weeks.

Treatment

Medication	Dose	Notes
predniSOLONE / predniSONE	If initial predniSOLONE/ predniSONE dose is being tapered, discontinue taper and increase dose to 1 mg/kg/dose (max 40 mg/dose) PO two times daily.	Discuss the predniSOLONE/ predniSONE dose increase with the Marrow Failure and Myelodysplasia team. Continue the increased predniSOLONE/ predniSONE dose for 1 week after symptoms of serum sickness have resolved and then taper.
Cetirizine	Administer PO once daily until recovery <ul style="list-style-type: none"> • age based dosing (Refer to e-formulary) • use upper end of dosing range • may give second dose of cetirizine daily if allergic symptoms • if <6 months or not able to tolerate cetirizine use diphenhydramine 0.5-1 mg/kg PO/IV q6h PRN 	

Consider hospitalization if symptoms are severe and/or hemodynamic instability is present.

3.4 Infection Prevention

Patients with aplastic anemia are immunocompromised and thus at increased risk for both bacterial and fungal infections.

3.4.1 Management of fever and neutropenia (Grades A & B)

Refer to the SickKids Formulary Antimicrobial Guidelines for: [Management of Haematology/Oncology & Haematopoietic Stem Cell Transplant \(HSCT\) Patients with Fever](#). Patients should be considered as high risk of life-threatening infections since neutropenia may be very severe and typically is not expected to improve during the current episode of fever.

Consider granulocyte transfusions if documented fungal/bacterial infection and profound neutropenia in clinically unwell children.

3.4.2 Use of filgrastim (G-CSF) (Grade C)

If there is persistent fever and neutropenia (neutrophils counts $\leq 0.5 \times 10^9/L$) for more than 3-5 days despite antibiotic therapy, then initiation of filgrastim should be considered. (Marsh, et al., 2009)

Medication	Dose	Notes
filgrastim	5 mcg/kg/dose SC daily	Discontinue if there is no significant increase in neutrophil count within 1 week

In case of severe infections, clinical instability or frequent infections and admissions, filgrastim should be initiated. In case of no response, the filgrastim dose should be increased by 5-10 mcg/kg/dose every 3-5 days, up to a maximum of 60 mcg/kg/dose or 1500 mcg/day whichever is less, until a response is achieved. If no response despite maximum dosing, filgrastim should be discontinued. In well VSAA or SAA with frequent infections, may consider starting filgrastim supportively.

3.4.3 Use of fungal prophylaxis (Grade C)

Consider fluconazole prophylaxis for patients with severe neutropenia (neutrophil count $<0.2 \times 10^9/L$), while on immunosuppressive therapy, particularly for patients who require courses of antibiotics that are frequent or prolonged.

Medication	Dose	Notes
fluCONAZOLE	10 mg/kg/day IV/PO once daily (max 400 mg/day)	Due to the interaction with cycloSPORINE & tacrolimus discuss potential need to adjust cyclosporine/tacrolimus doses with pharmacist.

3.4.4 Use of Pneumocystis jirovecii Pneumonia Prophylaxis (PJP) (Grade C)

Prophylaxis should be started on initiation of immunosuppressive therapy. Refer to [PJP guidelines](#) for treatment options. Avoid choice of sulfamethoxazole/trimethoprim due to risk of marrow suppression. Once the patient has responded and immunosuppressive therapy (cyclosporine/tacrolimus and corticosteroid) has been discontinued, PJCP prophylaxis may be discontinued (including related monitoring bloodwork).

4.0 Follow-up Management Post Immunosuppressive Therapy (Grade C)

Newly diagnosed patients in the community should be referred promptly to the Marrow Failure and Myelodysplasia clinic for urgent work-up and treatment. Those patients hospitalized at SickKids will begin their work-up while in hospital and should also be referred urgently to the Marrow Failure and Myelodysplasia program. Patients will also be seen within a few days after discharge post immunosuppressive therapy in the Marrow Failure and Myelodysplasia clinic. Initially, they should be seen twice a week to ensure transfusion requirements are met, cycloSPORINE/tacrolimus concentration targets are achieved, and adverse effects of therapy are identified. Continued frequency of visits will be determined by the required frequency of transfusions, as well as need for monitoring of adverse effects to therapy. Assessment of response to immunosuppressive therapy is based on evaluation of complete blood counts and transfusion requirements between 3-6 months after immunosuppressive therapy administration.

Follow-up Management Post Immunosuppressive Therapy (Grade C):

	Every visit	Weekly (until stable) ▲	Every 6 weeks (after stable) ▲	Monthly	Notes
Height & weight		X	X		Consider less frequent heights for older children
Vital signs (including blood pressure)	X				
Physical exam		X	X		More or less frequently as needed
CBC, differential, retic, smear	X				
CycloSPORINE/Tacrolimus level (except when tapering)	X				Adjust CsA dose to maintain levels between 150-200 mcg/L. Adjust Tacrolimus dose to maintain levels between 8-12 mcg/L.
Magnesium		X	X		May change according to the patient status
Electrolytes (Na, K,)		X	X		May change according to the patient status
Liver enzymes (ALT, , ALP, GGT, Bilirubin (conjugated and unconjugated)		X	X		May change according to the patient status
Renal function tests (, Cr)		X	X		May change according to the patient status
Ferritin				X	Evaluate for iron overload after 15+ PRBC transfusions with Ferriscan (liver MRI)
Methaemoglobin				X	

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	Every visit	Weekly (until stable) ▲	Every 6 weeks (after stable) ▲	Monthly	Notes
(if pt. is on Dapsone)					
PNH clones (without specific symptoms other than SAA)					Repeat PNH testing in 6 months. If additional PNH-specific symptoms appear, test earlier as indicated

▲ may be done less/more frequently based on individual patient assessment

4.1 Tapering CycloSPORINE/tacrolimus (Grade C)

Complete Response

Once a complete response has been achieved, cycloSPORINE/tacrolimus therapy will be continued for a period of about 6 months to consolidate response and maintain stable blood counts. The period of consolidation may be longer in patients with partial response and might be slightly shorter (e.g. 4 months) in patients and very rapid response. A slow taper of cyclosporine/tacrolimus will then be commenced over another 6 months. Clinic visits will be every 4 weeks during the taper, to monitor for relapse. CycloSPORINE/tacrolimus level monitoring will be discontinued once taper begins.

Partial Response

Hold at full dose cycloSPORINE/tacrolimus and consider slow taper once counts have been stable for at least 6 months. A taper of cycloSPORINE/tacrolimus should be carried out over a minimum of 6 months. Clinic visits will be every 4 weeks during the taper, to monitor for relapse. CycloSPORINE/tacrolimus level monitoring will be discontinued once taper begins.

No Response

A thorough investigation must be completed to rule out evolution to myelodysplastic syndrome or acute myeloid leukemia.

At the same time, consideration should be made for a bone marrow transplant from an unrelated HLA matched or haploidentical- hematopoietic stem cell donor. If there is no suitable donor available or patient is not a hematopoietic stem cell transplant candidate for other reasons, a second course of IST may be considered. A thorough discussion must occur between the Bone Marrow Transplant and Marrow Failure teams regarding potential donors and the approach to therapy that will yield the best possible outcome.

5.0 Immunizations (Grade C)

Patients can continue to receive recommended scheduled inactivated virus immunizations, including annual doses of the injectable form of the inactivated influenza vaccine. Nasal spray administration of the influenza vaccine is contraindicated as it is a live attenuated virus vaccine. There is a possibility that patients may not mount an appropriate immune response to immunization, thus re-immunization may be necessary once they are no longer immunosuppressed. Live attenuated viral vaccines, such as the MMR, are contraindicated while patients are on immunosuppressive therapy due to the increased risk of developing disease caused by the vaccine.

6.0 Funding for Immunosuppressive Therapy Treatment

For patients whose parents have extended health benefits, prescription medication may be fully or partially covered under their employee benefits plan. The OHIP+ program under the Ontario Drug Benefit (ODB) Program is a provincial program which covers the costs of some prescription medications for eligible patients. Private

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insurance coverage options must be considered first prior to applying to OHIP+ under the Ontario Drug Benefit Program (ODB). Anyone 24 years and under who has OHIP coverage and is not covered by a private plan is covered by OHIP+..

Special approval by the Exceptional Access Program (EAP) may be required for some prescription medications, including cyclosporine and tacrolimus. EAP approval is reviewed on a case-by-case basis and requires the request in writing by the patient's primary physician. EAP application templates are available through the haematology/oncology Data Warehouse. Applications and supporting documentation should be submitted as soon as possible, as the approval process may take up to 3-4 weeks or longer. Rejection of the request may require a revision and resubmission of the EAP application and/or further request for ODB funding through the compassionate review policy. Renewal of approved EAP products may be required if prolonged therapy is needed.

Families who do not have extended health benefits, who do not qualify for ODB, and who do not have the financial means to cover medication costs, should explore other funding options with the program social worker.

7.0 Follow-Up Post Immunosuppressive Therapy (Grade C)

Once the patient has completed the cycloSPORINE/tacrolimus taper, close monitoring during the first two years post-therapy is important to assess for signs and symptoms of relapse. Should the patient begin to exhibit clinical and/or haematological changes during post-therapy follow-up, a **bone marrow aspirate and biopsy** may be necessary. There is a 10-15% life-time risk of developing myelodysplastic syndrome or myeloid malignancy with severe aplastic anemia treated with immunosuppressive therapy.

	Year 1	Year 2	Year 3	Years 4 & 5	Year 5+
Frequency of Visits	1 month after stopping CycloSPORINE/Tacrolimus Then q2 months	q3 months	q4 months	q6 months	Annually
Vital signs, Height & Weight	With every visit				
CBC, differential, reticulocyte count, smear	With every visit				
urea, creatinine	q4 months*	q6 months*	Annually*	Annually*	Annually*
LFTs (ALT, AST, alk phosph, bilirubins – unconjugated & conjugated)	q4 months*	q6 months*	Annually*	Annually*	Annually*
Bone marrow testing will be considered in patients with partial response (e.g. q12months) or with					

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deteriorating counts.					
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* May be completed more frequently if clinically indicated.

8.0 Statement of Evidence

The following table serves as a guideline to the hierarchy of evidence available; with meta-analysis considered to be the highest level of evidence and expert opinion considered to be the lowest level of evidence that can be used to support each recommendation in this CPG.

Grades of Recommendation
A - At least one randomized controlled trial, systematic review, or meta-analysis
B - At least one cohort comparison, case study, or other experiment study
C- Expert opinion, experience of a consensus panel

9.0 References

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10.0 Guideline Group and Reviewers

Authors

Dr. Michaela Cada MD, FRCPC, Haematology/Oncology, Physician: Marrow Failure and Myelodysplasia Program
Amanda Wagner BSc, MN, NP, Haematology/Oncology, Nurse Practitioner: Marrow Failure and Myelodysplasia Program

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Reviewers

Dr. Yigal Dror MD, FRCPC, Haematology/Oncology, Director: Marrow Failure and Myelodysplasia Program
Laura Willis, MN, RN(EC), Haematology/Oncology, Nurse Practitioner: Marrow Failure and Myelodysplasia Program

Michelle Fantauzzi MScN, RN, Haematology/Oncology, Contact Nurse: Marrow Failure and Myelodysplasia Program

Diana Cottingham, Social Worker: Marrow Failure and Myelodysplasia Program

Dr. Donna Wall, Head of Section of Blood and Marrow Transplant

Dr. Tal Schechter-Finkelstein, Staff Physician, Blood and Marrow Transplant

Jennifer Drynan, Clinical Pharmacist, Haematology/Oncology, Blood and Marrow Transplant

Attachments:

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