PEDIATRIC BLOOD AND MARROW TRANSPLANT PROGRAM

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Guidelines for Management of Fever in Pediatric Patients with Athymia in the Peri-Implantation Period of RETHYMIC

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PBMT-GEN-072
GUIDELINES FOR THE MANAGEMENT OF FEVER IN PEDIATRIC PATIENTS WITH ATHYMIA IN THE PERI-IMPLANTATION PERIOD OF RETHYMIC

1 PURPOSE

1.1 To establish appropriate clinical care guidelines for the evaluation and treatment of pediatric athymia patients with fever in the peri-implantation period of RETHYMIC within the Pediatric Transplant and Cellular Therapy Program.

2 INTRODUCTION

2.1 Pediatric athymia patients are a unique subset of PTCT patients in that they experience immune dysregulation and are at risk for severe infection and other life-threatening health issues. Therefore, they require special considerations in their fever and infectious disease work-up.

2.1.1 Athymia patients are at particularly high risk for viral infections, respiratory infections and urinary tract infection (UTIs).

2.1.2 Even after cultured tissue thymus implantation (CTTI), patients remain severely immunocompromised for at least 6-12 months.

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	ANC	Absolute Neutrophil Count
4.2	C	Celsius
4.3	CBC	Complete Blood Count
4.4	CTTI	Cultured Tissue Thymus Implantation
4.5	CVL	Central Venous Line
4.6	CXR	Chest X-Ray
4.7	EBV	Epstein Barr Virus
4.8	F	Fahrenheit
4.9	HHV6	Human Herpes Virus 6
4.10	PCR	Polymerase Chain Reaction
4.11	PTCT	Pediatric Transplant and Cellular Therapy
4.12	RVP	Respiratory Viral Panel
4.13	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 Fever is defined as a:

8.1.1 Single temperature of greater than or equal to 38.5C/101.3F or

8.1.2 Temperature between 38.0C/100.4F and 38.4C/101.1F for four consecutive hours

8.2 Evaluation:

8.2.1 Patient needs to be evaluated in one of the following locations:

8.2.1.1 PTCT ambulatory clinic

8.2.1.2 Through a 4A BOPP encounter

8.2.2 Physical exam to evaluate possible sources of infection.

8.2.2.1 Pay special attention to CTTI implantation site if post-implantation and CVL sites

8.2.2.2 Specifically assess for URI symptoms and urinary symptoms

8.2.3 Blood cultures

8.2.3.1 From all lumens of CVL, including port if applicable, upon initial presentation with fever.

8.2.3.2 Consider peripheral blood cultures when clinically indicated, not routinely obtained in PTCT patients with central lines.

8.2.4 Infectious stool studies

8.2.4.1 Including C. diff, adenovirus, norovirus and rotavirus, if symptomatic with loose stools

8.2.5 Respiratory sputum culture from tracheostomy, if applicable

8.2.6 Urinalysis +/- Urine Culture

8.2.6.1 Urine Culture if able to collect clean catch urine sample.

8.2.6.2 Avoid routinely obtaining urine samples via urinary catheterization.

8.2.7 eRVP, including COVID

8.2.8 Consider repeating viral PCRs

8.2.8.1 Include CMV, adenovirus, HHV6, and EBV, if presenting from outpatient setting

8.2.9 CBC with manual diff, electrolyte panel, ionized calcium, renal function tests

8.2.10 CXR if clinically indicated

8.2.10.1 Consideration should include, but is lot limited to, increased respiratory distress, new or increased oxygen requirement, changes in pre-existing chronic cough, or new acute cough

8.2.11 **Antibiotics**

8.2.11.1 Reminder: All cultures should be obtained prior to initiation of antibiotics, however do not delay antibiotic administration if cultures are unable to be obtain in an acutely ill child.

8.2.11.2 Standard empiric administration of ceftriaxone within 1 hour of initial fever

8.2.11.3 Cefepime if neutropenic or any concern for clinical instability

8.2.11.4 Consider adding vancomycin if toxic, considering renal function, consider dosing based on troughs based on renal function

8.2.11.5 Obtain vancomycin trough level prior to 4th dose to guide further dosing, according to standard antibiotic administration guidelines

8.2.11.6 Adjust empiric antibiotics accordingly to target unique infectious history, if applicable

8.2.11.7 Discontinue empiric antibiotics after 48 hours if afebrile, not neutropenic (ANC >500) and no culture evidence of bacterial infection

8.2.11.8 Narrow/target antibiotics appropriately if/when evaluation identifies the source of infection

8.2.12 **Consults:**

8.2.12.1 Discuss management with Ped Transplant ID with specific consideration of unique infectious history

9 RELATED DOCUMENTS/FORMS

9.1 N/A

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.

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.

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

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