PEDIATRIC BLOOD AND MARROW TRANSPLANT PROGRAM

DOCUMENT NUMBER: PBMT-GEN-071

DOCUMENT TITLE:
Guidelines for the Management of Athymia Patients

DOCUMENT NOTES:

Document Information

Revision: 01	**Vault:** PBMT-General-rel
Status: Release	**Document Type:** PBMT

Date Information

Creation Date: 24 May 2024	**Release Date:** 25 Jun 2024
Effective Date: 25 Jun 2024	**Expiration Date:**

Control Information

Author: MOORE171	**Owner:** MOORE171
Previous Number: None	**Change Number:** PBMT-CCR-362

PBMT-GEN-071
GUIDELINES FOR THE MANAGEMENT OF ATHYMIA PATIENTS

1 PURPOSE

1.1 To outline the management of athymia patients within the Pediatric Transplant and Cellular Therapy (PTCT) Program.

2 INTRODUCTION

2.1 Pediatric athymia patients experience immune dysregulation and are at risk for severe infection and other life threatening health issues.

2.2 These patients require coordinated and ongoing complex care by an integrated healthcare team.

3 SCOPE AND RESPONSIBILITIES

3.1 Interdisciplinary: All healthcare staff providing care to the athymia patient in the PTCT program are responsible to adhering to the contents of this document.

4 DEFINITIONS/ACRONYMS

4.1	AI	Allergy/Immunology
4.2	BSA	Body Surface Area
4.3	CBC	Complete Blood Count
4.4	CMV	Cytomegalovirus
4.5	CTTI	Cultured Thymus Tissue Implantation
4.6	CXR	Chest X-ray
4.7	CYA	Cyclosporine
4.8	EBV	Epstein Barr Virus
4.9	FK	Tacrolimus
4.10	GFR	Glomerular Filtration Rate
4.11	GVHD	Graft Versus Host Disease
4.12	Hgb	Hemoglobin
4.13	HHV6	Human herpesvirus 6
4.14	Ical	Ionized Calcium
4.15	ID	Infectious Disease
4.16	Ig	Immunoglobulin
4.17	IV	Intravenous
4.18	MAC	Mycobacterium avium complex

CONFIDENTIAL - Printed by: ACM93 on 25 Jun 2024 01:52:22 pm

4.19	MWF	Monday, Wednesday, Friday
4.20	NPO	Nothing by Mouth
4.21	PACU	Post Anesthesia Care Unit
4.22	OR	Operating Room
4.23	OT	Occupational Therapy
4.24	PCR	Polymerase Chain Reaction
4.25	PHA	Phytohemagglutinin
4.26	PIV	Peripheral Intravenous
4.27	PJP	Pneumocystis jiroveci pneumonia
4.28	PLT	Platelet
4.29	PRA	Panel reactive Antibody
4.30	PRN	as needed, as required
4.31	PT	Physical Therapy
4.32	PTCT	Pediatric Transplant and Cellular Therapy
4.33	PTH	Parathyroid
4.34	ST	Speech Therapy
4.35	SOP	Standardized Operating Procedure
4.36	T&S	Type and Screen
4.37	URI	Upper Respiratory Infection
4.38	UTI	Urinary Tract Infection

5 MATERIALS

5.1 N/A

6 EQUIPMENT

6.1 N/A

7 SAFETY

7.1 N/A

8 PROCEDURE

8.1 Admission

8.1.1 Consults:

8.1.1.1 Standard consults (all patients):

8.1.1.1.1 Allergy/Immunology (AI)

8.1.1.1.2 Endocrinology

CONFIDENTIAL - Printed by: ACM93 on 25 Jun 2024 01:52:22 pm

8.1.1.1.3 Transplant Infectious Disease (ID)

8.1.1.1.4 Occupational/Physical/Speech Therapy (OT/PT/ST)

8.1.1.2 Additional Consults (as needed basis):

8.1.1.2.1 Pulmonology, Respiratory Therapy, Cardiology, Nephrology, Neurology, etc.

8.1.2 Body Habitus – Height, Weight, BSA

8.1.2.1 Accurate height is very important for cultured thymus issue implant (CTTI).

8.1.2.2 Document each in the medical record at admission.

8.1.3 Laboratory and Imaging:

8.1.3.1 Standard Admission Labs:

8.1.3.1.1 TPN2, ionized calcium (ica)

8.1.3.1.2 Parathyroid (PTH)

8.1.3.1.3 Coagulation screen - x1 initially, then repeat pre-op if no issues

8.1.3.2 Blood Counts:

8.1.3.2.1 CBC and MANUAL diff

8.1.3.2.2 Note: This should be drawn with the PHA and Lymphocyte Enumeration (LE); send on same day x1

8.1.3.3 Thyroid Profile:

8.1.3.3.1 Single panel includes: TSH and free T4

8.1.3.4 Transfusion Related Screening:

8.1.3.4.1 Type and Screen (T&S)

8.1.3.4.2 Confirmatory ABO

8.1.3.5 Immunosuppression - Medication Levels; only as applicable:

8.1.3.5.1 Cyclosporine (CYA) Level

8.1.3.5.2 Tacrolimus (FK506) Level

8.1.3.6 Imaging:

8.1.3.6.1 Chest X-ray (CXR)

8.1.3.7 Renal Studies:

8.1.3.7.1 Renal ultrasound

8.1.3.7.2 Nuc med GFR

8.1.3.7.3 Cystatin C

CONFIDENTIAL - Printed by: ACM93 on 25 Jun 2024 01:52:22 pm

8.1.3.8 Immunoglobulin profile

8.1.3.8.1 Single panel includes: IgG, IgA, IgM, IgE

8.1.3.9 Viral PCRs: See Table 1.

8.1.3.9.1 Adeno, EBV, HHV6 – as a single sample

8.1.3.9.2 CMV

8.1.3.9.3 Timing: can be sent shortly after admission to space out lab draws.

Table 1. Viral PCRs

Lab Sample	Notes	Location	Delivery Details
Adenovirus	Consolidate to be single sample (Adeno, EBV, HHV6)	Viracor	Can be sent shortly after admission if needed to space out lab draws
Epstein Barr Virus (EBV) *Gen code Test ID4501			
HHV6			
CMV		Duke	

8.1.3.10 Immunology Labs – Repeat at Duke

Table 2. Immunology labs to Repeat at Duke

Lab Sample	Notes	Location	Delivery Details
PRA	Within 30 days of implantation, repeated at Duke Needs repeated if patient receives a PRBC transfusion prior to CTTI	HLA lab	Courier or Tube station
PHA	Only if enough lymphocytes present – confirm with AI team	Immunology Lab: 919-684-6939	Courier
Lymphocyte Enumeration (LE)	Repeat after completion of ATG	Flow Cytometry lab	

CONFIDENTIAL - Printed by: ACM93 on 25 Jun 2024 01:52:22 pm

8.1.3.11 Additional Infectious Studies

8.1.3.11.1 Referring hospital to screen for C. Diff and Norovirus stool studies within 1-2 weeks of transfer to Duke (patients often chronically infected)

8.1.3.11.2 Referring hospital to screen for active respiratory viral infections with eRVP within 1 week prior to transfer to Duke (patients often chronically infected)

8.1.3.11.3 If applicable, referring hospital to obtain respiratory sputum culture with tracheostomy patients for future potential targeted antibiotic use

8.1.3.11.4 Trach respiratory sputum culture to be repeated at Duke on arrival

8.2 Conditioning and Immunosuppression for patients who require immunosuppression prior to implantation.

8.2.1 rATG

8.2.1.1 Peripheral IV (PIV) placed prior to or morning of rATG, if patient does not have multiple existing points of access

8.2.1.2 Treatment plan to be released morning of planned start of conditioning, with standard infusion time of 1400

8.2.1.3 After Day 1 of rATG and if patient is tolerating infusion without concern of reaction AND loses PIV, please transition supportive meds to enteral and leave emergency meds IV

8.2.1.4 Monitor ionized calcium daily and replete with PRN calcium gluconate to goal of 1.15-1.2 during rATG

8.2.2 Cyclosporine (and tacrolimus) levels based on PHA response (per Athymia handbook)

8.2.2.1 Standard cyclosporine goals 180-220 (tacrolimus: 7-10)

8.2.2.2 May need to target higher troughs based on PHA response or if patient presents with maternal T cell engraftment (see Athymia handbook)

8.2.2.3 Confirm target range with AI

8.2.2.4 *If CD3 cells fall and remain < 50/mm3, cyclosporine should be weaned to have a trough concentration of 100–150ng/mL. If CD3 cells remain ≥ 50/mm3, cyclosporine should be maintained at >180 until naive T cells are ≥ 10% of CD3 cells; When naïve T cells are >10% and there is no*

CONFIDENTIAL - Printed by: ACM93 on 25 Jun 2024 01:52:22 pm

evidence of autologous GVHD, cyclosporine can be weaned off over 10 weeks

8.2.2.5 *If T cells are fully suppressed by rATG (CD3 cells fall and remain < 50/mm3), cyclosporine can be weaned to have a trough concentration of 100–150 ng/mL 30 days following CTTI*

8.2.3 Discuss with AI need for additional immunosuppression with mycophenolate or steroids

8.3 Supportive Care Considerations

8.3.1 **Patients requiring respiratory support beyond 4L basic nasal cannula or a higher level of critical care support will be admitted to the Pediatric Intensive Care Unit. All other patients will be admitted to the inpatient Pediatric Transplant and Cellular Therapy Unit.**

8.3.2 Standard labs – unless otherwise clinically indicated; goal to consolidate to avoid iatrogenic anemia requiring transfusion

8.3.2.1 MWF CBC

8.3.2.2 Weekly differentials

8.3.2.3 MWF TPN2

8.3.2.4 MWF albumin (corrected calcium)

8.3.2.5 MWF ical, or daily if clinically indicated

8.3.2.6 During ATG: daily TPN1, ical

8.3.3 Standard antimicrobial prophylaxis – patient should arrive already receiving as prophylaxis

8.3.3.1 Fungal: Fluconazole 3-6mg/kg/day

8.3.3.2 MAC: Azithromycin 20mg/kg weekly

8.3.3.3 PJP: Trimethoprim/sulfamethoxazole 150/750 mg/m2 of body surface area/day divided into 2 equal doses given 3 times weekly on consecutive days

8.3.3.4 +/- Viral: Acyclovir; continue if patient arrives on, but do not initiate

8.3.4 IVIG

8.3.4.1 IgG level

8.3.4.1.1 Admission

8.3.4.1.2 Weekly (Mondays)

8.3.4.2 IVIG infusion

8.3.4.2.1 When IgG < 800 PRN

8.3.4.2.2 When required, infuse weekly (Tuesdays)

CONFIDENTIAL - Printed by: ACM93 on 25 Jun 2024 01:52:22 pm

8.3.5 Anemia

8.3.5.1 Often develops secondary to lab draws or iron-deficiency anemia

8.3.5.2 Standard transfusion thresholds: Hgb < 7, Plts < 10

8.3.5.3 All patients:

8.3.5.3.1 Irradiated, leuko-reduced blood products

8.3.5.4 If patient needs transfusion prior to CTTI:

8.3.5.4.1 Repeat PRA antibody screen – however, avoid if possible to avoid potential subsequent delays with CTTI

8.3.5.5 If applicable:

8.3.5.5.1 Continue enteral ferrous sulfate

8.3.5.5.2 Consider sending iron and total iron binding capacity (TIBC)

8.3.5.5.3 Consider parenteral iron administration (c/f poor absorption enterally)

8.3.6 Hypoparathyroidism and hypocalcemia

8.3.6.1 Continue enteral calcium, calcitriol, cholecalciferol as needed with recommendations from Endocrine

8.3.6.2 Calcium goals pre-implantation:

8.3.6.2.1 Serum calcium 9-10 and ical 1.15-1.2

8.3.6.2.2 Consider calcium gluconate 50mg/kg IV PRN for ical 1-1.14

8.3.6.2.3 Consider calcium gluconate 100mg/kg IV PRN for ical < 1

8.3.6.3 Calcium goals 24h post-implantation:

8.3.6.3.1 Serum calcium 8-9 and ical 1-1.15

8.3.6.3.2 Calcium gluconate 50mg/kg IV PRN for ical < 1

8.3.7 Hypomagnesemia

8.3.7.1 Magnesium goals >/= 2 peri-CTTI

8.3.7.1.1 Maintain with standard PTCT as needed (PRN) order

8.3.7.2 Continue or initiate enteral magnesium as indicated

8.3.7.3 Magnesium goal >/= 1.7 acceptable at time of discharge

8.4 Day of Implantation

8.4.1 NPO at midnight with IVF

CONFIDENTIAL - Printed by: ACM93 on 25 Jun 2024 01:52:22 pm

8.4.2 Anticipate stress dose steroids if needed (not common)

8.4.3 Standard OR time is 1400, **extremely time-sensitive, this is determined by GMP lab**

8.4.4 Patient should be transported off the floor at least 1 hour prior to OR time

8.4.4.1 Inpatient APP Team to contact peri-op RN to confirm transport plans and confirm PACU awareness of immunocompromised status

8.4.4.2 Anesthesia team lead of the day, if needed: (Pager: 919-970-7337)

8.4.5 Bedside RN to communicate with pre-op/PACU in AM and anticipate reverse isolation needs

8.4.5.1 Peri-Op Immunocompromised Status Letter to travel with patient

8.4.6 Post-op pain: scheduled Tylenol x24h, ibuprofen PRN (if platelets and renal function appropriate), oxycodone PRN for breakthrough pain

8.5 Discharge considerations

8.5.1 Patients remain admitted post-CTTI for an approximate minimum of two weeks

8.5.2 PTCT team to follow outpatient for a minimum of two weeks

8.5.3 If discharged locally, family instructed to contact PTCT on-call pager with any concerns (PTCT On call pager: 919-970-1424)

8.5.4 Specific considerations

8.5.4.1 CTTI site changes: erythema, drainage, swelling, new movement restriction or inability to bear weight

8.5.4.2 Fever:

8.5.4.2.1 See separate athymia fever management guidelines titled*: PBMT-GEN-072 Guidelines for management of fever in pediatric patients with athymia in the peri-implantation period of RETHYMIC*.

8.5.4.3 Symptoms of new infection: URI signs and symptoms, worsening diarrhea, vomiting, dysuria

8.5.4.4 High risk for viral infections and UTIs

8.5.4.5 Risk for seizures secondary to hypocalcemia

8.5.4.6 Feeding intolerance, enteral tube dislodgement, g-tube site changes

CONFIDENTIAL - Printed by: ACM93 on 25 Jun 2024 01:52:22 pm

9 RELATED DOCUMENTS/FORMS

9.1 PBMT-GEN-072 Guidelines for management of fever in pediatric patients with athymia in the peri-implantation period of RETHYMIC.

10 REFERENCES

10.1 Collins C, Sharpe E, Silber A, Kulke S, Hsieh EWY. Congenital athymia: genetic etiologies, clinical manifestations, diagnosis, and treatment. J Clin Immunol. 2021;41(5):881-895.

10.2 Bousfiha A, Jeddane L, Picard C, et al. Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. J Clin Immunol. 2020;40(1):66-81.

10.3 Markert ML, Gupton SE, McCarthy EA. Experience with cultured thymus tissue in 105 children. J Allergy Clin Immunol. 2021;Aug 4: Epub ahead of print.

10.4 Markert ML, Devlin BH, Alexieff MJ, et al. Review of 54 patients with complete DiGeorge anomaly enrolled in protocols for thymus transplantation: outcome of 44 consecutive transplants. Blood. 2007;109(10):4539-4547.

10.5 RETHYMIC (allogeneic processed thymus tissue – agdc). [Package insert] Cambridge, MA: Enzyvant Therapeutics Inc; 2021.

10.6 Markert ML, Sarzotti M, Ozaki DA, et al. Thymus transplantation in complete DiGeorge syndrome: immunologic and safety evaluations in 12 patients. Blood. 2003;102(3):1121-1130.

10.7 Lewis DE, Blutt SE. Organization of the immune system. In: Rich RR, Fleisher TA, Shearer WT, Schroeder HW, Frew AJ, Weyand CM, eds. Clinical Immunology. 5th ed: Elsevier; 2019:19- 38.e11.

10.8 McGhee SA, Lloret MG, Stiehm ER. Immunologic reconstitution in 22q deletion (DiGeorge) syndrome. Immunol Res. 2009;45(1):37-45.

10.9 Markert ML, Devlin BH, McCarthy EA. Thymus transplantation. Clin Immunol. 2010;135(2):236- 246.

10.10 Markert ML, Alexieff MJ, Li J, et al. Postnatal thymus transplantation with immunosuppression as treatment for DiGeorge syndrome. Blood. 2004;104(8):2574-2581.

10.11 Cleveland WW, Fogel BJ, Brown WT, Kay HE. Foetal thymic transplant in a case of DiGeorge's syndrome. Lancet. 1968;2(7580):1211-1214.

10.12 August CS, Rosen FS, Filler RM, Janeway CA, Markowski B, Kay HE. Implantation of a foetal thymus, restoring immunological competence in a patient with thymic aplasia (Digeorge's syndrome). Lancet. 1968;2(7580):1210-1211.

10.13 Markert ML, Devlin BH, McCarthy EA, Chinn IK, Hale LP. Thymus transplantation. In: Lavini C, Moran CA, Morandi U, Schoenhuber R, eds. Thymus Gland Pathology: Springer, Milano; 2008:255-267.

10.14 Markert ML, Watson TJ, Kaplan I, Hale LP, Haynes BF. The human thymic microenvironment during organ culture. Clin Immunol Immunopathol. 1997;82(1):26-36.

CONFIDENTIAL - Printed by: ACM93 on 25 Jun 2024 01:52:22 pm

10.15 Hong R, Moore AL. Organ culture for thymus transplantation. Transplantation. 1996;61(3):444- 448.

10.16 Markert ML, Kostyu DD, Ward FE, et al. Successful formation of a chimeric human thymus allograft following transplantation of cultured postnatal human thymus. J Immunol. 1997;158(2):998-1005.

10.17 Markert ML, Boeck A, Hale LP, et al. Transplantation of thymus tissue in complete DiGeorge syndrome. N Engl J Med. 1999;341(16):1180-1189

10.18 Markert ML, Marques JG, Neven B, et al. First use of thymus transplantation therapy for FOXN1 deficiency (nude/SCID): a report of 2 cases. Blood. 2011;117(2):688-696.

10.19 Lee JH, Markert ML, Hornik CP, et al. Clinical course and outcome predictors of critically ill infants with complete DiGeorge anomaly following thymus transplantation. Pediatr Crit Care Med. 2014;15(7):e321-326.

10.20 Davies EG, Cheung M, Gilmour K, et al. Thymus transplantation for complete DiGeorge syndrome: European experience. J Allergy Clin Immunol. 2017;140(6):1660-1670.e1616.

10.21 Immune Deficiency Foundation. History of newborn screening. Towson, MD: Immune Deficiency Foundation; 2020.

10.22 Puck JM. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia. Immunol Rev. 2019;287(1):241-252.

10.23 Shearer WT, Rosenblatt HM, Gelman RS, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. J Allergy Clin Immunol. 2003;112(5):973-980.

10.24 Markert ML. Defects in thymic development. In: Sullivan KE, Stiehm ER, eds. Stiehm's Immune Deficiencies. 2nd ed: Academic Press; 2020:357-379.

10.25 Yu GP, Nadeau KC, Berk DR, et al. Genotype, phenotype, and outcomes of nine patients with $T^{-}B^{+}NK^{+}$ SCID. Pediatr Transplant. 2011;15(7):733-741.

10.26 Roifman CM, Somech R, Kavadas F, et al. Defining combined immunodeficiency. J Allergy Clin Immunol. 2012;130(1):177-183.

10.27 Shearer WT, Fleisher TA, Buckley RH, et al. Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts. J Allergy Clin Immunol. 2014;133(4):961-966.

10.28 Markert ML, Li J, Devlin BH, et al. Use of allograft biopsies to assess thymopoiesis after thymus transplantation. J Immunol. 2008;180(9):6354-6364.

10.29 Markert ML, Alexieff MJ, Li J, et al. Complete DiGeorge syndrome: development of rash, lymphadenopathy, and oligoclonal T cells in 5 cases. J Allergy Clin Immunol. 2004;113(4):734- 741.

10.30 Gupton SE, McCarthy EA, Markert ML. Care of children with DiGeorge before and after cultured thymus tissue implantation. J Clin Immunol. 2021;41(5):896-905.

CONFIDENTIAL - Printed by: ACM93 on 25 Jun 2024 01:52:22 pm

10.31 Selim MA, Markert ML, Burchette JL, Herman CM, Turner JW. The cutaneous manifestations of atypical complete DiGeorge syndrome: a histopathologic and immunohistochemical study. J Cutan Pathol. 2008;35(4):380-385.

10.32 McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. Nat Rev Dis Primers. 2015;1:15071.

10.33 National Center for Advancing Translational Sciences, Genetic and Rare Diseases Information Center. CHARGE syndrome. https://rarediseases.info.nih.gov/diseases/29/chargesyndrome#ref_4191. Published 2013. Updated 2021. Accessed August 3, 2021.

10.34 van Ravenswaaij-Arts CM, Hefner M, Blake K, Martin DM. CHD7 disorder. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, eds. GeneReviews® [Internet]. September 17, 2020 ed. Seattle, WA: University of Washington, Seattle; 1993-2021.

10.35 Shearer WT, Dunn E, Notarangelo LD, et al. Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: the Primary Immune Deficiency Treatment Consortium experience. J Allergy Clin Immunol. 2014;133(4):1092-1098.

10.36 Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep. 2009;58(RR-11):1-166.

10.37 Markert ML, McCarthy EA, Gupton SE, Lim AP. Cultured thymus tissue transplantation. In: Sullivan KE, Stiehm ER, eds. Stiehm's Immune Deficiencies. 2nd ed: Academic Press; 2020:1229-1239.

10.38 Lee SJ. Classification systems for chronic graft-versus-host disease. Blood. 2017;129(1):30-37.

10.39 Marino J, Paster J, Benichou G. Allorecognition by T lymphocytes and allograft rejection. Front Immunol. 2016;7:582.

11 REVISION HISTORY

Revision No.	Author	Description of Change(s)
01	MC Author: S. McCollum SME: Kris Mahadeo Taylor McMichael	New Document

CONFIDENTIAL - Printed by: ACM93 on 25 Jun 2024 01:52:22 pm

Signature Manifest

Document Number: PBMT-GEN-071 **Revision:** 01
Title: Guidelines for the Management of Athymia Patients
Effective Date: 25 Jun 2024

All dates and times are in Eastern Time.

PBMT-GEN-071 Guidelines for the Management of Athymia Patients

Author

Name/Signature	Title	Date	Meaning/Reason
Sally McCollum (MOORE171)		03 Jun 2024, 08:36:18 AM	Approved

Medical Director

Name/Signature	Title	Date	Meaning/Reason
Kris Mahadeo (KM193)		03 Jun 2024, 09:07:48 AM	Approved

Quality

Name/Signature	Title	Date	Meaning/Reason
Bing Shen (BS76)	Associate Director, Quality Assurance	07 Jun 2024, 09:00:43 PM	Approved

Document Release

Name/Signature	Title	Date	Meaning/Reason
Amy McKoy (ACM93)	Document Control Specialist	11 Jun 2024, 09:34:54 AM	Approved