Evidence Based Clinical Practice
Guideline
Management of EBV-Associated Post-Transplant Lymphoproliferative Disease (PTLD) in Solid Organ Transplant
Revision Date: January, 2012
Original Publication Date: February, 2003

Target Population

Inclusion: These guidelines are intended for use in the following:
- Pediatric age recipients of heart, kidney, liver and intestinal transplant

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

Introduction

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 pathophysiologic processes have been explored in the recent literature, mostly through in vitro cell studies and tissue analyses (Preiksaitis 2009b [4b]):

- 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

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td>EBV viremia</td>
<td>EBV DNA detectible in blood by PCR analysis</td>
</tr>
<tr>
<td>EBV-associated PTLD</td>
<td>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 detection of EBV DNA in blood samples (Preiksaitis 2009b [4b], Preiksaitis 2009a [4b])</td>
</tr>
<tr>
<td>PTLD</td>
<td>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 (Paya 1999 [5], Local Consensus [5]). Most, but not all cases of PTLD are associated with concomitant EBV viremia (Cohen 2000 [4a], So 2001 [5]).</td>
</tr>
<tr>
<td>EBV-Naive</td>
<td>An individual with no known or demonstrable serologic evidence of prior infection with EBV</td>
</tr>
<tr>
<td>Primary EBV Infection</td>
<td>the detection of serum anti-VCA IgM antibodies followed by a rise in the VCA-IgG or detection of EBV in blood by PCR in a previously EBV-naive (unexposed) individual</td>
</tr>
<tr>
<td>Latent (Long Past) EBV Infection</td>
<td>the detection of serum IgG antibodies against EBV, in a patient who has not received passive immunoglobulin in the previous three months</td>
</tr>
<tr>
<td>EBV Reactivation</td>
<td>the detection of EBV in the blood of a patient with previous latent infection, usually by PCR</td>
</tr>
<tr>
<td>Persistent disease (PTLD)</td>
<td>ongoing clinical, histologic or radiologic evidence despite intervention</td>
</tr>
<tr>
<td>Progressive disease (PTLD)</td>
<td>Increased involvement at the primary site and/or development of PTLD lesions at new sites.</td>
</tr>
<tr>
<td>Rejection</td>
<td>defined by findings on allograft biopsy</td>
</tr>
<tr>
<td>Fulminant PTLD</td>
<td>PTLD accompanied by fever, hypotension, and multiple organ involvement</td>
</tr>
</tbody>
</table>

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 45%. 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])

- 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 (Lau 2010 [4a], Schubert 2008 [4a], 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 detectable EBV DNA typically found during surveillance of peripheral blood but may begin in the patient with concerning clinical 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). In patients with EBV, calcineurin inhibitor immunosuppression is reduced according to the health of the allograft. Calcineurin inhibitors are stopped in patients failing to adequately respond to reduced immunosuppression and in patients whose allograft health allows it. These patients receive further therapy with rituximab or chemotherapy initiated depending upon the clinical status as described below:
• 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 virologic, clinical, pathological and radiologic findings (Local Consensus [5]).

Evaluation

Laboratory screening and monitoring

2. 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>
<thead>
<tr>
<th>Infection</th>
<th>VCA IgM</th>
<th>VCA IgG</th>
<th>EBNA (EBV Nuclear antigen) (often not produced by transplant patients)</th>
<th>Early Ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Primary</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Reactivated or late phase primary infection</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Latent</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>
3. 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 EBV DNA detection
- need and timing for intervention in the case of isolated EBV DNA detection (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 DNA detection in blood. 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], Faß-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 2009a [4b], Preiksaitis 2009b [4b]).

### Table 2: Suggested EBV PCR Screening Schedules

<table>
<thead>
<tr>
<th>Transplant Type</th>
<th>Suggested Frequency from transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Baseline and with presentation of symptoms</td>
</tr>
<tr>
<td>Liver</td>
<td>Every 2 weeks for 3 months, then monthly for 9 months, then yearly and with presentation of symptoms</td>
</tr>
<tr>
<td>Heart</td>
<td>Baseline, every 3 months and with presentation of symptoms or rising PCR</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>Every 2 weeks x 3 months then monthly for 9 months, then yearly and with presentation of symptoms</td>
</tr>
</tbody>
</table>

(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 DNA detection in blood, 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])
  - allograft dysfunction (11%) (Quintana-Martinez 2000 [3b], Randhava 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], Lattyak 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 [5b]).

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Lesion</td>
<td>• Reactive plasmacytic hyperplasia</td>
</tr>
<tr>
<td></td>
<td>• Infectious mononucleosis-like</td>
</tr>
<tr>
<td>PTLD, polymorphic</td>
<td>1. Polyclonal</td>
</tr>
<tr>
<td></td>
<td>2. Monoclonal</td>
</tr>
<tr>
<td>PTLD, monomorphic</td>
<td>• B-cell lymphomas</td>
</tr>
<tr>
<td></td>
<td>• Diffuse large B-cell lymphoma (immunoblastic, centroblastic, anaplastic)</td>
</tr>
<tr>
<td></td>
<td>• Burkitt/Burkitt-like lymphoma</td>
</tr>
<tr>
<td></td>
<td>• Plasma cell myeloma</td>
</tr>
<tr>
<td></td>
<td>• T-cell lymphomas</td>
</tr>
<tr>
<td></td>
<td>• Peripheral T-cell lymphoma, not otherwise categorized</td>
</tr>
<tr>
<td></td>
<td>• Other types (hematopiosenic, gammada, T/NK)</td>
</tr>
<tr>
<td>Other types, rare</td>
<td>• Hodgkin’s disease-like lesions (associated with methotrexate therapy)</td>
</tr>
<tr>
<td></td>
<td>• Plasmacytoma-like lesions</td>
</tr>
</tbody>
</table>

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 the use of radiographic imaging for PTLD screening be limited to patients with clinical symptoms or detectable EBV DNA in the blood; this is due to the lack of specificity and sensitivity of radiologic studies for PTLD (Donnelly 1998 [4a], Dodd 1992 [4a], McCormack 2006 [4b], Pickhardt 1999 [4b], Pickhardt 1998 [4b]).
Evidence Based Clinical Care Guideline (EBCG) For Management of EBV

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’Connor 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 tomodigraphy (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 (!!! INVALID CITATION !!!).

Note 2: Limited PET sensitivity in detecting mucosa associated lymphoid tissue (MALT) lymphoma (!!! INVALID CITATION !!!) 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 (!!! INVALID CITATION !!!). Lung parenchyma cannot be evaluated with ultrasound (Herth 2003 [5]), MRI evaluation of the lung parenchyma is limited (!!! INVALID CITATION !!!).

Note 4: Lung parenchyma cannot be evaluated with ultrasound (Herth 2003 [5]), MRI evaluation of the lung parenchyma is limited (!!! INVALID CITATION !!!).

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 patients with detectable EBV DNA in blood and no clinical symptoms be maintained within protocol range of immunosuppression levels (Local Consensus [5]).

Note: Reduction of immunosuppression from standard protocols at this stage is controversial (!!! INVALID CITATION !!!).

13. It is recommended to consider antiviral agents (e.g. ganciclovir, valganciclovir, acyclovir, or cidofovir) for asymptomatic patients with detectable blood EBV DNA (Local Consensus [5]).

14. It is recommended to consider on an individual case basis the use of rituximab in patients with detectable EBV DNA in their blood and who are 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 (Helslop 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:
   a. Anti-T cell monoclonal antibodies when possible in patients with PTLD (Local Consensus [5]).
   b. 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 (!!! INVALID CITATION !!!).

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:
   a. evidence of persistent or progressive PTLD after reduction of immunosuppression
   b. PTLD refractory to Rituximab monotherapy
   c. when PTLD is present with concurrent evidence of allograft rejection
   d. fulminant PTLD

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 hypogammaglobulinemia (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 hypogammaglobulinemia, 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 antiproliferative and autophagic role of mTOR inhibition (Mathew 2004 [2a], Kirk 2007 [4a], 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 DNA detection in the blood
  ○ of patients treated for PTLD
● Effective and safe immune-modulatory regimens that decrease the risk for PTLD while preserving allograft health
● Expansion of innovative therapies such as EBV-specific T-cell therapy. GM-CSF as adjuvant therapy with rituximab (Barker 2010 [2b], Haque 2007 [2b], Savoldo 2006 [2b], Santodonato 2003 [2b])

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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/EBFiles/Table-EvidenceLevels.pdf
• Grading a Body of Evidence to Answer a Clinical Question
• Judging the Strength of a Recommendation (abbreviated table below)
  http://groups/ce/NewEBC/Judgingthestrengthofarecommendation.pdf
Table of Evidence Levels (see note above)

<table>
<thead>
<tr>
<th>Quality level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a† or 1b†</td>
<td>Systematic review, meta-analysis, or meta-synthesis of multiple studies</td>
</tr>
<tr>
<td>2a or 2b</td>
<td>Best study design for domain</td>
</tr>
<tr>
<td>3a or 3b</td>
<td>Fair study design for domain</td>
</tr>
<tr>
<td>4a or 4b</td>
<td>Weak study design for domain</td>
</tr>
<tr>
<td>5</td>
<td>Other: General review, expert opinion, case report, consensus report, or guideline</td>
</tr>
</tbody>
</table>

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

<table>
<thead>
<tr>
<th>Strength</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Strongly recommended”</td>
<td>There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).</td>
</tr>
<tr>
<td>“Recommended”</td>
<td>There is consensus that benefits are closely balanced with risks and burdens.</td>
</tr>
<tr>
<td>No recommendation made</td>
<td>There is lack of consensus to direct development of a recommendation.</td>
</tr>
</tbody>
</table>

Dimensions: 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.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient (direct benefit)
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 externally appraised by three reviewers using the AGREE instrument and the results by domain are:

- Scope and Purpose 78%
- Stakeholder Involvement 50%
- Rigor of Development 87%
- Clarity and Presentation 75%
- Applicability 59%
- Editorial Independence 94%

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 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.
Suspicion for PTLD in transplant patient due to:
- positive PCR, or
- ill (with or without positive PCR)

**Symptomatic?** (with or without positive PCR)  
*see Addendum (clinical checklist)

**Algorithm 1: PTLD Evaluation**

- Continue protocol immunosuppression
- Increase frequency of EBV PCR monitoring to weekly x 3
- Consider ganciclovir or valganciclovir for EBV viremia
- Monitor clinically
- Consider rituximab in high risk patients

**Symptoms develop?**

1) Organ specific evaluation (e.g. physical exam, laboratory analysis, radiography, endoscopy)  
2) Heme/Onc consult

Mass or tissue lesion detected or suspected?

**Biopsy or surgical resection positive for PTLD?**

Algorithm 2
Algorithm 2: Treatment algorithm for EBV-associated PTLD

Refer to text for details

Staging

- CT scans
- PET scan
- bone marrow evaluation if: fulminant PTLD, cytopenia, or lymphoma
- LP if: fulminant PTLD, neurological symptoms, or lymphoma

Non-fulminant PTLD

“Minimally ill”?  
- no allograft rejection  
- mass <2 cm  
- polymorphic histology  
- normal LDH

NO

YES

1. REDUCE IS from target range*
2. Weekly EBV, CMV and PCR monitoring of peripheral blood
3. Radiographic surveillance as needed
4. Assess response to therapy (e.g. in 2 and 4 weeks)

Improvement?  
- resolving symptoms  
- reduction in mass  
- no rejection

NO

YES

Treatment response?

NO

Add rituximab

YES

Treatment response?

NO

YES

*If no residual PTLD present after biopsy or surgical resection, may continue IS protocol target range. See narrative page 6 no.16 note 1 for details

Fulminant PTLD

1. Low dose chemotherapy
2. rituximab
3. stop IS or reduce below range

Burkitt or Hodgkin’s Lymphoma

Stop or reduce IS

Conventional dose chemotherapy treatment

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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.


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Evidence Based Clinical Care Guideline (EBCG) For Management of EBV


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Evidence Based Clinical Care Guideline (EBCG) For Management of EBV

Guideline 18


53. **Local Consensus:** During guideline development timeframe. ed., [5]  


Evidence Based Clinical Care Guideline (EBCG) For Management of EBV


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