



*James M. Anderson Center for
Health Systems Excellence*
**Evidence Based Clinical
Practice Guideline
Management of EBV-
Associated Post-Transplant
Lymphoproliferative Disease (PTLD) in
Solid Organ Transplant¹**
Revision Date: June, 2011
**Original Publication Date: February,
2003**

Target Population

Inclusion: These guidelines are intended for use in the following:

- Solid organ transplant recipients from birth to 18 years of age

Exclusion: These guidelines are not intended for use in the following:

- Non-transplant patients
- Patients with EBV-negative PTLD (in tissue)
- Patients with T cell PTLD
- Patients with Bone Marrow Transplant

Target Users

Includes but is not limited to:

- Attending inpatient physicians
- Community physicians
- Fellows/residents
- Patient care staff
- Patients/families

¹ Please cite as: **EBV Work Group, Cincinnati Children's Hospital Medical Center:** Evidence-based clinical care guideline for Management of EBV-Associated Post-Transplant Lymphoproliferative Disease in Solid Organ Transplant, <http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/guidelines.htm>, Guideline 18, pages 1-18, June, 2011.

Introduction

*References (), Evidence strengths []
(See last page for Evidence strengths)*

PTLD induced by Epstein Barr Virus (EBV) is a major cause of morbidity and mortality in solid organ recipients.

Despite a growing understanding of the pathogenesis of EBV infection and EBV-associated diseases in transplant recipients there remains uncertainty regarding the best clinical management of these patients.

These guidelines are offered to improve care by establishing consistent evidence-based care. Where evidence in the pediatric population is lacking, literature from adult patients was reviewed and used where applicable and/or local consensus was used to form the recommendations. These guidelines do not address EBV negative PTLD.

Pathophysiology & Epidemiology

Pathophysiology

EBV is a DNA virus of the herpes family that targets oropharyngeal epithelial cells and B-lymphocytes. EBV infection causes variable degrees of B-cell activation and proliferation and results in the development of immortalized B cells. In the presence of an intact immune system B-cell activation and proliferation is kept under control through B cell apoptosis-triggering mechanisms, as well as cytotoxic T cell response. In the presence of immunosuppression (i.e. post-transplant), this control can be lost leading to the development of PTLD.

The pathophysiology of PTLD remains an active area of investigation with hopes of finding targeted therapies for treatment and importantly for prevention and pre-emptive management.

Four different but complementary pathophysiological processes have been explored in the recent literature, mostly through *in vitro* cell studies and tissue analyses (Nourse 2011 [5]):

- decreased T cell function (decreased Th1 response) (VanBuskirk 2006 [4a], Yun 2005 [4a], Bakker 2005 [4b])
- decreased apoptosis (Snow 2006 [4a], VanBuskirk 2006 [4a], Mancao 2005 [4a], Capello 2004 [4a], Capello 2003 [4a])

- oxidative stress (*Chen 2009 [4a], Ranjan 2006 [4a], Pascual 2007 [4b]*)
- dysregulated cytokines production (*Vakiani 2008 [4a], Rinaldi 2006 [4a], Capello 2005 [4a], Dierksheide 2005 [4a], Ozdemir 2004 [4a]*).

Definitions

EBV viremia	EBV DNA detectible in blood by PCR analysis
EBV - associated PTLD	Lymphoproliferation or lymphoma occurring in the post-transplant setting with EBV detected by in situ in diseased tissue. Most, but not all cases of PTLD are associated with concomitant EBV viremia (<i>Preiksaitis 2009 [4b], Bitzan 2010a [5]</i>)
PTLD	Ranges from reactive polyclonal B-cell hyperplasia to polyclonal or monoclonal B-cell lymphoma. PTLD comprises a wide spectrum of EBV lymphoproliferative processes, both hyperplastic and neoplastic entities, including severe post-transplant infectious mononucleosis syndrome, EBV positive plasma cell hyperplasia, and polymorphic B-cell lymphoma (<i>Paya 1999 [5], Local Consensus [5]</i>). Most, but not all cases of PTLD are associated with concomitant EBV viremia (<i>Cohen 2000 [4a], So 2001 [5]</i>).
EBV-Naïve	An individual with no known or demonstrable serologic evidence of prior infection with EBV
Primary EBV Infection	the detection of serum anti-VCA IgM antibodies followed by a rise in the VCA-IgG or a positive serum EBV PCR in a previously EBV-naive (unexposed) individual
Latent (Long Past) EBV Infection	the detection of serum IgG antibodies against EBV, in a patient who has not received passive immunoglobulin in the previous three months
EBV Reactivation	the detection of EBV in the blood of a patient with previous latent infection, usually by PCR
Persistent disease (PTLD)	ongoing clinical, histologic or radiologic evidence despite intervention
Progressive disease (PTLD)	Increased involvement at the primary site and/or development of PTLD lesions at new sites.
Rejection	defined by findings on allograft biopsy
Fulminant PTLD	PTLD accompanied by fever, hypotension, and multiple organ involvement

Incidence

The reported incidence of PTLD is dependent on the transplanted organ type (*Dror 1999 [4b], Davis 1998 [5]*) and patient-specific risk factors (*Newell 1996 [4a]*). In the pediatric population, the incidence ranges from 1% to 10%. This incidence is highest in the first year post transplantation, and subsequently decreases with time, but remains higher than that in

adults. Because detection of PTLD requires clinical, histological and molecular assessment, not all of which are universally available, it is difficult to ascertain a true incidence of PTLD (*Fernandez 2008 [4a], Webber 2006 [4a], Dharnidharka 2009 [5]*).

Risk Factors

- Organ-specific transplant incidence of PTLD includes:
 - A. Liver transplant recipients – an incidence of 5.7% with 18% mortality reported, highlighting the importance of a high index of suspicion and early diagnosis (*Fernandez 2008 [4a]*)

- B. Kidney transplant recipients - an incidence of 2% to 4% observed, with the average diagnosis at 3 to 5 years post-transplant (*Dharnidharka 2009 [5]*)
- C. Heart transplant recipients – an incidence of 3.5% to 9.4% has been reported (*Schubert 2008 [4a]*, *Mendoza 2006 [4a]*, *Webber 2006 [4a]*, *Katz 2007 [4b]*)
- D. Intestinal transplant recipients – an incidence of 10% to 45%, often early within the first year post transplant (*Abu-Elmagd 2009 [3a]*)

- Patient Specific Risk Factors

A. EBV-naive transplant recipients are at an increased risk for the development of PTLD (*McDonald 2008 [2a]*, *Walker 1995 [3a]*, *Kauffman 2005 [3b]*, *Schubert 2008 [4a]*, *Mendoza 2006 [4a]*, *Aris 1996 [4a]*, *Ho 1988 [4a]*, *Katz 2007 [4b]*, *Dharnidharka 2009 [5]*).

B. Children less than five years of age are at greatest risk for PTLD, with the risk declining with increasing age (*Swerdlow 2000 [3a]*, *Schubert 2008 [4a]*).

C. Immunosuppression

- Risk of PTLD is the greatest in the first 12 months post transplantation presumably due to the immunosuppression being at its highest level.
 - Type of immunosuppression may be a potential risk factor for the development of PTLD. While T-cell directed antibodies have been reported as independent risk factors, there is insufficient evidence to independently implicate specific induction or maintenance agents in PTLD risk (*Haddad 2006 [1a]*, *Ganschow 2005 [2b]*, *Schubert 2009 [3b]*, *Ganschow 2005 [3b]*, *Schubert 2008 [4a]*, *Kirk 2007 [4a]*, *Dharnidharka 2009 [5]*).

D. Patients with a high persistent level of circulating EBV PCR may have an increased risk for PTLD (*Schubert 2008 [4a]*, *Szymanski 2010 [4b]*, *D'Antiga 2007 [4b]*).

E. Other

- Use of Growth hormone in patients with end-stage renal disease may have increased risk for PTLD (*Dharnidharka 2008 [4a]*)
- CMV seronegativity at transplantation might confer an increased risk for PTLD (*Katz 2007 [4b]*)
- Primary disease might be an independent risk factor for PTLD development. Studies suggesting primary disease as a risk factor did not control for the higher use of immunosuppressants reported in their patient population (*Newell 1997 [5b]*).
- Splenectomy and Graft Versus Host Disease in multivisceral transplant patients (*Abu-Elmagd*

2009 [3a]) were associated with higher risk of PTLD.

Guideline Recommendations

An algorithm for the evaluation and initial management of solid organ recipients and therapeutic intervention is presented (see PTLD Evaluation Algorithm). Initial assessment begins in the patient with EBV viremia typically found during surveillance of peripheral blood but may begin in the patient with concerning symptoms. Radiographic assessment is dictated by clinical symptoms with surgical intervention for diagnostic biopsy or resection when a mass lesion is detected. When lymphoproliferation is not detected immunosuppression is continued with monitoring of the patient for PTLD. Antiviral therapy for EBV is considered if not already in use. Although the diagnosis of PTLD requires supportive histologic findings, some patients may initially be too ill for surgical evaluation or biopsy. In such cases a presumptive diagnosis of PTLD may be made, empiric therapy initiated, and confirmational biopsy performed when patient is thought able to safely endure invasive procedure.

An algorithm for the treatment of EBV-associated PTLD is presented (see Treatment Algorithm for EBV-Associated PTLD). Calcineurin inhibitor immunosuppression is reduced depending upon the health of the allograft, in patients failing to adequately respond to reduced immunosuppression, calcineurin inhibitors are stopped when allograft health allows it, receive further therapy with rituximab or chemotherapy initiated depending upon the clinical status:

- Rituximab for patients minimally ill, without evidence of graft rejection, having polymorphic histology and small mass lesions
- low dose chemotherapy with rituximab for patients with monomorphic histology, a large mass lesion, fulminant PTLD or evidence of graft rejection
- conventional dose chemotherapy for patients with Burkitt's Lymphoma and those failing to respond to low dose chemotherapy.

1. It is recommended that confirmation of PTLD be based on the combination of compatible viremic, clinical, pathological and radiologic findings (*Local Consensus [5]*).

Evaluation

Laboratory screening and monitoring

- It is recommended that serum EBV Viral Capsid Antigen IgG (VCA IgG) and IgM antibodies be obtained and evaluated in the recipient and donor at the time of transplantation to assess risk (see Table 1) (Walker 1995 [3a], Aris 1996 [4a], Ho 1988 [4a], Local Consensus [5]).

Table 1: Expected patterns of EBV Serology in the Pediatric Immunocompetent Host (see definitions)

Infection	VCA IgM	VCA IgG	EBNA (EBV Nuclear antigen) (often not produced by transplant patients)	Early Ag
Naïve	-	-	-	-
Primary	+	+/-	-	+
Reactivated or late phase primary infection	+	+	+	+/-
Latent	-	+	+/-	-

- It is recommended that all patients be monitored for evidence of increased EBV-induced B-cell proliferation or EBV reactivation (McDiarmid 1998 [3b]) by measuring blood quantitative EBV PCR at regular intervals after transplantation (see Table 2). The time intervals and duration of monitoring may vary depending on identified risk factors (Local Consensus [5]).

Note 1: What is clearly and consistently concluded from most studies is that monitoring of EBV copy numbers in the blood is useful in managing the patients and alerting the clinicians to the possible development of PTLD.

Monitoring also helps in developing a plan for managing patients with this complication (Meerbach 2008 [3a], Sebelin-Wulf 2007 [3b], Cesaro 2005 [3b], Rowe 1997 [3b], Rogers 1998 [4a], Piriou 2004 [4b], Groen 2001 [4b], Stevens 2002 [5], Local Consensus [5]).

Controversy still remains regarding:

- EBV DNA threshold levels.
- significance of chronic viremia
- need and timing for intervention in the case of isolated viremia (Lee 2005 [3a], Schubert 2009 [3b], Inomata 2005 [4a], Holmes 2002 [4a], D'Antiga 2007 [4b]).

Note 2: It is clear that, although monitoring of blood levels of EBV copies can be useful in recognizing patients who are at risk for PTLD, it does not exclude the possibility of patients

developing PTLD in the absence of any concomitant EBV viremia. This is particularly true in patients who have been treated with anti CD-20 antibodies (Local Consensus [5]).

Note 3: There is ongoing controversy over whether plasma values for EBV are more predictive than whole blood values (Kullberg-Lindh 2008 [4a], Fafi-Kremer 2004 [4a]).

The quantitative PCR assay used at Cincinnati Children's Hospital Medical Center is a whole blood assay that specifically amplifies the region of the EBV genome that encodes nuclear antigen (EBNA) (Groen 2001 [4b], Local Consensus [5])

Note 4: PCR values are dependent upon the assay used, therefore caution must be used in comparing PCR values between laboratories (Preiksaitis 2009 [4b], Bitzan 2010a [5]).

Table 2: Suggested EBV PCR Screening Schedules

Transplant Type	Suggested Frequency from transplantation
Renal	Baseline and with presentation of symptoms
Liver	Every 2 weeks for 3 months, then monthly for 9 months, then yearly and with presentation of symptoms
Heart	Baseline, every 3 months and with presentation of symptoms or rising PCR
Small Intestine	Every 2 weeks x 3 months then monthly for 9 months, then yearly and with presentation of symptoms

(Local Consensus [5])

Clinical Assessment of PTLD

Compared to adult recipients, more PTLD cases occur in the first post-transplant year in the pediatric population and are associated with concomitant EBV viremia, and B-cell lineage (Dharnidharka 2009 [5]). No symptom is pathognomonic for PTLD. Therefore, a high index of suspicion and clinical vigilance must be maintained at all times, allowing for timely evaluation and intervention for PTLD. The transplanted organ is often but not always involved in the lymphoproliferation.

4. It is recommended that a high index of suspicion be maintained for PTLD in all solid organ transplant patients:
 - Most frequently reported clinical findings and symptoms of PTLD are:
 - lymph node enlargement, lymphadenopathy , splenomegaly (33%)(*Cacciarelli 1998 [3a], Harwood 1999 [3b], Srivastava 1999 [3b], Cao 1998 [4a], Dharnidharka 2009 [5], Green 1999 [5], Markin 1994 [5]*)
 - abdominal symptomatology (29%) (*Dharnidharka 2009 [5]*) gastrointestinal (GI) disturbances - diarrhea, abdominal pain, GI bleeding, vomiting, anorexia, protein losing enteropathy, weight loss, intestinal ulcers, or bowel obstruction/perforation (*Cacciarelli 1998 [3a], Smets 2000 [3b], Sarkar 2006 [4a], Webber 2006 [4a], Cao 1998 [4a], Shapiro 1988 [4b], Green 1999 [5], Kingma 1996 [5], Cohen 1991 [5]*)
 - allograft dysfunction (11%) (*Quintanilla-Martinez 2000 [3b], Randhawa 1996 [4b], Dharnidharka 2009 [5]*)

Note: Allograft dysfunction may often be mistaken for rejection (*Local Consensus [5]*)
 - central nervous system (CNS) related symptoms (11%) (*Dharnidharka 2009 [5]*).
 - Other Symptoms may include:
 - fever - the most frequently reported symptom, alone or with other symptoms (*Cacciarelli 1998 [3a], Quintanilla-Martinez 2000 [3b], Smets 2000 [3b], Harwood 1999 [3b], Srivastava 1999 [3b], Cao 1998 [4a], Shapiro 1988 [4b], Green 1999 [5], Markin 1994 [5]*)
 - hypotension or septic-like syndrome
 - genitourinary (GU) or gynecological (GYN) disturbances – renal or ovarian dysfunction, vaginal bleeding (*Local Consensus [5]*)
 - tonsillar hypertrophy, upper respiratory obstruction/sleep apnea, (*Cacciarelli 1998 [3a], Broughton 2000 [4a], Cao 1998 [4a], Lattak 1998 [4b]*) adenoidal hypertrophy (*Srivastava 1999 [3b]*)
 - infectious mononucleosis syndrome –sore throat, fatigue, anorexia, headache (*Broughton 2000 [4a], Markin 1994 [5]*) rash (*Cao 1998 [4a]*)
 - hepatic or splenic enlargement (*Quintanilla-Martinez 2000 [3b], Smets 2000 [3b], Green 1999 [5]*)
 - anemia, cytopenia, hemophagocytosis, hemolysis (*Quintanilla-Martinez 2000 [3b], Okano 1996 [5]*)
 - respiratory symptoms - shortness of breath, cough, upper airway obstruction (*Webber 2006 [4a]*)

- A PTLD Clinical checklist is included (see Addendum)for a list of possible clinical manifestations of PTLD

Diagnosis of PTLD

Tissue Analysis

5. It is recommended that a biopsy of the involved organ/site be performed once symptoms of PTLD are identified. The use of the World Health Organization (WHO) criteria may be considered for biopsy, assessment, and evaluation (*Local Consensus [5], Harris 1999 [5a]*) (see Table 3).

Note 1: Some patients may initially be too ill for surgical evaluation or biopsy.

Note 2: Patients can have different histology and clonality at different sites of disease (*Chadburn 1995 [5]*).

Table 3: Pathologic Categories of PTLD (Harris 1999 [5a])

Category	Description
Early Lesion	<ul style="list-style-type: none"> • Reactive plasmacytic hyperplasia • Infectious mononucleosis-like
PTLD, polymorphic	<ol style="list-style-type: none"> 1. Polyclonal 2. Monoclonal
PTLD, mono-morphic (classify according to lymphoma classification)	<ul style="list-style-type: none"> • B-cell lymphomas <ul style="list-style-type: none"> • Diffuse large B-cell lymphoma (immunoblastic, centroblastic, anaplastic) • Burkitt/Burkitt-like lymphoma • Plasma cell myeloma • T-cell lymphomas <ul style="list-style-type: none"> • Peripheral T-cell lymphoma, not otherwise categorized • Other types (hepatosplenic, gamma-delta, T/NK)
Other types, rare	<ul style="list-style-type: none"> • Hodgkin's disease-like lesions (associated with methotrexate therapy) • Plasmacytoma-like lesions

6. It is recommended that in situ hybridization for EBER (Epstein Barr Encoding RNA) be performed on the biopsy specimen (*Local Consensus [5]*).

7. It is recommended that additional diagnostic tests be conducted to determine the extent of disease once diagnosis of PTLD is confirmed:

- bone marrow biopsy, indicated if cytopenias, lymphocytosis, or lymphoblasts in the peripheral blood
- lumbar puncture, indicated by central nervous system signs/symptoms
- endoscopy indicated if GI or pulmonary symptoms are present
- radiologic evaluation (described below).

(Local Consensus [5])

Radiologic Testing

There is insufficient published evidence for the use and value of imaging in asymptomatic EBV viremia. The recommendations in this section are based on studies that used either a surveillance transplant protocol or the presence of clinical symptoms to direct imaging.

8. It is recommended that non-viremic and/or asymptomatic patients not be screened for PTLD using routine imaging because imaging appearance is not specific for PTLD (Donnelly 1998 [4a], Dodd 1992 [4a], McCormack 2006 [4b], Pickhardt 1999 [4b], Pickhardt 1998 [4b]).
9. It is recommended to image the head, sinuses, neck, chest, abdomen, and pelvis only when PTLD is suspected, to detect the full extent of organ involvement (Roy 2008 [4a], O'Conner 2005 [4a], Dodd 1992 [4a], Marom 2004 [4b], Pickhardt 1999 [4b]).
10. It is recommended that contrast enhanced CT be used for primary evaluation if PTLD is detected. Chest radiographs, ultrasound, magnetic resonance imaging (MRI), and 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) have been used to detect PTLD, but best serve as non-invasive follow up tools, and targeted first line tools for specific organs (Maturen 2004 [4a], Donnelly 1998 [4a], Dodd 1992 [4a], Riebel 2007 [4b], von Falck 2007 [4b], McCormack 2006 [4b], Lopez-Ben 2000 [4b], Pickhardt 1998 [4b]).

Note 1: With the exception of PET, these imaging modalities provide morphologic evaluation only. PET provides functional rather than morphologic information with increased signal on PET scanning reflecting increased metabolic activity. Limited data suggest that PET scanning is a sensitive means of detecting PTLD and that it may provide complimentary information to CT or MRI

(O'Conner 2005 [4a], von Falck 2007 [4b], Marom 2004 [4b]).

Note 2: Limited PET sensitivity in detecting mucosa associated lymphoid tissue (MALT) lymphoma (Hoffmann 1999 [3b], Perry 2007 [4b]) suggests that PET scanning may be less sensitive in less aggressive types of PTLD.

Note 3: CT scanning detects more thoracic disease than chest radiographs (Dodd 1992 [4a], Pickhardt 1998 [4b]).

Note 4: Lung parenchyma cannot be evaluated with ultrasound (Herth 2003 [5]), MRI evaluation of the lung parenchyma is limited (Hirsch 2008 [5], Local Consensus [5]).

Note 5: Caretakers need to be aware of the ongoing risk of high cumulative doses of radiation and contrast material from imaging studies performed for the detection and treatment of PTLD (DJ 2010 [5], Robbins 2008 [5], Local Consensus [5]).

PTLD Management

Preventive Treatment

11. It is recommended to adopt in all solid organ transplant recipients clinical vigilance and close clinical monitoring for possible onset of tissue involvement or systemic symptoms. (Local Consensus [5]).
12. It is recommended that EBV viremic patients be maintained within protocol range of immunosuppression levels (Local Consensus [5]).
Note: Reduction of immunosuppression from standard protocols at this stage is controversial (Schubert 2008 [4a], Dharnidharka 2009 [5]).
13. It is recommended to consider ganciclovir or valganciclovir for asymptomatic viremic patients (Local Consensus [5]).
14. It is recommended to consider on an individual case basis the use of rituximab in viremic patients at high risk for rejection with low immunosuppression, (e.g. multivisceral transplant patients and heart transplant patients) (Local Consensus [5]).

PTLD Treatment

The wide clinical spectrum of PTLD necessitates that therapy be individualized based upon the histological findings and clinical setting. Observational studies consistently imply that decreased immunosuppression is associated with regression of PTLD. Beyond reduction of immune suppression, the optimal management of EBV disease and PTLD in solid organ transplant recipients is controversial. Antiviral agents inhibit EBV deoxyribonucleic acid (DNA) replication *in vitro* and *in vivo*, however there is inconclusive data regarding their efficacy in the treatment of PTLD in the pediatric population. Similarly, there is inconclusive data supporting the use of intravenous immunoglobulin (IVIG), cytomegalovirus (CMV)-hyperimmune globulin in the treatment of PTLD. Surgical resection is beneficial when a complete resection can be safely accomplished. Other therapeutic modalities include immunotherapy with the anti-CD20 monoclonal antibody (Rituximab) and both low-dose and conventional dose chemotherapy. Therapy with autologous EBV stimulated cytotoxic T-cells has shown benefit in early clinical investigations but is not widely available for clinical use (*Helstrop 2010 [3a], Gross 2005 [3a], Orjuela 2003 [3b]*).

PTLD Staging and Disease Monitoring

- 15.** It is recommended that patients with PTLD be appropriately staged for the extent of their disease and subsequently monitored using physical exam, laboratory, radiological, and pathological evaluations for evidence of persistent, progressive or recurrent PTLD as well as allograft rejection (*Local Consensus [5]*).

Reduction of Immunosuppression

- 16.** It is recommended that calcineurin inhibitors (CNI) be decreased from transplant protocol range in patients following the diagnosis of PTLD whenever possible (*Local Consensus [5]*).
- Note 1:** In the 1st year post transplantation, decrease the dose of CNI to achieve trough levels, 1/3 the target transplant protocol range for patients without PTLD (*Local Consensus [5]*). After the first year post-transplantation, decrease CNI daily dose by half.
- Note 2:** It is important to take into account the relative risk of morbidity and/or mortality due to rejection, secondary to decreased immunosuppression for each specific organ type and patient (*Local Consensus [5]*).

- 17.** It is recommended to avoid use of:
- Anti-T cell monoclonal antibodies when possible in patients with PTLD (*Local Consensus [5]*).
 - Alpha-interferon as a first line therapy due to concerns of toxicity and availability of newer agents (*Local Consensus [5]*).

Surgical Resection

- 18.** It is recommended that surgical resection of tumor masses be performed when a complete resection can be obtained with low risk of morbidity (*Local Consensus [5]*).

Rituximab

- 19.** It is recommended that Rituximab treatment be considered in high risk patients at the same time immunosuppression is being reduced. High risk patients include patients at high risk for rejection with lower immunosuppression (e.g. multivisceral transplant patients and heart transplant patients) (*Local Consensus [5]*).
- 20.** It is recommended to treat with Rituximab patients with evidence of persistent or progressive PTLD, in the absence of allograft rejection (*Local Consensus [5]*).

Note 1: Usual dosing of Rituximab is 375 mg/m² weekly for 4 weeks (*Choquet 2006 [3a], Genetech 2010 [5b]*).

Note 2: Extended administration for an additional 4 weeks may be considered in patients achieving a partial response (*Gonzalez-Barca 2007 [3a]*).

Note 3: Premedication is encouraged to decrease incidence of infusion reactions (anti-histamine medications, corticosteroids and acetaminophen) (*Local Consensus [5]*).

Low Dose Chemotherapy & Stopping Immunosuppression

- 21.** It is recommended to stop or minimize the CNI, and treat with low-dose cyclophosphamide and corticosteroids patients with:
- evidence of persistent or progressive PTLD after reduction of immunosuppression
 - PTLD refractory to Rituximab monotherapy
 - when PTLD is present with concurrent evidence of allograft rejection
 - fulminant PTLD
- (*Local Consensus [5]*)

Note 1: Low dose chemotherapy is effective without Rituximab (*Gross 2005 [3a]*), but may also be given concurrently with Rituximab (*Orjuela 2003 [3b]*).

Note 2: CNI is frequently discontinued in Liver and Kidney recipients. CNI is often minimized in Heart and Intestinal recipients due to the relative rejection risk. (*Local Consensus [5]*)

Conventional Dose Chemotherapy

22. It is recommended that patients with PTLD refractory to low-dose chemotherapy and patients with Burkitt Lymphoma receive conventional-dose multi-agent chemotherapy (*Local Consensus [5]*).

Note 1: Experience in adults with PTLD supports the use of multi-agent chemotherapy regimens (e.g. CHOP- Cyclophosphamide, doxorubicin, vincristine, and prednisone) in patients with refractory PTLD after rituximab therapy (*Trappe 2007 [3b]*).

Note 2: Histology specific multi-agent chemotherapy regimens developed for pediatric patients should be used (*Local Consensus [5]*).

Supportive Care

23. It is recommended that all patients undergoing PTLD treatment have serum IgG levels monitored at monthly intervals, particularly in those receiving Rituximab or chemotherapy (*Local Consensus [5]*).

24. It is recommended that IVIG supplementation be given if hypogammaglobinemia (IgG<500) is detected in order to decrease risk of infection (*Local Consensus [5]*).

Post Therapy Monitoring

25. It is recommended that patients who have completely responded to therapy be monitored for recurrent PTLD and therapy-related complications such as hypogammaglobinemia, infection, bladder carcinoma, and graft health (*Local Consensus [5]*).

Note 1: Monitoring might reasonably include blood EBV monitoring by PCR with surveillance radiographic studies as clinically indicated. Evidence supporting specific monitoring approaches is lacking.

Note 2: A surveillance protocol used at CCHMC includes:

- Every 2 week EBV monitoring by PCR for 3 months, then monthly during first year after cessation of therapy.
- Radiographic evaluation of previous sites of disease every 3 months for first year, every 4 months for second year, every 6 months for third year, then as clinically indicated.
- Yearly UA monitoring for hematuria/proteinuria in patients that have received cyclophosphamide. (*Local Consensus [5]*)

Re-initiation of Immune Suppression

- 26.** It is recommended to restart immunosuppression for patients responding to treatment:
- Use T-cell antibody therapy such as Muromonab-CD3 (OKT3) or antithymocyte globulin (ATG) with extreme caution in patients with PTLD or history of PTLD (*Local Consensus [5]*).
 - Restart calcineurin inhibitors at doses to achieve 50% of standard target level for the organ type and time since transplant in patients who have successfully responded to therapy without evidence of allograft rejection (*Local Consensus [5]*).
 - Consider the use of Sirolimus when resuming immunosuppressive therapy because of the anti-proliferative and autophagic role of mTOR inhibition (*Kirk 2007 [4a]*, *Bitzan 2010b [5]*, *Local Consensus [5]*).

Prognosis

While the therapy for PTLD has a moderately high success rate, the prognosis for children that develop PTLD is guarded. Death due to infection or progressive PTLD remains a high concern. Comparison and interpretation of outcomes in published studies is hindered by studies with relatively small numbers of patients, different eras of transplantation therapy, few prospective studies, and lack of a uniform approach to diagnosis, definitions, monitoring and therapy. Many reports include both adult and pediatric populations. Some reported response rates for various therapeutic modalities in children are listed below.

- Reduction of immunosuppression alone yielded an objective response in 21 of 34 (62%) pediatric patients with PTLD (*Hayashi 2001 [4a]*). Children responding to immunotherapy reduction were more likely to have polymorphic histology (16 of 17 patients, 94%) whereas only 29% of patients with

monomorphic histology demonstrated an objective response.

- Reduction of immunosuppression combined with rituximab yielded a complete response (CR) in 9 of 16 (56%) pediatric patients with PTLD (Messahel 2006 [4b]).
- Low dose chemotherapy with cyclophosphamide and prednisone yielded a 75% CR, 67% 2-year FFS in pediatric patients with PTLD that failed to respond to reduction of immunosuppression (Gross 2005 [3a]).

Prognostic factors in PTLD are inconsistently defined or verified. Several studies in adults have identified elevated lactate dehydrogenase (LDH), multifocal lesions, and poor performance score as poor prognostic features. Other possible poor prognostic features in children include CNS or bone marrow involvement, monomorphic histology, EBV negative PTLD, and Burkitt lymphoma/leukemia.

Future Research Questions

PTLD remaining also a rare disease, pooling resources and learning opportunities through cross-solid organ transplant data bases will likely optimize learning resources, interventional capabilities, and quality improvement checks.

Collaborative research will lead to:

- Improved methods for early detection of PTLD
- Safer and cost-effective PTLD therapy
- Better understanding of long term outcomes
 - of chronic EBV viremia
 - of patients treated for PTLD
- Effective and safe immune-modulatory regimens that decrease the risk for PTLD while preserving allograft health

Team Members 2008-2011

Nada Yazigi, MD, Gastroenterology, Hepatology, & Nutrition
 Michael Absalon, MD, Ph.D, Hematology/Oncology
 Alan Brody, MD, Radiology
 Jens Goebel, MD, Division of Nephrology
 Trina Hemmelgarn, PharmD, Division of Pharmacy
 Robert Spicer, MD, Cardiology
 Karen Uzark, PhD, CPNP, Cardiology
 David Witte, MD, Pathology

James M. Anderson Center for Health Systems Excellence

Eloise Clark, MPH, MBA, Guidelines Program Administrator,
 Evidence Facilitator
 Danette Stanko-Lopp, MA, MPH, Epidemiologist
 Karen Vonderhaar, MS, RN, Guidelines Program
 Administrator, Methodologist

Ad Hoc Advisors

Rebecca Brady, MD, Division of Infectious Disease
 John Bucuvalas, MD, Gastroenterology, Hepatology, &
 Nutrition
 John Perentesis, MD, Hematology/Oncology
 Tom Gross, MD, Division of Hematology/Oncology,
 Nationwide Hospital

Development Process

The process by which this guideline was developed is documented in the Guideline Development Process Manual; the team leader maintains relevant development materials. The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic and critical literature reviews, using the grading scale that follows, and examined current local clinical practices. Appropriate companion documents have been developed to assist in the effective dissemination and implementation of the guideline.

To select evidence for critical appraisal by the group for this guideline, the Medline, EmBase and the Cochrane databases were searched for dates of February, 2003 to June, 2011 to generate an unrefined, "combined evidence" database using a search strategy focused on answering clinical questions relevant to EBV/PTLD and employing a combination of Boolean searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on words in the title, abstract, and indexing terms. The citations were reduced by: eliminating duplicates, review articles, non-English articles, and adult articles. The resulting abstracts were reviewed by a methodologist to eliminate low quality and irrelevant citations. During the course of the guideline development, additional clinical questions were generated and subjected to the search process, and some relevant review articles were identified. February, 2003 was the last date for which literature was reviewed for the previous version of this guideline. The details of that review strategy are not documented. However, all previous citations were reviewed for appropriateness to this revision.

Note: Full tables of evidence grading system available in separate document:

- Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality (abbreviated table below)
<http://groups/ce/NewEBC/EBCFiles/Table-EvidenceLevels.pdf>
- Grading a Body of Evidence to Answer a Clinical Question
<http://groups/ce/NewEBC/EBCFiles/GradingBodyOfEvidence.pdf>
- Judging the Strength of a Recommendation (abbreviated table below)
<http://groups/ce/NewEBC/Judgingthestrengthofarecommendation.pdf>

Table of Evidence Levels (see note above)

<i>Quality level</i>	<i>Definition</i>
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain

5	Other: General review, expert opinion, case report, consensus report, or guideline
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†a = good quality study; b = lesser quality study

care preventing selective variances from the guidelines to meet the specific and unique requirements of individual patients. Adherence to this pathway is voluntary. The physician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

For more information about these guidelines and their supporting evidences, contact the James M. Anderson Center for Health Systems Excellence office HPCEInfo@cchmc.org.

Table of Recommendation Strength (see note above)

<i>Strength</i>	<i>Definition</i>
“Strongly recommended”	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
“Recommended”	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.
<i>Dimensions:</i> In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.	
<ol style="list-style-type: none"> 1. Grade of the Body of Evidence (see note above) 2. Safety / Harm 3. Health benefit to patient (<i>direct benefit</i>) 4. Burden to patient of adherence to recommendation (cost, hassle, discomfort, pain, motivation, ability to adhere, time) 5. Cost-effectiveness to healthcare system (balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis) 6. Directness (the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome]) 7. Impact on morbidity/mortality or quality of life 	

Once the guideline has been in place for five years, the development team reconvenes to explore the continued validity of the guideline. This phase can be initiated at any point that evidence indicates a critical change is needed.

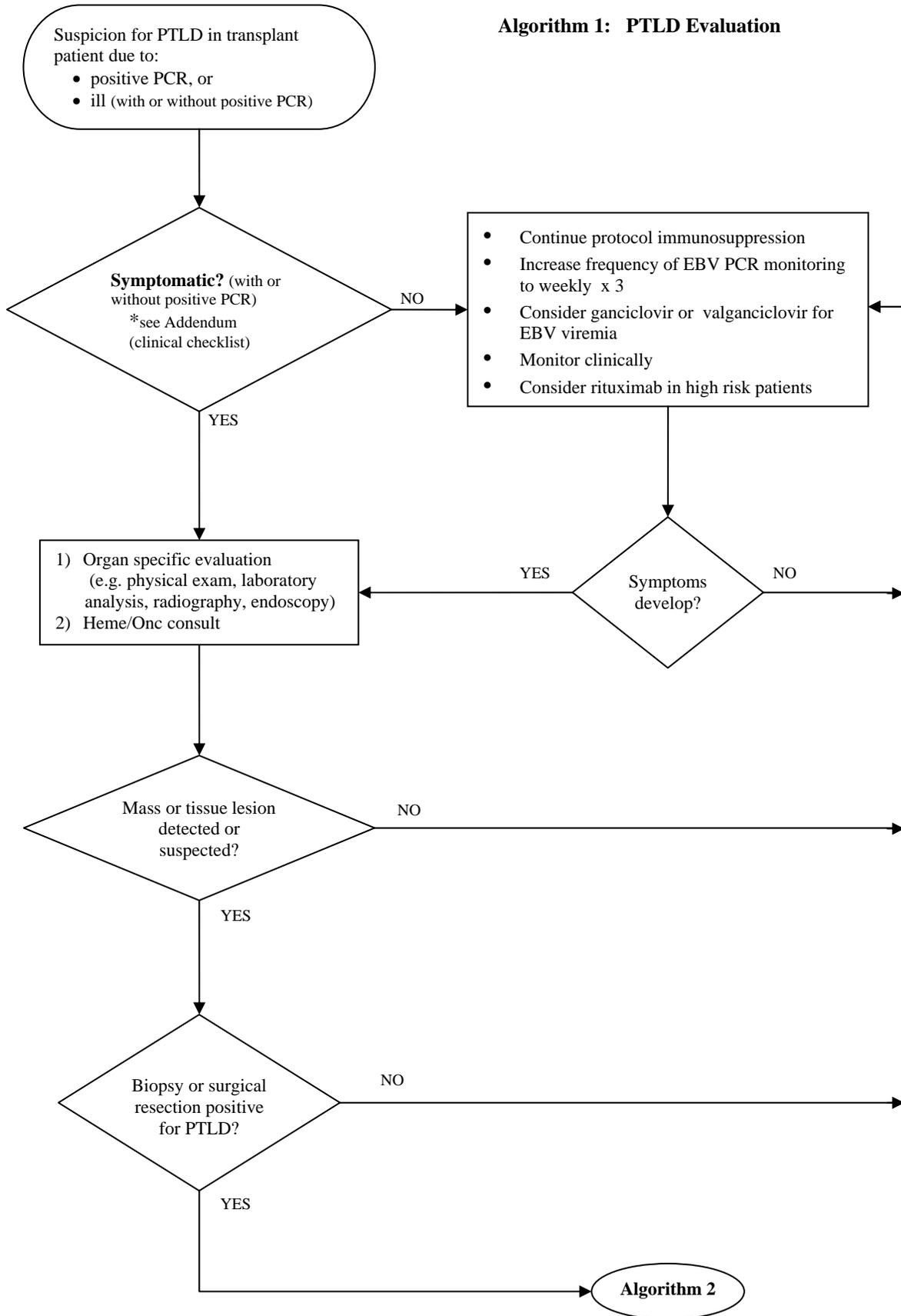
During formulation of these guidelines, the team members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

The guidelines have been reviewed and approved by clinical experts not involved in the development process, distributed to senior management, and other individuals as appropriate to their intended purposes.

The guideline was developed without external funding.

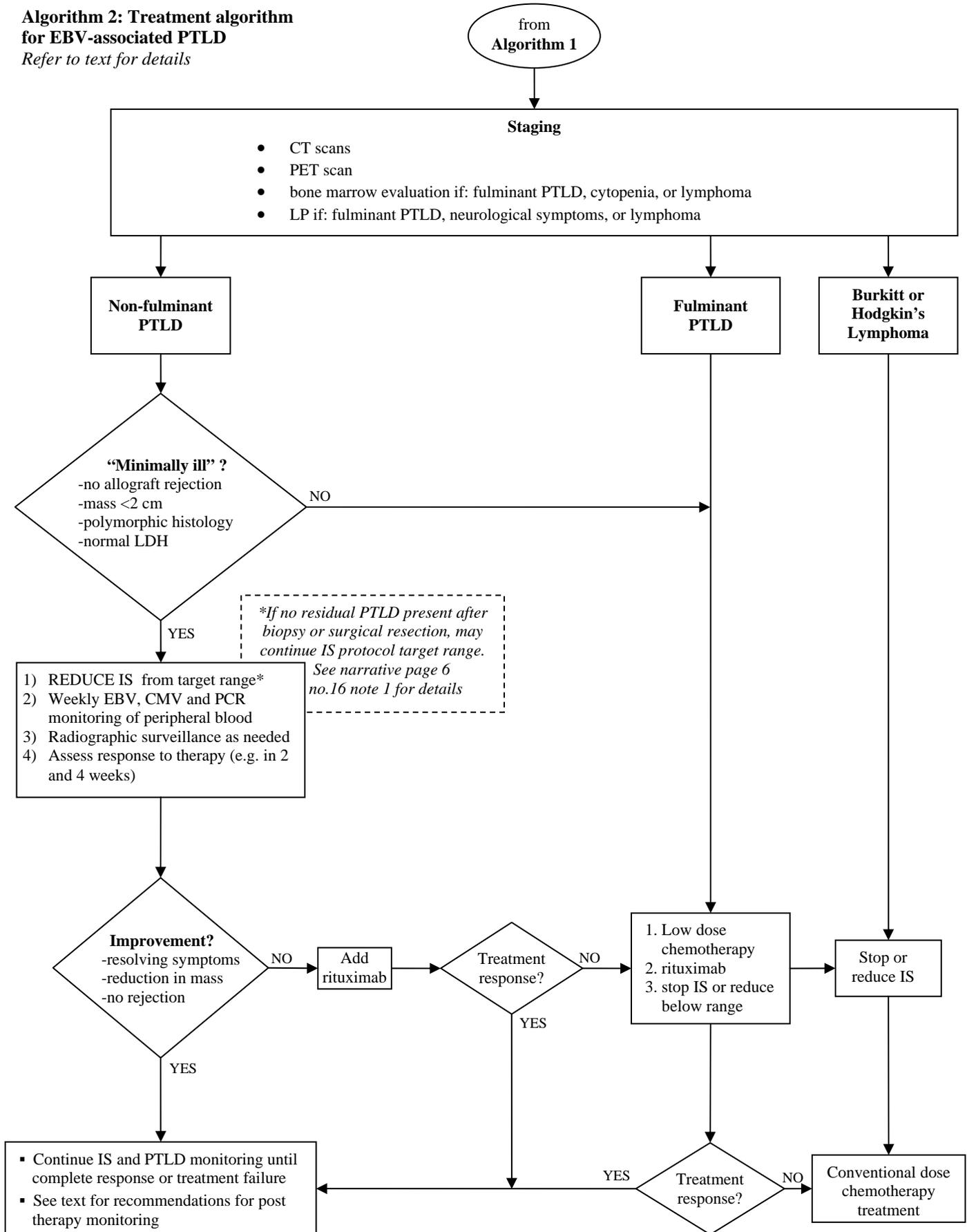
NOTE: These recommendations result from review of literature and practices current at the time of their formulations. This protocol does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of

Algorithm 1: PTLD Evaluation



Algorithm 2: Treatment algorithm for EBV-associated PTLD

Refer to text for details



References (evidence grade in []; see Table of Evidence Levels following references) Note: When using the electronic version of this document,  indicates a hyperlink to the PubMed abstract. A hyperlink following this symbol goes to the article PDF when the user is within the CCHMC network.

1. **Abu-Elmagd, K. M. et al.:** Lymphoproliferative disorders and de novo malignancies in intestinal and multivisceral recipients: improved outcomes with new outlooks. *Transplantation*, 88(7): 926-34, 2009, [3a] 
2. **Aris, R. M.; Maia, D. M.; Neuringer, I. P.; Gott, K.; Kiley, S.; Gertis, K.; and Handy, J.:** Post-transplantation lymphoproliferative disorder in the Epstein-Barr virus-naive lung transplant recipient. *Am J Respir Crit Care Med*, 154(6 Pt 1): 1712-7, 1996, [4a] 
3. **Bakker, N. A. et al.:** HLA antigens and post renal transplant lymphoproliferative disease: HLA-B matching is critical. *Transplantation*, 80(5): 595-9, 2005, [4b] 
4. **Bitzan, M.; Ouahed, J. D.; Carpineta, L.; Bernard, C.; and Bell, L. E.:** Cryptogenic organizing pneumonia after rituximab therapy for presumed post-kidney transplant lymphoproliferative disease. *Pediatr Nephrol*, 25(6): 1163-7, 2010a, [5] 
5. **Bitzan, M.; Schaefer, F.; and Reymond, D.:** Treatment of typical (enteropathic) hemolytic uremic syndrome. *Semin Thromb Hemost*, 36(6): 594-610, 2010b, [5] 
6. **Broughton, S.; McClay, J. E.; Murray, A.; Timmons, C.; Sommerauer, J.; Andrews, W.; and Harkins, P.:** The effectiveness of tonsillectomy in diagnosing lymphoproliferative disease in pediatric patients after liver transplantation. *Arch Otolaryngol Head Neck Surg*, 126(12): 1444-7, 2000, [4a] 
7. **Cacciarelli, T. V.; Green, M.; Jaffe, R.; Mazariegos, G. V.; Jain, A.; Fung, J. J.; and Reyes, J.:** Management of posttransplant lymphoproliferative disease in pediatric liver transplant recipients receiving primary tacrolimus (FK506) therapy. *Transplantation*, 66(8): 1047-52, 1998, [3a] 
8. **Cao, S. et al.:** Posttransplant lymphoproliferative disorders and gastrointestinal manifestations of Epstein-Barr virus infection in children following liver transplantation. *Transplantation*, 66(7): 851-6, 1998, [4a] 
9. **Capello, D.; Berra, E.; Cerri, M.; and Gaidano, G.:** Post-transplant lymphoproliferative disorders. Molecular analysis of histogenesis and pathogenesis. *Minerva Med*, 95(1): 53-64, 2004, [4a] 
10. **Capello, D. et al.:** Molecular histogenesis of posttransplantation lymphoproliferative disorders. *Blood*, 102(10): 3775-85, 2003, [4a] 
11. **Capello, D.; Rossi, D.; and Gaidano, G.:** Post-transplant lymphoproliferative disorders: molecular basis of disease histogenesis and pathogenesis. *Hematol Oncol*, 23(2): 61-7, 2005, [4a] 
12. **Cesaro, S. et al.:** The real-time polymerase chain reaction-guided modulation of immunosuppression enables the pre-emptive management of Epstein-Barr virus reactivation after allogeneic haematopoietic stem cell transplantation. *Br J Haematol*, 128(2): 224-33, 2005, [3b] 
13. **Chadburn, A.; Cesarman, E.; Liu, Y. F.; Addonizio, L.; Hsu, D.; Michler, R. E.; and Knowles, D. M.:** Molecular genetic analysis demonstrates that multiple posttransplantation lymphoproliferative disorders occurring in one anatomic site in a single patient represent distinct primary lymphoid neoplasms. *Cancer*, 75(11): 2747-56, 1995, [5] 
14. **Chen, C.; Johnston, T. D.; Jeon, H.; Gedaly, R.; McHugh, P.; and Ranjan, D.:** Cyclosporin A Up-Regulates and Activates Protein Kinase C-zeta in EBV-Infected and EBV-Transformed Human B-Cells. *J Surg Res*, 153(1): 156-161, 2009, [4a] 
15. **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*, 107(8): 3053-7, 2006, [3a] 
16. **Cohen, A. H.; Sweet, S. C.; Mendeloff, E.; Mallory, G. B., Jr.; Huddleston, C. B.; Kraus, M.; Kelly, M.; Hayashi, R.; and DeBaun, M. R.:** High incidence of posttransplant lymphoproliferative disease in pediatric patients with cystic fibrosis. *Am J Respir Crit Care Med*, 161(4 Pt 1): 1252-5, 2000, [4a] 
17. **Cohen, J. I.:** Epstein-Barr virus lymphoproliferative disease associated with acquired immunodeficiency. *Medicine (Baltimore)*, 70(2): 137-60, 1991, [5] 
18. **D'Antiga, L.; Del Rizzo, M.; Mengoli, C.; Cillo, U.; Guariso, G.; and Zancan, L.:** Sustained Epstein-Barr virus detection in paediatric liver transplantation. Insights into the occurrence of late PTLD. *Liver Transpl*, 13(3): 343-8, 2007, [4b] 
19. **Davis, C. L.:** The antiviral prophylaxis of post-transplant lymphoproliferative disorder. *Springer Semin Immunopathol*, 20(3-4): 437-53, 1998, [5] 
20. **Dharnidharka, V. R., and Araya, C. E.:** Post-transplant lymphoproliferative disease. *Pediatric Nephrology*, 24(4): 731-6, 2009, [5] 
21. **Dharnidharka, V. R.; Talley, L. I.; Martz, K. L.; Stablein, D. M.; and Fine, R. N.:** Recombinant growth hormone use pretransplant and risk for post-transplant lymphoproliferative disease – A report of the NAPRTCS. *Pediatric Transplantation*, 12(6): 689-695, 2008, [4a] 
22. **Dierksheide, J. E.; Baiocchi, R. A.; Ferketich, A. K.; Roychowdhury, S.; Pelletier, R. P.; Eisenbeis, C. F.; Caligiuri, M. A.; and VanBuskirk, A. M.:** IFN-gamma gene polymorphisms associate with development of EBV+ lymphoproliferative disease in hu PBL-SCID mice. *Blood*, 105(4): 1558-65, 2005, [4a] 

23. **DJ, B.:** Should we be concerned about the rapid increase in CT usage? *Rev Environ Health.*, 25(1): 63-8., 2010, [5]
24. **Dodd, G. D., 3rd; Ledesma-Medina, J.; Baron, R. L.; and Fuhrman, C. R.:** Posttransplant lymphoproliferative disorder: intrathoracic manifestations. *Radiology*, 184(1): 65-9, 1992, [4a]
25. **Donnelly, L. F.; Frush, D. P.; Marshall, K. W.; and White, K. S.:** Lymphoproliferative disorders: CT findings in immunocompromised children. *AJR Am J Roentgenol*, 171(3): 725-31, 1998, [4a]
26. **Dror, Y. et al.:** Lymphoproliferative disorders after organ transplantation in children. *Transplantation*, 67(7): 990-8, 1999, [4b]
27. **Fafi-Kremer, S.; Brengel-Pesce, K.; Bargues, G.; Bourgeat, M. J.; Genoulaz, O.; Seigneurin, J. M.; and Morand, P.:** Assessment of automated DNA extraction coupled with real-time PCR for measuring Epstein-Barr virus load in whole blood, peripheral mononuclear cells and plasma. *J Clin Virol*, 30(2): 157-64, 2004, [4a]
28. **Fernandez, M. C.; Bes, D.; De Davila, M.; Lopez, S.; Cambaceres, C.; Dip, M.; and Inventarza, O.:** Post-transplant lymphoproliferative disorder after pediatric liver transplantation: Characteristics and outcome. *Pediatr Transplant*, 2008, [4a]
29. **Ganschow, R.; Englert, C.; Grabhorn, E.; Richter, A.; Hinrichs, B.; Broering, D. C.; Rogiers, X.; and Burdelski, M.:** Hypogammaglobulinemia in pediatric liver transplant recipients. *Pediatr Transplant*, 9(2): 215-9, 2005, [3b]
30. **Ganschow, R.; Grabhorn, E.; Schulz, A.; Von Hugo, A.; Rogiers, X.; and Burdelski, M.:** Long-term results of basiliximab induction immunosuppression in pediatric liver transplant recipients. *Pediatr Transplant*, 9(6): 741-5, 2005, [2b]
31. **Genetech, I.:** Rituxan. 2010, [5b]
32. **Green, M.; Michaels, M. G.; Webber, S. A.; Rowe, D.; and Reyes, J.:** The management of Epstein-Barr virus associated post-transplant lymphoproliferative disorders in pediatric solid-organ transplant recipients. *Pediatr Transplant*, 3(4): 271-81, 1999, [5]
33. **Groen, P., and Witte, D.:** Quantitative EBV assay using the LightCycler instrument to monitor transplant patients at risk for PTLN. *Pediatr Dev Pathol*, 4(4): 414-415, 2001, [4b]
34. **Gross, T. G. et al.:** Low-dose chemotherapy for Epstein-Barr virus-positive post-transplantation lymphoproliferative disease in children after solid organ transplantation. *J Clin Oncol*, 23(27): 6481-8, 2005, [3a]
35. **Haddad, E. M.; McAlister, V. C.; Renouf, E.; Malthaner, R.; Kjaer, M. S.; and Glud, L. L.:** Cyclosporin versus tacrolimus for liver transplanted patients. *Cochrane Database Syst Rev*, (4): CD005161, 2006, [1a]
36. **Harris, N. L.; Jaffe, E. S.; Diebold, J.; Flandrin, G.; Muller-Hermelink, H. K.; Vardiman, J.; Lister, T. A.; and Bloomfield, C. D.:** World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol*, 17(12): 3835-49, 1999, [5a]
37. **Harwood, J. S.; Gould, F. K.; McMaster, A.; Hamilton, J. R.; Corris, P. A.; Hasan, A.; Gennery, A. R.; and Dark, J. H.:** Significance of Epstein-Barr virus status and post-transplant lymphoproliferative disease in pediatric thoracic transplantation. *Pediatr Transplant*, 3(2): 100-3, 1999, [3b]
38. **Hayashi, R. J. et al.:** Posttransplant lymphoproliferative disease in children: correlation of histology to clinical behavior. *J Pediatr Hematol Oncol*, 23(1): 14-8, 2001, [4a]
39. **Helslop, H. et al.:** Long-term outcome of EBV-specific T-cell infusions to prevent or treat EBV-related lymphoproliferative disease in transplant recipients. *Blood.*, 115(5): 925-35. Epub 2009 Oct 30., 2010, [3a]
40. **Herth, F. J., and Becker, H. D.:** Transthoracic ultrasound. *Respiration*, 70(1): 87-94, 2003, [5]
41. **Ho, M. et al.:** The frequency of Epstein-Barr virus infection and associated lymphoproliferative syndrome after transplantation and its manifestations in children. *Transplantation*, 45(4): 719-27, 1988, [4a]
42. **Holmes, R. D.; Orban-Eller, K.; Karrer, F. R.; Rowe, D. T.; Narkewicz, M. R.; and Sokol, R. J.:** Response of elevated Epstein-Barr virus DNA levels to therapeutic changes in pediatric liver transplant patients: 56-month follow up and outcome. *Transplantation*, 74(3): 367-72, 2002, [4a]
43. **Inomata, Y.; Hamamoto, R.; Yoshimoto, K.; and Zeledon, M.:** [Current status and perspective of pediatric liver transplantation in Japan]. *Nippon Rinsho*, 63(11): 1986-92, 2005, [4a]
44. **Katz, B. Z.; Pahl, E.; Crawford, S. E.; Kostyk, M. C.; Rodgers, S.; Seshadri, R.; Proytcheva, M.; and Pophal, S.:** Case-control study of risk factors for the development of post-transplant lymphoproliferative disease in a pediatric heart transplant cohort. *Pediatr Transplant*, 11(1): 58-65, 2007, [4b]
45. **Kauffman, H. M.; Cherikh, W. S.; Cheng, Y. S.; Hanto, D. W.; and D., K. B.:** Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation*, 80(7): 883-9., 2005, [3b]
46. **Kingma, D. W. et al.:** Epstein-Barr virus (EBV)-associated smooth-muscle tumor arising in a post-transplant patient treated successfully for two PT-EBV-associated large-cell lymphomas. Case report. *Am J Surg Pathol*, 20(12): 1511-9, 1996, [5]
47. **Kirk, A. D. et al.:** Dissociation of depletion induction and posttransplant lymphoproliferative disease in kidney recipients treated with alemtuzumab. *American Journal of Transplantation*, 7(11): 2619-25, 2007, [4a]
48. **Kullberg-Lindh, C.; Olofsson, S.; Brune, M.; and Lindh, M.:** Comparison of serum and whole blood levels of cytomegalovirus and Epstein-Barr virus DNA.

- Transpl Infect Dis*, 10(5): 308-315, 2008, [4a]
49. **Lattyak, B. V.; Rosenthal, P.; Mudge, C.; Roberts, J. P.; Renze, J. F.; Osorio, R. W.; Emond, J. C.; and Lalwani, A. K.:** Posttransplant lymphoproliferative disorder presenting in the head and neck. *Laryngoscope*, 108(8 Pt 1): 1195-8, 1998, [4b]
 50. **Lee, T. C. et al.:** Quantitative EBV viral loads and immunosuppression alterations can decrease PTLTD incidence in pediatric liver transplant recipients. *Am J Transplant*, 5(9): 2222-8, 2005, [3a]
 51. **Local Consensus:** During guideline development timeframe. ed., [5]
 52. **Lopez-Ben, R.; Smith, J. K.; Kew, C. E., 2nd; Kenney, P. J.; Julian, B. A.; and Robbin, M. L.:** Focal posttransplantation lymphoproliferative disorder at the renal allograft hilum. *AJR Am J Roentgenol*, 175(5): 1417-22, 2000, [4b]
 53. **Mancao, C.; Altmann, M.; Jungnickel, B.; and Hammerschmidt, W.:** Rescue of "crippled" germinal center B cells from apoptosis by Epstein-Barr virus. *Blood*, 106(13): 4339-44, 2005, [4a]
 54. **Markin, R. S.:** Manifestations of Epstein-Barr virus-associated disorders in liver. *Liver*, 14(1): 1-13, 1994, [5]
 55. **Marom, E. M.; McAdams, H. P.; Butnor, K. J.; and Coleman, R. E.:** Positron emission tomography with fluoro-2-deoxy-D-glucose (FDG-PET) in the staging of post transplant lymphoproliferative disorder in lung transplant recipients. *J Thorac Imaging*, 19(2): 74-8, 2004, [4b]
 56. **Maturen, K. E.; Blane, C. E.; Strouse, P. J.; and Fitzgerald, J. T.:** Pulmonary involvement in pediatric lymphoma. *Pediatr Radiol*, 34(2): 120-4, 2004, [4a]
 57. **McCormack, L.; Hany, T. I.; Hubner, M.; Petrowsky, H.; Mullhaupt, B.; Knuth, A.; Stenner, F.; and Clavien, P. A.:** How useful is PET/CT imaging in the management of post-transplant lymphoproliferative disease after liver transplantation? *Am J Transplant*, 6(7): 1731-6, 2006, [4b]
 58. **McDiarmid, S. V. et al.:** Prevention and preemptive therapy of posttransplant lymphoproliferative disease in pediatric liver recipients. *Transplantation*, 66(12): 1604-11, 1998, [3b]
 59. **McDonald, R. A. et al.:** Incidence of PTLTD in pediatric renal transplant recipients receiving basiliximab, calcineurin inhibitor, sirolimus and steroids. *Am J Transplant*, 8(5): 984-9., 2008, [2a]
 60. **Meerbach, A.; Wutzler, P.; Hafer, R.; Zintl, F.; and Gruhn, B.:** Monitoring of Epstein-Barr virus load after hematopoietic stem cell transplantation for early intervention in post-transplant lymphoproliferative disease. *J Med Virol*, 80(3): 441-54, 2008, [3a]
 61. **Mendoza, F.; Kunitake, H.; Laks, H.; and Odim, J.:** Post-transplant lymphoproliferative disorder following pediatric heart transplantation. *Pediatr Transplant*, 10(1): 60-6, 2006, [4a]
 62. **Messahel, B.; Taj, M. M.; Hobson, R.; Hadzic, N.; Ramsay, A.; Hann, I.; and Pinkerton, R.:** Single agent efficacy of rituximab in childhood immunosuppression related lymphoproliferative disease: a United Kingdom Children's Cancer Study Group (UKCCSG) retrospective review. *Leuk Lymphoma*, 47(12): 2584-9, 2006, [4b]
 63. **Newell, K.; Alonso, E.; Kelly, S.; Rubin, C.; Thistlethwaite, J.; and Whittington, P.:** Association between liver transplantation for Langerhans cell histiocytosis, rejection, and development of posttransplant lymphoproliferative disease in children. *J Pediatr*, 131(1 Pt 1): 98-104., 1997, [5b]
 64. **Newell, K. A. et al.:** Posttransplant lymphoproliferative disease in pediatric liver transplantation. Interplay between primary Epstein-Barr virus infection and immunosuppression. *Transplantation*, 62(3): 370-5, 1996, [4a]
 65. **Nourse, J. P.; Jones, K.; and Gandhi, M. K.:** Epstein-barr virus-related post-transplant lymphoproliferative disorders: pathogenetic insights for targeted therapy. *Am J Transplant*, 11(5): 888-95, 2011, [5]
 66. **O'Conner, A. R., and Franc, B. L.:** FDG PET imaging in the evaluation of post-transplant lymphoproliferative disorder following renal transplantation. *Nucl Med Commun*, 26(12): 1107-11, 2005, [4a]
 67. **Okano, M., and Gross, T. G.:** Epstein-Barr virus-associated hemophagocytic syndrome and fatal infectious mononucleosis. *Am J Hematol*, 53(2): 111-5, 1996, [5]
 68. **Orjuela, M.; Gross, T. G.; Cheung, Y. K.; Alobeid, B.; Morris, E.; and Cairo, M. S.:** A pilot study of chemoimmunotherapy (cyclophosphamide, prednisone, and rituximab) in patients with post-transplant lymphoproliferative disorder following solid organ transplantation. *Clin Cancer Res*, 9(10 Pt 2): 3945S-52S, 2003, [3b]
 69. **Ozdemir, F.; Aydin, F.; Yilmaz, M.; Kavgaci, H.; Bektas, O.; Yavuz, M. N.; and Yavuz, A. A.:** The effects of IL-2, IL-6 and IL-10 levels on prognosis in patients with aggressive Non-Hodgkin's Lymphoma (NHL). *J Exp Clin Cancer Res*, 23(3): 485-8, 2004, [4a]
 70. **Pascual, J.:** Post-transplant lymphoproliferative disorder--the potential of proliferation signal inhibitors. *Nephrol Dial Transplant*, 22 Suppl 1: i27-35, 2007, [4b]
 71. **Paya, C. V. et al.:** Epstein-Barr virus-induced posttransplant lymphoproliferative disorders. ASTS/ASTP EBV-PTLD Task Force and The Mayo Clinic Organized International Consensus Development Meeting. *Transplantation*, 68(10): 1517-25, 1999, [5]
 72. **Pickhardt, P. J., and Siegel, M. J.:** Posttransplantation lymphoproliferative disorder of the abdomen: CT evaluation in 51 patients. *Radiology*, 213(1): 73-8, 1999, [4b]
 73. **Pickhardt, P. J.; Siegel, M. J.; Anderson, D. C.; Hayashi, R.; and DeBaun, M. R.:** Chest radiography as a predictor of outcome in posttransplantation lymphoproliferative disorder in lung allograft recipients. *AJR Am J Roentgenol*, 171(2): 375-82, 1998, [4b]
 74. **Piriou, E. R.; van Dort, K.; Nanlohy, N. M.; Miedema, F.; van Oers, M. H.; and van Baarle, D.:**

- Altered EBV viral load setpoint after HIV seroconversion is in accordance with lack of predictive value of EBV load for the occurrence of AIDS-related non-Hodgkin lymphoma. *J Immunol*, 172(11): 6931-7, 2004, [4b]
75. **Preiksaitis, J. K.; Pang, X. L.; Fox, J. D.; Fenton, J. M.; Caliendo, A. M.; and Miller, G. G.:** Interlaboratory comparison of Epstein-Barr virus viral load assays. *Am J Transplant*, 9(2): 269-79, 2009, [4b]
76. **Quintanilla-Martinez, L. et al.:** Fulminant EBV(+) T-cell lymphoproliferative disorder following acute/chronic EBV infection: a distinct clinicopathologic syndrome. *Blood*, 96(2): 443-51, 2000, [3b]
77. **Randhawa, P. S.; Magnone, M.; Jordan, M.; Shapiro, R.; Demetris, A. J.; and Nalesnik, M.:** Renal allograft involvement by Epstein-Barr virus associated post-transplant lymphoproliferative disease. *Am J Surg Pathol*, 20(5): 563-71, 1996, [4b]
78. **Ranjan, D.; Chen, C.; Johnston, T. D.; Jeon, H.; Ibrahim, M.; Drake, J.; and Butterfield, D. A.:** Stimulation of Epstein-Barr virus-infected human B cell growth by physiological concentrations of 4-hydroxynonenal. *Cell Biochem Funct*, 24(2): 147-52, 2006, [4a]
79. **Riebel, T.; Kebelmann-Betzing, C.; and Scheer, I.:** Ultrasound in abdominal and soft-tissue childhood PTLD (post-transplant lymphoproliferative disease). *Ultraschall Med*, 28(2): 201-5, 2007, [4b]
80. **Rinaldi, A. et al.:** Comparative genome-wide profiling of post-transplant lymphoproliferative disorders and diffuse large B-cell lymphomas. *Br J Haematol*, 134(1): 27-36, 2006, [4a]
81. **Robbins, E.:** Radiation risks from imaging studies in children with cancer. *Pediatr Blood Cancer*, 51(4): 453-7, 2008, [5]
82. **Rogers, B. B.; Sommerauer, J.; Quan, A.; Timmons, C. F.; Dawson, D. B.; Scheuermann, R. H.; Krisher, K.; and Atkins, C.:** Epstein-Barr virus polymerase chain reaction and serology in pediatric post-transplant lymphoproliferative disorder: three-year experience. *Pediatr Dev Pathol*, 1(6): 480-6, 1998, [4a]
83. **Rowe, D. T.; Qu, L.; Reyes, J.; Jabbour, N.; Yunis, E.; Putnam, P.; Todo, S.; and Green, M.:** Use of quantitative competitive PCR to measure Epstein-Barr virus genome load in the peripheral blood of pediatric transplant patients with lymphoproliferative disorders. *J Clin Microbiol*, 35(6): 1612-5, 1997, [3b]
84. **Roy, S.; Vivero, R. J.; and Smith, L. P.:** Adenotonsillar pathology in post-transplant patients. *Int J Pediatr Otorhinolaryngol*, 72(6): 865-8, 2008, [4a]
85. **Sarkar, S.; Selvaggi, G.; Mittal, N.; Cenk Acar, B.; Weppler, D.; Kato, T.; Tzakis, A.; and Ruiz, P.:** Gastrointestinal tract ulcers in pediatric intestinal transplantation patients: etiology and management. *Pediatr Transplant*, 10(2): 162-7, 2006, [4a]
86. **Schubert, S. et al.:** Diagnosis and treatment of post-transplantation lymphoproliferative disorder in pediatric heart transplant patients. *Pediatric Transplantation*, 13(1): 54-62, 2009, [3b]
87. **Schubert, S. et al.:** Diagnosis and treatment of post-transplantation lymphoproliferative disorder in pediatric heart transplant patients. *Pediatr Transplant*, 2008, [4a]
88. **Sebelin-Wulf, K.; Nguyen, T. D.; Oertel, S.; Papp-Vary, M.; Trappe, R. U.; Schulzki, A.; Pezzutto, A.; Riess, H.; and Subklewe, M.:** Quantitative analysis of EBV-specific CD4/CD8 T cell numbers, absolute CD4/CD8 T cell numbers and EBV load in solid organ transplant recipients with PLTD. *Transpl Immunol*, 17(3): 203-10, 2007, [3b]
89. **Shapiro, R. S. et al.:** Epstein-Barr virus associated B cell lymphoproliferative disorders following bone marrow transplantation. *Blood*, 71(5): 1234-43, 1988, [4b]
90. **Smets, F.; Bodeus, M.; Goubau, P.; Reding, R.; Otte, J. B.; Buts, J. P.; and Sokal, E. M.:** Characteristics of Epstein-Barr virus primary infection in pediatric liver transplant recipients. *J Hepatol*, 32(1): 100-4, 2000, [3b]
91. **Snow, A. L.; Vaysberg, M.; Krams, S. M.; and Martinez, O. M.:** EBV B lymphoma cell lines from patients with post-transplant lymphoproliferative disease are resistant to TRAIL-induced apoptosis. *Am J Transplant*, 6(5 Pt 1): 976-85, 2006, [4a]
92. **So, S.:** CMV and EBV-PTLD after liver transplantation. *Transplant Proc*, 33(1-2): 1317-9, 2001, [5]
93. **Srivastava, T.; Zwick, D. L.; Rothberg, P. G.; and Warady, B. A.:** Posttransplant lymphoproliferative disorder in pediatric renal transplantation. *Pediatr Nephrol*, 13(9): 748-54, 1999, [3b]
94. **Stevens, S. J. C.; Verschuuren, E. A. M.; Verkuujlen, S. A. W. M.; Van Den Brule, A. J. C.; Meijer, C. J. L. M.; and Middeldorp, J. M.:** Role of Epstein-Barr virus DNA load monitoring in prevention and early detection of post-transplant lymphoproliferative disease. *Leukemia & Lymphoma*, 43(4): 831-40, 2002, [5]
95. **Swerdlow, A. J.; Higgins, C. D.; Hunt, B. J.; Thomas, J. A.; Burke, M. M.; Crawford, D. H.; and Yacoub, M. H.:** Risk of lymphoid neoplasia after cardiothoracic transplantation. a cohort study of the relation to Epstein-Barr virus. *Transplantation*, 69(5): 897-904, 2000, [3a]
96. **Szymanski, K. M.; Bitzan, M.; and Capolicchio, J. P.:** Is retroperitoneoscopy the gold standard for endoscopic nephrectomy in children on peritoneal dialysis? *J Urol*, 184(4 Suppl): 1631-7, 2010, [4b]
97. **Trappe, R.:** CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. *Haematologica*, 92(2): 273-4, 2007, [3b]
98. **Vakiani, E. et al.:** Genetic and phenotypic analysis of B-cell post-transplant lymphoproliferative disorders

- provides insights into disease biology. *Hematol Oncol*, 2008, [4a] _____
99. **VanBuskirk, A. M.; Lesinski, G. B.; Nye, K. J.; Carson, W. E.; and Yee, L. D.:** TGF-beta inhibition of CTL re-stimulation requires accessory cells and induces peroxisome-proliferator-activated receptor-gamma (PPAR-gamma). *Am J Transplant*, 6(8): 1809-19, 2006, [4a] _____
100. **von Falck, C.; Maecker, B.; Schirg, E.; Boerner, A. R.; Knapp, W. H.; Klein, C.; and Galanski, M.:** Post transplant lymphoproliferative disease in pediatric solid organ transplant patients: a possible role for [18F]-FDG-PET(/CT) in initial staging and therapy monitoring. *Eur J Radiol*, 63(3): 427-35, 2007, [4b] _____
101. **Walker, R. C.; Paya, C. V.; Marshall, W. F.; Strickler, J. G.; Wiesner, R. H.; Velosa, J. A.; Habermann, T. M.; Daly, R. C.; and McGregor, C. G.:** Pretransplantation seronegative Epstein-Barr virus status is the primary risk factor for posttransplantation lymphoproliferative disorder in adult heart, lung, and other solid organ transplantations. *J Heart Lung Transplant*, 14(2): 214-21, 1995, [3a] _____
102. **Webber, S. A.; Naftel, D. C.; Fricker, F. J.; Olesnevich, P.; Blume, E. D.; Addonizio, L.; Kirklin, J. K.; and Canter, C. E.:** Lymphoproliferative disorders after paediatric heart transplantation: a multi-institutional study. *Lancet*, 367(9506): 233-9, 2006, [4a] _____
103. **Yun, A. J., and Lee, P. Y.:** The link between T helper balance and lymphoproliferative disease. *Med Hypotheses*, 65(3): 587-90, 2005, [4a] _____

Addendum
PTLD Clinical Checklist

This list is inclusive of most but not all possible clinical manifestations of PTLD

1. Heme positive stools
2. Hypoalbuminemia, GI protein losses
3. Feeding intolerance
4. Chronic diarrhea, change in bowel habits
5. Unexplained anemia
6. Poor weight gain
7. Airway obstruction due to tonsillar hypertrophy
8. CNS symptoms
9. Fever without source
10. Mono-type illness/lymphadenopathy
11. Unexplained cough, wheezing or tachypnea
12. Unexplained increased serum transaminases
13. Rashes
14. Kidney dysfunction, kidney enlargement, proteinuria
15. Ovarian/testicular mass
16. Auto-immune cytopenias
17. Ascites
18. Graft dysfunction
19. Joint pains or swelling