Provincial Clinical Knowledge Topic
Post-transplant lymphoproliferative disorder (PTLD), Pediatric – Inpatient
V 1.0

Revision History

Version	Date of Revision	Description of Revision	Revised By
1.0	December 2018	Topic Completed	See Acknowledgements

Important Information Before you Begin

The recommendations contained in this knowledge topic have been provincially adjudicated and are based on best practice and available evidence. Clinicians applying these recommendations should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care. This knowledge topic will be reviewed periodically and updated as best practice evidence and practice change.

The information in this topic strives to adhere to Institute for Safe Medication Practices (ISMP) safety standards and align with Quality and Safety initiatives and accreditation requirements such as the Required Organizational Practices. Some examples of these initiatives or groups are: Health Quality Council Alberta (HQCA), Choosing Wisely campaign, Safer Healthcare Now campaign etc.

This topic is based on the following guideline(s):

1. Cincinnati Children's Hospital Medical Center 2008 (Updated 2011). Evidence Based Clinical Practice Guideline Management of EBV-Associated Post- Transplant Lymphoproliferative Disease (PTLD) in Solid Organ Transplant

2. National Comprehensive Cancer Network Clinical Practice Guideline in Oncology. Non-Hodgkin's Lymphomas (2015)

3. Alberta Bone Marrow and Blood Cell Transplant Program: Standard Practice Manual

Rationale

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphoid neoplasms associated with immunosuppression following solid organ transplantation (SOT) or allogeneic hematopoietic stem cell transplant (HSCT). The majority of PTLD following both allogeneic HSCT and SOT are of B-cell origin and are usually associated with Epstein Barr virus (EBV).[3] Early PTLD are usually associated with concomitant detection of EBV DNA in blood samples in pediatrics, whereas late PTLD often present with no EBV DNA in blood.[6]

PTLD rates are reported to be higher in pediatric transplant recipients than in adult transplant recipients.[7] The incidence of PTLD following allogeneic HSCT ranges from 1 to 3 %. The incidence of PTLD in children following SOT ranges from 1 to 20 % depending upon the type of organ transplant.[8]

After SOT, PTLD generally originates in cells that are recipient in origin, although it has been found to originate in donor cells after liver transplantation. Most frequently PTLD presents in the first year post transplant however it can also have late onset. The incidence of PTLD varies depending on several factors: type of organ transplant (e.g. highest risks in bowel, lung-heart/lung transplant), EBV serology mismatch (i.e. negative recipient/positive donor), cytomegalovirus (CMV) serology mismatch (i.e. negative recipient/positive donor), human leukocyte antigen (HLA) mismatch and anti-T-cell therapy (e.g. anti-thymocyte globulin [ATG] or anti-CD3 monoclonal antibody [OKT3]) for prevention or treatment of graft rejection, and for younger age.[7-14] Reported rates are higher in heart, heart-lung, and small bowel transplants compared with kidney and liver transplants. This presumably reflects, in part, the need for more intense immunosuppression to maintain certain types of allografts. In terms of lymphoproliferative disease occurring within the allograft itself, this also depends on the type of graft. The lungs are frequently a site of involvement in patients undergoing heart-lung or heart-alone transplantation. Similarly, in small bowel transplants, the grafted bowel is commonly a site of PTLD. In cardiac transplants, the heart itself seldom is involved.[9,11,15,16]

In contrast to SOT, PTLD after HSCT is almost exclusively of donor origin and develops during the first 2 to 3 months after transplant. This unique feature is a consequence of the profound T-cell–depleting conditioning regimen, leading to lack of EBV-specific T-cells and, therefore, the often rapid growth of an EBV-positive clone, even within the first weeks.[17] In patients post HSCT, factors associated with increased risk for PTLD include ex-vivo T-cell depletion of the allograft, unrelated or HLA-mismatched grafts, anti-T-cell therapy (e.g. antithymocyte globulin or anti-CD3 monoclonal antibody) for prophylaxis and treatment of graft-versus-host disease (GvHD), second transplant and immunocompromised recipient pre-transplant (i.e. Severe combined immunodeficiency [SCID]). Alemtuzumab is associated with low rates of PTLD (~2%), and this serotherapy is increasingly used as GVHD prophylaxis for non-malignant HSCT.[16,18]

The diagnosis and classification of PTLD can be challenging given the nonspecific clinical presentation and heterogeneity in histopathological and immunophenotypic presentations. There is now broad agreement that serial viral load monitoring is very helpful in defining the onset of primary EBV infection post transplantation (thus defining the patient as being at risk for PTLD), and in raising the suspicion of EBV disease/PTLD in the symptomatic patient. New-onset early PTLD in children is generally (though not universally) associated with very high peripheral blood EBV viral loads. Nevertheless, high EBV viral loads may occur in patients without symptoms at the time of primary infection, and in some patients, very high EBV viral

loads can persist for a long time. Thus high EBV viral loads are sensitive for the diagnosis of PTLD but not specific.

In the 2008 WHO classification, PTLD are classified into 4 major categories: early lesions, polymorphic PTLD, monomorphic PTLD and classical Hodgkin Lymphoma (cHL) type PTLD.[19] Note: Most recently the WHO 2016 is no longer using early lesions as part of the classification and has added three more categories instead: encompassing plasmacytic hyperplasia, infectious mononucleosis and florid follicular hyperplasia.[20] Since most of the evidence is based on previous nomenclature, the previous classification will be used to provide recommendations.[21]

Table 1. WHO Classification of PTLD (2008)

Category	Description
Early lesions	• Typically develop within a year of transplantation and are more common in transplant recipients who are EBV naïve. • Show oligo- or polyclonal proliferations of EBV-positive B-cells while the underlying tissue architecture is preserved. • Consist of 2 histological subtypes: plasmacytic hyperplasia and infectious mononucleosis-like PTLD.
Polymorphic PTLD	• Demonstrate oligo- or polyclonal B-cell proliferations, the infiltrating cells destroy the original architecture of the host tissue. • While polymorphic PTLD can easily be differentiated from early lesions in lymph nodes, this can be very difficult in extranodal PTLD.
Monomorphic PTLD (B- and T-/NK-cell types)	• Histology appears to be the most common subtype and can resemble Non-Hodgkin Lymphomas in immunocompetent patients, usually originating from B-cell. • Most monomorphic type B cell PTLD are EBV positive whereas T-cell origin PTLD are usually EBV negative.
Classical Hodgkin Lymphoma (cHL) type PTLD	• HL-like PTLD resembles Hodgkin Lymphoma same as in an immunocompetent host.

Source: Campo E, Swerdlow S, Harris N et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood 117:5019-5032, 2011.

It should be noted that exact classification in 1 of these 4 categories will not always be possible because of overlap between several categories or because PTLD can present as different morphologic subtypes within different locations in the body or even within a single biopsy sample. The latter finding is in concordance with the hypothesis that in some cases, there might be a progressive transition from early PTLD through polymorphic PTLD to monomorphic PTLD.[22,23]

Table 2. Important Definitions

Donor (D)	A human being, living or deceased, who is a source of cells, tissues or organs for the purpose of transplantation.[24]
Recipient (R)	The human being into whom allogeneic human cells, tissues or organs were transplanted.[24]
EBV viremia	EBV DNA detectible in blood by PCR analysis.[25]
Primary EBV infection	EBV detected (nucleic acid or serologically) in an EBV-seronegative patient. [25]
Recurrent EBV infection	Detection of EBV DNA in the blood in an EBV-seropositive patient.[25]
Prophylaxis	Any agent given to EBV-seropositive patient to prevent EBV DNA-viremia.[25]
Pre-emptive therapy	Drug or cellular therapy given to a patient with EBV DNA-emia to prevent EBV disease.[25]
Treatment of EBV disease/PTLD	Therapeutic interventions for patients with probable or proven EBV disease.[25]
Complete response (CR)	Complete disappearance of all clinical evidence of disease by physical examination, by imaging studies, by bone marrow biopsy (where indicated), by CNS evaluation (where indicated) and by biopsy where there is a residual abnormality on an imaging study.[26,27]
Partial response (PR)	Regression of measurable disease and no new sites.[27]
Stable disease (SD)	Ongoing clinical, histologic or radiologic evidence of disease despite treatment. Failure to attain CR/PR.[27]
Progressive disease (PD)	Increased involvement at the primary site and/or development of PTLD lesions at new sites. Any new lesion or increased from nadir by more or equal to 50%.[26,27]
Graft rejection	The immunological destruction of transplanted organs or tissues. The rejection may be based on both cell-mediated and antibody-mediated immunity against cells of the graft by a histoincompatible recipient. These findings are determined by allograft biopsy.

Fulminant PTLD	PTLD accompanied by fever, hypotension, and multiple organ involvement presenting with pancytopenia without detectable B-cell proliferation, liver impairment (usually coagulopathy but may also include transaminitis and/or hyperbilirubinemia), lungs (interstitial pneumonitis, with or without pleural effusions) or gastrointestinal tract hemorrhage.[26]
EBV specific Cytotoxic T-cells (EBV-CTL)	EBV-specific cytotoxic T-lymphocyte (CTL) lines that have been reactivated and expanded in vitro to prevent the development of post-transplant lymphoproliferative disease or treat pre-existing disease.[28]

Decision Making

Screening and Monitoring Patients Post-transplant

- Recipient and donor status at the time of the transplant should be determined to assess risk: serum EBV Viral Capsid Antigen immunoglobulin G (VCA IgG) and Immunoglobulin M (IgM) antibodies.[29]
- Whenever possible, EBV-negative recipients should receive grafts from EBV-negative donors.[30]
- Close monitoring for evidence of increased EBV-induced B-cell proliferation or EBV reactivation by measuring blood quantitative EBV polymerase chain reaction (PCR) at regular intervals after transplantation is required. The time intervals and duration of monitoring may vary depending on identified risk factors. Whole blood, plasma and serum are appropriate biological specimens for monitoring EBV DNA-viremia. In Alberta, whole blood sample is processed using Nucleic Acid Test (NAT) using RealStar EBV PCR kit from Altona diagnostics. The lower limit of detection is approximately 550 IU/mL.
- The monitoring of EBV copy numbers in the blood is useful in managing patients and alerting clinicians to the possible development of PTLD.[5]

Specific screening and monitoring based on graft:

1. **For Solid Organ Transplant (SOT)** suggested EBV PCR screening schedules[31]:
    a. **EBV-seronegative recipients (including all children less than 1 year of age regardless of their pre-transplant EBV serostatus)**
    First 1 year post transplant:
    EBV viral load should be obtained at least once a month for EBV R negative patients. While the D-/R- patient might be at decreased risk of developing EBV disease compared to D+/R-, they are still at increased risk relative to the R+ patient and therefore warrant close monitoring. Some centers may choose to measure EBV loads more frequently.

    Beyond 1st year post transplant:
    Selective monitoring, such as in those with persistently high viral loads or in those with higher than normal immunosuppression, may be performed based on center

preferences. Some centers recommend continued monitoring for an indefinite period for all patients.

b. Seropositive individuals (except for children less than 1 year of age)
These individuals are at lower risk of developing PTLD compared with their R- counterparts. For new immunosuppressive agents, with undetermined infectious diseases risk potential, selective monitoring may be considered. EBV viral loads should be determined for all recipients with symptoms of PTLD.

2. For Hematopoietic Stem Cell Transplantation (HSCT)

Alberta Provincial guidelines suggest:

- Use ProvLab assay expressing EBV DNA-viremia as number of genome copies IU/mL per mL whole blood.
- For allograft recipients, monitor weekly until 3 months and then monthly until 12 months post-transplant.
- For autograft recipients, do not monitor.
- If DNA-viremia greater than 30,000 IU/mL, watch for symptoms/signs of PTLD.
- If DNA-viremia greater than 300,000 IU/mL, treat PTLD preemptively.
- Monitor weekly for 4 weeks, then continue as per physician discretion.

The frequency of monitoring might be directed by the transplant team based on individual circumstances, for example in patients with rising EBV DNA-viremia. Longer period of monitoring is recommended in patients considered to have poor T-cell reconstitution: severe acute/chronic GvHD, haploidentical HSCT, T-cell depletion, conditioning with ATG/alemtuzumab, or early EBV reactivation[25,32]

Clinical Assessment of PTLD

Having a high index of suspicion and clinical vigilance is critical, because patients may present with nonspecific symptoms or systemic signs such as fever, unexplained weight loss, fatigue, lymphadenopathy, or hepatosplenomegaly that may otherwise not initially be suggestive of a diagnosis of PTLD. There are no symptoms specifically characteristic or indicative for PTLD. In general, a rising blood level of EBV viral load by quantitative polymerase chain reaction (PCR) measurement in this clinical setting should raise concern for PTLD.[33-35]

Involvement of the allograft tissue can cause declining organ function, and organ failure may be the presenting symptom.

Initial assessment should include:

1. **Detailed history:** Complete medical history including on-going symptoms, detailed history of EBV/CMV status of the donor and recipient at the time of transplant, immunosuppressive medications at the time of the transplant and at the time of presentation (at least 6 months), rejection events and the interventions required. In case of HSCT, detailed history should also include conditioning, pre-existing immunodeficiency, details about GVHD prophylaxis (medications currently or previously administered), and the presence of GVHD and its treatment.

2. **Physical exam:** Meticulous physical examination is required for clinical diagnosis and for possible identifiable lymph node/mass that can be accessible for biopsy. Also includes performance status.

   Most frequently reported clinical findings and symptoms of PTLD[36-38]
   - Fever is the most frequently reported symptom, alone or with other symptoms. PTLD must be suspected in patients with fever with no clear etiology.
   - Lymph node enlargement, lymphadenopathy, splenomegaly (33%)
   - Abdominal symptomatology (29%), including gastrointestinal (GI) disturbances - diarrhea, abdominal pain, GI bleeding, vomiting, anorexia, protein losing enteropathy, feeding intolerance, weight loss, intestinal ulcers, or bowel obstruction/perforation
   - Allograft dysfunction (11%): Allograft dysfunction may often be mistaken for rejection
   - Central nervous system (CNS) related symptoms (11%)
   - B symptoms may also occur (fever, weight loss, night sweats)

   Other symptoms may include:
   - Hypotension or septic-like syndrome
   - Infectious mononucleosis syndromes: sore throat, fatigue, malaise, anorexia, headache
   - Tonsillar hypertrophy, upper respiratory obstruction/sleep apnea, adenoidal hypertrophy
   - Respiratory symptoms: shortness of breath, cough, upper airway obstruction, wheezing or tachypnea
   - Hematological findings - unexplained anemia, cytopenias (possibly autoimmune), hemophagocytosis.
   - Hepatic or splenic enlargement, unexplained increased serum transaminases, ascites
   - Kidney dysfunction, kidney enlargement, proteinuria
   - Genitourinary (GU) or gynecological (GYN) disturbances: renal or ovarian dysfunction, vaginal bleeding
   - Rashes
   - Bone pain, joint pain or swelling

3. **Bloodwork:** Should include complete blood cell count, comprehensive chemistry panel including Lactate dehydrogenase **(**LDH), liver function (albumin, bilirubin, aspartate aminotransferase [AST] and alanine aminotransferase [ALT], gamma glutamyl-transferase [GGT], prothrombin time [INR], activated partial thromboplastin time [PTT]), EBV viral load, CMV viral load, Hepatitis B serology (baseline pre-rituximab) and immunoglobulins.

Diagnosis and Staging of PTLD

Diagnosis

The diagnosis of PTLD must be based on symptoms and/or signs consistent with PTLD together with detection of PTLD by an appropriate method applied to a specimen from the involved area (based on clinical findings and imaging). Diagnostic confirmation should include biopsy as it is the gold standard for diagnosis. Histology should be consistent with PTLD and must include histological examination with EBV detection. Expert review of the biopsy specimen is required since pathology interpretation can be challenging and have a significant impact in the treatment decision making.

Every effort should be made to obtain a tissue biopsy and only in exceptional circumstances where tissue biopsy is not possible, non-invasive methods will be accepted.

Non-invasive methods:

- Quantitative EBV DNA-viremia. A single elevated EBV PCR value is less informative than a trend of rising (or falling) values over time. A negative EBV PCR does not rule out the presence of PTLD[35]
- Radiological imaging: please see staging.

Biopsy

The use of the World Health Organization (WHO) criteria should be considered for biopsy and evaluation.[39]

Some patients may initially be too ill for surgical evaluation or biopsy and diagnosis is determined based on clinical assessment and radiological findings. **Fine needle aspiration is not an acceptable technique to determine diagnosis.** Core needle biopsy or excisional biopsy are acceptable techniques.

EBV detection requires in situ hybridization for the EBER transcripts or detection of viral antigens and should be performed on the biopsy specimen.[19,25]

Histopathology and adequate immunophenotyping are essential to confirm the diagnosis of PTLD. Immunophenotyping should include both B-cell and T-cell markers. Histopathology work-up should be directed by an expert pathologist and might include:[19,20,40]

- IHC panel: CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, ki-67, kappa, lambda.
- Cell surface marker analysis by flow cytometry: CD 3, CD5, CD7, 8, 9, 19, 20, 10, kappa, lambda.
- EBV virus evaluation by EBV-LMP1 or EBER-ISH
- Molecular analysis to detect: The lineage and clonality of the specimens will be determined by gene rearrangement analysis to determine Immunoglobulin (Ig) heavy chain gene and T-cell receptor (TCR) γ chain gene Analysis.[2]

Staging

Additional diagnostic testing can be required to obtain diagnosis and for evaluation of the extent of disease on:

1. **Radiologic evaluation:**
   - It is recommended that the use of radiographic imaging for PTLD diagnosis be limited to patients with clinical symptoms or detectable EBV DNA in the blood.[36]
   - Radiological evaluation includes 18 fluodeoxyglucose positron emission tomography (PET)/computerized tomography (CT), CT or magnetic resonance imaging (MRI/DWIBS MRI) of the head, neck, chest, abdomen, pelvis, looking for evidence of any abnormal nodal or extranodal masses. Radiological evaluation can also include chest radiographs and ultrasound as non-invasive follow up tests.
   - It is suggested to perform PET/CT as a baseline staging investigation; this test is complementary at initial staging of pediatric PTLD. PET/CT scanning can be helpful to guide biopsies, document nodal and extra nodal disease (PET-CT is superior to CT for extranodal disease) and assess response to therapy.[41-44] If PET/CT is not feasible, CT or DWIBS MRI neck, chest, abdomen and pelvis are appropriate.
   - CT head might be required if CNS involvement is suspected clinically. Consider MRI brain in consultation with radiology (e.g. focal neurological deficit).
   - PET/CT is the standard Diagnostic Imaging for PTLD. DWI MRI is being investigated as a possible substitution for PET/CT Imaging.

2. **Bone marrow aspirate and biopsy:** Obtaining bone marrow aspirate and biopsy may be appropriate to determine if marrow is involved in the disease process. Consider if there is evidence of cytopenias, lymphocytosis, or lymphoid blasts in the peripheral blood.[36] Also, may be required depending on the underlying specific diagnosis.

3. **Lumbar puncture:** Indicated by central nervous system signs/symptoms. If suspicion of CNS or neurological involvement exists, lumbar puncture should be performed for routine cerebrospinal fluid (CSF) evaluation and examination of the CSF for malignant cells. In addition to the standard tests, the fluid may also be analyzed using PCR for EBV DNA.

4. **Endoscopy/Bronchoscopy:** Consider if gastrointestinal or pulmonary symptoms are present. Endoscopy may be required to obtain tissue for diagnosis depending on the clinical presentation. It may also be required for ongoing follow up to assess response.

5. **Other ancillary tests that may be required prior to start of treatment:**
   - Echocardiogram
   - GFR

Management

Pre-emptive Treatment

Solid Organ Transplant (SOT)

- It is recommended to adopt in all transplant recipients clinical vigilance and close clinical monitoring for possible onset of tissue involvement or systemic symptoms of PTLD.[36]
- It is recommended that patients with detectable EBV DNA in blood and no clinical symptoms be maintained within protocol range of immunosuppression levels. Reduction of immunosuppression from standard protocols at this stage is controversial.[36] Some studies have shown to decrease incidence of PTLD when immunosuppression was

decreased with rising EBV DNA levels.[30,34] Any changes to immunosuppression should be done by primary SOT team to prevent complications of rejection.
- It is recommended to consider on an individual case basis the use of preemptive 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).[36]
- There is no data to support any positive impact of antiviral drugs on the development of EBV-PTLD. Antiviral drugs are not recommended for EBV prophylaxis.[45]
- Interferon and IVIG are not recommended for EBV prophylaxis.

Hematopoietic stem cell transplantation (HSCT)
- Some studies have shown a decreased incidence of PTLD when immunosuppression was decreased with rising EBV DNA levels.[25]
- Significant EBV DNA-viremia without clinical symptoms of EBV disease can be an indication for preemptive therapy with rituximab. No specific threshold of EBV DNA-viremia can currently be recommended for initiation of preemptive therapy.[25]
- Alberta BMT guidelines suggest: If EBV DNA-viremia >30,000 IU/mL, watch for symptoms/signs of post- transplant lymphoproliferative disorder (PTLD). If DNA viremia >300,000 IU/mL, recommended to treat PTLD preemptively with rituximab.
- Rituximab once weekly (1-4 doses) is recommended until EBV DNA-viremia negativity.[25] Rituximab can be associated with neutropenia and marrow suppression, which is undesirable and may pose risk to the HSCT allograft and long-term B-cell reconstitution, and so for this population it is suggested to provide the minimal number of doses to achieve negative EBV viral load in blood.
- Rituximab should be combined with reduction of immunosuppression if possible, in consultation with the transplant team.
- Consider use of prophylactic EBV-CTLs on clinical trial if available.[25]
- There is no data to support any positive impact of antiviral drugs on the development of EBV-PTLD. Antiviral drugs are not recommended for EBV prophylaxis.[25]
- Interferon and IVIG are not recommended for EBV prophylaxis.[25]

Treatment

*****Approach should be step-wise providing minimal effective therapy to prevent secondary organ damage, increased morbidity and mortality.**

The choice of therapy ideally attempts to balance the risk of life-threatening PTLD with the risk of allograft failure and treatment-related morbidity. In patients who have undergone solid organ transplantation (SOT), reduction of immunosuppression may risk allograft rejection. In addition, SOT recipients are often at greater risk for organ toxicity and opportunistic infections that may complicate chemotherapy administration. In hematopoietic stem cell transplantation (HSCT) patients with PTLD, reduction of immunosuppression may increase the risk of graft versus host disease.

The treatment approach for PTLD should involve a multidisciplinary team including: primary transplant team, pediatric oncologists, radiologists, infectious diseases and other allied health care professionals depending on the supportive care required.

Solid Organ Transplant:

Step 1) Reduction of Immunosuppression (RIS)

- Evidence supports continued use of RIS as initial therapy for most PTLD patients with the degree of reduction dependent on individual patient factors (e.g., risk of graft rejection, type of SOT, etc.); however RIS may be insufficient as a single therapeutic modality, especially for patients with multi-organ dysfunction, high disease burden and/or aggressive clinical disease in need of immediate therapeutic response.[8]
- Reduction of immunosuppression can cause allograft dysfunction or loss and is not always feasible depending on the grafted organ or clinical situation. 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.[36]
- It is recommended to decrease immunosuppressive treatment whenever possible as guided by primary transplant team. Very close monitoring is mandatory to recognize progressive disease and/or rejection as early as possible. Response to RIS therapy is variable and patients need to be closely monitored on a weekly based in case further therapy escalation is required.[38,46]
- This approach is the usual recommended approach in patients with early lesions and some cases of polymorphic PTLD. RIS may be sufficient to induce CR as a single therapeutic strategy in some patients.[17,47]
- Patients at high risk for rejection when immunosuppression is decreased should have other treatment options including Rituximab and/or chemotherapy (e.g.: multivisceral, lung and heart transplants).

Step 2) Rituximab

- Rituximab has become standard element of the treatment for CD20 positive PTLD. Rituximab has shown to be effective when used as monotherapy[48,49] or in combination with RIS.[50]
- Rituximab + RIS may not be sufficient for high grade or monomorphic PTLD
- It is recommended that rituximab treatment be considered as a first line for patients with poor clinical condition, multi-organ dysfunction at the same time immunosuppression is being reduced (if possible).
- It is recommended to use rituximab as a first line therapy for patients with high risk for rejection when immunosuppression is decreased (e.g., multi-visceral transplant, lung and heart transplant patients).
- Usual dosing of rituximab is 375 mg/m2 intravenously weekly for 4 weeks.[48]
- It is recommended to assess response at the end of 4 weeks (clinical and radiological). If obvious progression or no response, chemotherapy may be required to obtain remission.
- Extended administration for an additional 4 weeks may be considered in patients achieving a partial response.[40]
- Some patients will require chemotherapy if there is obvious clinical progression despite of use of Rituximab. Patients with high disease burden and/or aggressive clinical disease may also require chemotherapy.

Step 3) Low Dose Chemotherapy

- Consider treating patient on a clinical trial if available.

- Given the risk of treatment-related morbidity and mortality, this strategy is often reserved for patients with the following conditions:
    - PTLD refractory to first line treatment with rituximab monotherapy or rituximab + RIS
    - PTLD present with concurrent evidence of allograft rejection.
    - High disease burden and/or aggressive clinical disease.
- Low dose chemotherapy can be given concomitantly with rituximab.[26,51-53]
- Monomorphic PTLD is typically treated with low dose or conventional chemotherapy depending on the histopathology and institutional practice.
- Low dose chemotherapy may not be appropriate for treatment of Hodgkin and Non Hodgkin Lymphoma based on underlying pathology, including: Burkitt's lymphoma, CD20-negative PTLD and patients with CNS involvement (see Step 4).

Suggested Low Dose Chemotherapy

- If no clinical trial is available, suggest starting with low intensity chemotherapy.
  R-COP (rituximab, cyclophosphamide, prednisone) is the recommended initial chemo-immunotherapy drug combination[26]:
    - Rituximab (375 mg/m^2) to be given weekly x 3 weeks with chemotherapy every 21 days (4-6 cycles).
    - For cycles 1 and 2:
        - Cyclophosphamide 600 mg/m^2 IV in NaCl 0.9% or D5W over 30-60 minutes on day 1 of each cycle
        - Prednisone 1 mg/kg PO every 12 hours or methylprednisolone 0.8 mg/kg IV every 12 hours on days 1,2,3,4 and 5 of each cycle.
        - Rituximab 375 mg/m^2 IV in NaCl 0.9% on days 1, 8 and 15 of cycles 1 and 2.
        - Assess response after first 2 cycles of chemotherapy.
    - For cycles 3 – 6 continue cyclophosphamide and prednisone if patient had good response to initial 2 cycles of chemotherapy.

Step 4) Conventional Dose Chemotherapy

- Consider including patients in clinical trials if available.
- It is recommended that patients with PTLD refractory to low-dose chemotherapy, or patients with aggressive Burkitt[54] or T-cell/NK cell[55], receive standard lymphoma-specific chemotherapy regimens[56].
- Patients with Classical Hodgkin Lymphoma or Classical Hodgkin-like PTLD should be treated based on current treatment for Hodgkin lymphoma. Radiation guidelines should be followed based on stage and response to treatment as per protocol guidelines.
- Adjust chemotherapy dose based on specific drugs guidelines if there is an underlying kidney, liver or heart impairment. Consider dexrazoxane prophylaxis for patients who require anthracyclines.
- For CNS PTLD disease, treatment will be guided based on underlying diagnosis and disease extension. Treatment for PTLD affecting the central nervous system (CNS) is difficult because most drugs used in standard therapy (especially rituximab) do not sufficiently cross the blood-brain barrier.

Therapeutic options in EBV-PTLD in central nervous system include: rituximab +/- chemotherapy, rituximab systemic or intrathecal monotherapy, anti-EBV T-cell therapy, radiotherapy[8], or high dose chemotherapy.

Step 5) Other Therapies

- Surgical Resection: It is recommended that surgical resection of tumor masses be performed when a complete resection can be obtained with low risk of morbidity. Other adjuvant treatment (as described previously) is usually required to obtain CR.
- IVIG, interferon and antiviral agents are not recommended for therapy of PTLD.[8,36]
- Radiation: There is very limited data on the significance of radiation therapy in the treatment of pediatric PTLD. In first-line treatment, cranial irradiation for CNS-PTLD may represent curative treatment elements. However, radiotherapy in pediatric PTLD patients is usually considered only as second line treatment, both as part of salvage concepts and in palliative care situations.[8]

Hematopoietic Stem Cell transplantation (HSCT)

First line therapy in EBV-PTLD[25]:
Strongly recommend to have radiographic and/or histopathologic confirmation prior to start of treatment to differentiate PTLD from EBV viremia.

a. Rituximab, 375 mg/m^2 intravenously, once weekly for 4 weeks.
b. Reduction of immunosuppressive therapy combined with rituximab should always be considered, if possible[35,57]
c. Cellular therapy as adoptive immunotherapy with in vitro generated donor or third-party EBV-specific CTL, if clinical trial available.[28,58,59]

Second line therapy in EBV-PTLD[25]:
Second line therapy should be used if no response to rituximab with immunosuppression taper in 2-4 weeks.[18]

d. Cellular therapy (EBV specific-CTLs if clinical trial available[28,58] or Donor Lymphocyte Infusion (DLI)).[25]
e. Chemotherapy +/- rituximab is a potential option after failure of other methods. Chemotherapy should be based on specific pathology. Starting low dose chemotherapy and escalating if there is evidence of progressive disease as previously described is suggested.

Supportive Care Recommendations:

- Close monitoring for tumor lysis syndrome at diagnosis and initiation of treatment in patients with significant disease burden or turnover.
- Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary.
- Pneumocystis pneumonia (PJP) prophylaxis should be given to patients receiving chemotherapy. *Pneumocystis jirovecci Pneumonia (PJP)*

Prophylaxis, Pediatric Oncology and Blood and Marrow Transplant – All Locations clinical knowledge topic currently under development – refer to local institutional practices until provincial content available. Begin prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMZ), 5 mg trimethoprim/m2 /day PO BID with maximum dose of 320mg TMP per day at the start of therapy. Give on 2 - 3 consecutive days each week. Continue for at least 6 months of treatment. TMP/SMZ prophylaxis should be avoided in patients with a history of TMP/SMZ-related myelosuppression. Pentamidine should be given to patients not receiving TMP/SMZ.

- It is recommended that all patients undergoing PTLD treatment have serum immunoglobulin G (IgG) levels monitored at monthly intervals, particularly in those receiving rituximab or chemotherapy.
- It is recommended that intravenous immunoglobulin (IVIG) 400mg/kg once a month be given if hypogammaglobinemia (IgG<4.0 g/L) is detected in order to decrease risk of infection.[18]

Post Therapy Monitoring

- It is recommended that patients who have completely responded to therapy be monitored for recurrent PTLD and therapy-related complications such as hypogammaglobinemia, infection and rejection.
- Monitoring might reasonably include blood EBV monitoring by PCR with surveillance radiographic studies as clinically indicated. Evidence supporting specific monitoring approaches is lacking.
- We suggest every 2 week EBV monitoring by PCR for 3 months, then monthly during first year after cessation of therapy.[36] Clinical evaluation every 3 months for first year, every 4 months for second year, every 6 months for third year, then as clinically indicated. Consider radiological imaging including US and Chest X rays for follow up if required. Consider repeating PET/CT scan only if patient has ongoing residual disease or is clinically symptomatic.
- Consider long term follow-up for patients that have received chemotherapy.

Re-initiation of Immune Suppression

- Re-escalation of immunosuppressive therapy should be individualized taking into account the extent of initial RIS and the nature of the organ allograft. These decisions should be made in conjunction with the transplant team.
- Use T-cell antibody therapy such as antithymocyte globulin (ATG) with extreme caution in patients with PTLD or history of PTLD.[36]
- Consider the use of sirolimus when resuming immunosuppressive therapy because of the antiproliferative and autophagic role of mammalian target of rapamycin (mTOR) inhibition.[60]

Name of Order Set: Post-transplant lymphoproliferative disorder (PTLD) Screening and Monitoring Pediatric Order Set

Order Set Keywords: Epstein-Barr Virus, PTLD, SOT, Solid Organ Transplant, Hematopoietic Stem Cell Transplant, HSCT

Laboratory Investigations

At time of transplant (*required in both recipient and donor*):

- ☐ Epstein-Barr Virus Antibody Panel
- ☐ Epstein-Barr Virus Viral Load – Blood

Post-transplant:

Epstein-Barr Virus Seronegative solid organ transplant recipients:

- ☐ Epstein-Barr Virus Viral Load – Blood every month until 1 year post transplant

For Hematopoietic Stem Cell Transplant allograft recipients:

- ☐ Epstein-Barr Virus Viral Load – Blood every week for 12 weeks and then monthly until 1 year post transplant

Name of Order Set: Post-transplant lymphoproliferative disorder (PTLD) Assessment, Diagnosis and Staging Pediatric Order Set

Order Set Keywords: PTLD, Post-transplant, SOT, Solid Organ Transplant, Hematopoietic Stem Cell Transplant, HSCT

Laboratory Investigations

Hematology

- ☐ Complete Blood Count with differential

Chemistry

- ☐ Electrolytes (NA, K, Cl, CO2)
- ☐ Creatinine LEVEL
- ☐ Glucose Random LEVEL
- ☐ Urea
- ☐ Magnesium (Mg) LEVEL
- ☐ Phosphate LEVEL
- ☐ Calcium (Ca) LEVEL
- ☐ Lactate dehydrogenase (LD)
- ☐ Albumin LEVEL
- ☐ Alkaline Phosphatase (ALP)
- ☐ Alanine aminotransferase (ALT)
- ☐ Bilirubin Total
- ☐ Gamma-glutamyl transferase (GGT)
- ☐ Lipase

- ☐ Protein Total
- ☐ Urate LEVEL
- ☐ Creatinine Clearance/GFR prior to start chemotherapy

Coagulation
- ☐ INR
- ☐ PTT

Viral Serology
- ☐ Epstein-Barr Virus Viral Load – Blood
- ☐ Cytomegalovirus Viral Load – Blood
- ☐ Hepatitis B Surface Antigen
- ☐ Anti-HBs (Hepatitis B Surface Antibody)
- ☐ Anti-HBc Total

Immunoglobulins
- ☐ Immunoglobulin G

Cerebrospinal Fluid
If suspicion of Central Nervous System or neurological involvement exists, lumbar puncture should be performed for routine cerebrospinal fluid (CSF) evaluation and examination of the CSF for malignant cells. In addition to the standard tests, the fluid may also be analyzed using PCR for EBV DNA.
- ☐ CSF Cell Count
- ☐ Cytopathology request
- ☐ CSF Protein
- ☐ CSF Glucose
- ☐ CSF Immunoglobulin G
- ☐ CSF Infection Panel (Viral)
- ☐ EBV viral load PCR

Consider if ongoing cytopenias or documented monomorphic PTLD for staging.
- ☐ Bone Marrow Aspirate and Biopsy

Diagnostic Investigations
Radiographic imaging for PTLD diagnosis should be limited to patients with clinical symptoms or detectable EBV DNA in the blood. PET/CT F-18 FDG Tumor Imaging should be used as baseline for staging investigations and can be helpful to guide biopsies, document nodal and extra nodal disease and assess response to therapy:
- ☐ PT Whole Body (tracer F18-FDG)

If PET/CT is not feasible consider CT or magnetic resonance imaging (MRI) scan. Also consider CT Head and/or MR brain if Central Nervous System is suspected clinically (e.g. focal neurological deficit):
- ☐ CT Head
- ☐ CT Soft Tissue Neck
- ☐ CT Chest Abdomen & Pelvis
- ☐ MR Brain

Prior to treatment (if anthracyclines are required)
- ☐ Echocardiogram

Consults

- ☐ Pediatric Oncology. Reason for referral_____.
- ☐ Pediatric Anesthesia. Reason for referral_____.

Consider referral to Pediatric Gastroenterologist if gastrointestinal or pulmonary symptoms are present. Endoscopy may be required to obtain tissue for diagnosis depending on the clinical presentation.

- ☐ Pediatric Gastroenterologist. Reason for referral_____.
- ☐ Pediatric Surgery. Reason for referral_____.
- ☐ Pediatric Radiology. Reason for referral_____.

Name of Order Set: Rituximab Infusion Pediatric Order Set

Order Set Requirements: Weight, BSA
Order Set Keywords: PTLD, Post-transplant, rituximab

Medications

- ☑ acetaminophen _____mg (15mg/kg/dose; maximum 650 mg) PO once 60 minutes pre-riTUXimab **AND THEN** acetaminophen _____mg (15mg/kg/dose; maximum 650 mg) PO every 4 hours PRN
- ☑ diphenhydrAMINE _____mg (1 mg/kg/dose; maximum dose 50 mg) IV once 45 minutes pre-riTUXimab **AND THEN** diphenhydrAMINE _____mg (1 mg/kg/dose; maximum dose 50 mg) IV every 6 hours PRN

If a patient is currently receiving steroids, they should be used as the pre-medication instead of hydrocortisone. Premedication with corticosteroids should not be systematic. Administration will depend on the recommendations of the protocol being followed or if administration is clinically indicated.

- ☐ hydrocortisone sodium succinate _____ mg (1 mg/kg/dose) IV once 30 minutes pre-riTUXimab

First riTUXimab infusion:

- ☐ riTUXimab _____ mg (375 mg/m2/dose) IV once. Refer to local institutional practices for riTUXimab infusion protocol/ administration guidelines.

Subsequent riTUXimab infusions, if first infusion tolerated.

- ☐ riTUXimab _____ mg (375 mg/m^2/dose) IV once weekly for 3 weeks in Solid Organ Transplant. *For Hematopoietic Stem Cell Transplant (HSCT) patients reassess weekly prior to dose of rituximab.* Refer to local institutional practices for riTUXimab infusion protocol/ administration guidelines.

Analytics

1. Epstein-Barr Virus Viral Load – Blood level over time

References

1. Schubert S, Renner C, Hammer M et al. Relationship of immunosuppression to Epstein-Barr viral load and lymphoproliferative disease in pediatric heart transplant patients. *J Heart Lung Transplant* 2008;27(1):100-5.
2. Vakiani E, Basso K, Klein U et al. Genetic and phenotypic analysis of B-cell post-transplant lymphoproliferative disorders provides insights into disease biology. *Hematol Oncol* 2008;26(4):199-211.
3. Webber SA,; Naftel DC, Fricker FJ et al. Lymphoproliferative disorders after paediatric heart transplantation: a multi-institutional study. *Lancet* 2006;367(9506):233-9.
4. Schubert S, Abdul-Khaliq H, Lehmkuhl HB et al. Diagnosis and treatment of post-transplantation lymphoproliferative disorder in pediatric heart transplant patients. Pediatr Transplant 2009;13(1):54-62.
5. Holman CJ, Karger AB, Mullan BD et al. Quantitative Epstein-Barr virus shedding and its correlation with the risk of post-transplant lymphoproliferative disorder. *Clin Transplant* 2012;26(5):741-7.
6. Preiksaitis J, Pang, X, Fox J et al. Interlaboratory comparison of epstein-barr virus viral load assays. *Am J Transplant* 2009;9(2):269-79.
7. Dharnidharka, VR., and Araya, CE. Post-transplant lymphoproliferative disease. *Pediatr Nephrol* 2009;24(4):731-6.
8. Mynarek M, Schober T, Behrends U et al. Posttransplant Lymphoproliferative Disease after Pediatric Solid Organ Transplantation. *Clin Dev Immuno.* 2013;2013:1-14.
9. Swerdlow AJ, Higgins CD, Hunt BJ, Thomas JA, Burke, MM, Crawford DH, and Yacoub MH: Risk of lymphoid neoplasia after cardiothoracic transplantation. a cohort study of the relation to Epstein-Barr virus. Transplantation, 69(5): 897-904, 2000, [3a]
10. Fernandez MC, Bes D, De Davila M et al. Post-transplant lymphoproliferative disorder after pediatric liver transplantation: Characteristics and outcome. *Pediatr Transplant* 2009;13(3):307-10.
11. Evens A, David K, Helenowski I et al. Multicenter Analysis of 80 Solid Organ Transplantation Recipients with Post-Transplantation Lymphoproliferative Disease: Outcomes and Prognostic Factors in the Modern Era. *J Clin Oncol* 2010;28:1038-1046.
12. Katz, B. Z.; Pahl, E.; Crawford, S. E et al. Case-control study of risk factors for the development of post-transplant lymphoproliferative disease in a pediatric heart transplant cohort. *Pediatr Transplant* 2007;11(1): 58-65.
13. Mendoza, F, Kunitake H, Laks et al. Post-transplant lymphoproliferative disorder following pediatric heart transplantation. *Pediatr Transplant* 2006;10(1):60-6.
14. Narkewicz MR, Green M, Dunn S et al. Decreasing incidence of symptomatic Epstein-Barr virus disease and posttransplant lymphoproliferative disorder in pediatric liver transplant recipients: report of the studies of pediatric liver transplantation experience. *Liver Transpl* 2013;19(7):730-34.
15. Jacobson CA, LaCasce AS. Lymphoma: risk and response after solid organ transplant. *Oncology* 2010;24:936-944.

16. Wagner HJ, Rooney CM, Heslop HE et al. Diagnosis and treatment of PTLD after HSCT. *Biol Blood Marrow Transplant* 2002;8(1):1-8.
17. Heslop HE. How I treat EBV lymphoproliferation. *Blood* 2009;114(19):4002-4008.
18. Alberta Bone Marrow and blood cell transplant program: Standard practice manual. *Alberta Health Services,* 2017.
19. Campo E, Swerdlow S, Harris N et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood* 2011;117:5019-5032.
20. Swerdlow S, Campo E, Pileri S et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016; 127:2375-2390.
21. Swerdlow SH, Webber SA, Chadburn A: Post-transplant lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris NL, et al., eds.: *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press, *2008:*343-9.
22. Taoka K, Nannya Y, Yamamoto G, et al. Progressive transition of Epstein-Barr virus associated lymphoproliferative disease subtypes with the development of lung cancer. *Am J Hematol* 2009;84(9):600-603.
23. Parker A, Bowles K, Bradley A et al. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients – BCSH and BTS Guidelines. *Br J Haematol* 2010;149:693–705.
24. World Health Organization. Global Glossary of Terms and Definitions on Donation and Transplantation. *World Health Organization*. Geneva, Nov 2009.
25. Styczynski J, Van der Velden W, Fox C et al. Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. *Haematologica* 2016;101(7):803-11.
26. Gross TG, Orjuela MA, Perkins EL et al., Low-dose chemotherapy and rituximab for posttransplant lymphoproliferative disease (PTLD): A Children's Oncology Group Report. *Am J Transplant* 2012;12:3069–3075.
27. Cheson BD. New response criteria for lymphomas in clinical trials. Ann Oncol 2008;19 (Suppl 4):iv35–iv38.
28. Bollard CM, Gottschalk S, Torrano V, et al.: Sustained complete responses in patients with lymphoma receiving autologous cytotoxic T lymphocytes targeting Epstein-Barr virus latent membrane proteins. *J Clin Oncol* 2014;32(8):798-808.
29. Walker RC, Paya CV, Marshall WF et al. 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* 1995;14(2):214-21.
30. Glotz D, Chapman JR, Dharnidharka VR et al. The Seville expert workshop for progress in posttransplant lymphoproliferative disorders. *Transplantation* 2012;94(8):784-93.
31. Humar A and Michaels M. American Society of Transplantation for Screening, Monitoring and Reporting of Infectious Complications in Immunosuppression Trials in Recipients of Organ Transplantation. *Am J Transplant* 2006;6:262–274.
32. Faraci M, Caviglia I, Morreale G et al. Viral-load and B-lymphocyte monitoring of EBV reactivation after allogeneic hemopoietic SCT in children. *Bone Marrow Transplant* 2010;45(6):1052-5.
33. Green M, Michaels MG, Webber SA et al. The management of Epstein-Barr virus associated post-transplant lymphoproliferative disorders in pediatric solid-organ transplant recipients. *Pediatr Transplant* 1999;3(4): 271-81.
34. Lee TC., Savoldo B, Rooney CM et al.: Quantitative EBV viral loads and immunosuppression alterations can decrease PTLD incidence in pediatric liver transplant

recipients. *Am J Transplant* 2005;5(9):2222-8.
35. Meerbach A, Wutzler P, Hafer R. et al. Monitoring of Epstein-Barr virus load after hematopoietic stem cell transplantation for early intervention in post-transplant lymphoproliferative disease. *J Med Virol* 2008;80(3):441-54.
36. Evidence based clinical practice guideline for management of EBV-associated post-transplant lymphoproliferative disease (PTLD) in solid organ transplant. (EBGL). *Cincinnati Children's Hospital Medical Center*. Published 2003 (revised 2011).
37. Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. *Crit Rev Oncol Hematol* 2005;56(1):155-67.
38. Al-Mansour Z, Nelson B, Evens AM et al. Post-Transplant Lymphoproliferative Disease (PTLD): Risk Factors, Diagnosis, and Current Treatment Strategies. *Curr Hematol Malig Rep* 2013;8(3): 173-183.
39. Swerdlow, SH, International Agency for Research on Cancer, World Health Organization. (2017). *WHO classification of tumours of haematopoietic and lymphoid tissues*. Lyon: International Agency for Research on Cancer.
40. National Comprehensive Cancer Network Clinical Practice Guidelines. Non-Hodgkin's Lymphoma. PTLD. Version 2, 2015.
41. Von Falck C, Maecker B, Schirg et al. 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* 2007;63(3):427-35.
42. Borhani A, Hosseinzadeh K, Almusa O et al. Imaging of Post transplantation Lymphoproliferative Disorder after Solid Organ Transplantation. *RadioGraphics* 2009;29:981-1002.
43. McCormack L., Hany T I, Hubner, M et al. How useful is PET/CT imaging in the management of post-transplant lymphoproliferative disease after liver transplantation? *Am J Transplant* 2006;6(7):1731-6.
44. O'Conner AR, and Franc BL. FDG PET imaging in the evaluation of post-transplant lymphoproliferative disorder following renal transplantation. *Nucl Med Commun* 2005;26(12): 1107-11.
45. AlDabbagh MA, Gitman MR, Kumar D et al. The Role of Antiviral Prophylaxis for the Prevention of Epstein–Barr Virus–Associated Post-transplant Disease in Solid Organ Transplant Recipients: A Systematic Review. *Am J Transplant* 2016;20:1-12.
46. Caillard S, Dharnidharka V, Agodoa L et al. Post-transplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. *Transplantation* 80(9):1233–1243, 2005.
47. Starzl TE, Nalesnik MA and Porter K. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. *Lancet* 1984;1(8377):583–587.
48. Choquet S, Leblond V, Herbrecht R et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. *Blood* 2006;107(8):3053–3057.
49. Serinet MO, Jacquemin E, Habes D et al. Anti-CD20 monoclonal antibody (rituximab) treatment for Epstein-Barr virus-associated, B-cell lymphoproliferativedisease in pediatric liver transplant recipients. *J Pediatr Gastroenterol Nutr* 2002;34(4):389–393.
50. Messahel B, Taj MM, Hobson R. et al. Single agent efficacy of rituximab in childhood immunosuppression related lymphoproliferative disease: a United Kingdom Children's Cancer Study Group (UKCCSG) retrospective review. *Leuk Lymphoma* 2006;47(12):2584-9.burn
51. Gallego S, Llort A, Gros L et al. Post-transplant lymphoproliferative disorders in children: The role of chemotherapy in the era of rituximab. *Pediatr Transplant* 2010;14: 61–66.

52. Gross TG, Bucuvalas J, Park J et al. Low dose chemotherapy for the treatment of refractory post-transplant lymphoproliferative disease in children. *J Clin Oncol* 2005;23:6481-6488.
53. Gupta S, Fricker FJ, Gonzalez-Peralta R et al. Post-transplant lymphoproliferative disorder in children: recent outcomes and response to dual rituximab/low-dose chemotherapy combination, *PediatrTransplant* 2010;14(7):896–902.
54. Picarsic J, Jaffe R, Mazariegos G et al. Post-transplant Burkitt lymphoma is a more aggressive and distinct form of post-transplant lymphoproliferative disorder. *Cancer* 2011;117(19):4540–4550.
55. Yang F, Li Y, Braylan R, et al. Pediatric T-cell post-transplant lymphoproliferative disorder after solid organ transplantation. *Pediatr Blood Cancer* 2008;50 (2):415-8.
56. Kampers J, Orjuela-Grimm M, Schober T et al. Classical Hodgkin lymphoma-type PTLD after solid organ transplantation in children: a report on 17 patients treated according to subsequent GPOH-HD treatment schedules. *Leuk Lymphoma* 2007;58(3):633-638.
57. Styczynski J, Gil L, Tridello G et al. Response to rituximab-based therapy and risk factor analysis in Epstein Barr Virus-related lymphoproliferative disorder after hematopoietic stem cell transplant in children and adults: a study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Clin Infect Dis* 2013;57(6):794-802.
58. Burnsa DA and Crawford DH. Epstein–Barr virus-specific cytotoxic T-lymphocytes for adoptive immunotherapy of post-transplant lymphoproliferative disease. *Blood Rev* 2004;18:193-209.
59. Haque, T. et al.: Allogeneic cytotoxic T-cell therapy for EBV-positive post transplantation lymphoproliferative disease: results of a phase 2 multicenter clinical trial. *Blood* 2007;110(4): 1123-31.
60. Kauffman HM.; Cherikh WS.; Cheng et al. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation* 2005;80(7):883-9.

Additional Readings and General References

Choquet S, Trappe R, Leblond V et al. CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. *Haematologica* 2007;92(2):273-4.

Dierickx D, Tousseyn T et Gheysens O. How I treat post transplant lymphoproliferative disorders. *Blood* 2015;126:2274-2283.

Dierickx D, Tousseyn T, Requilé A, et al. The accuracy of positron emission tomography in the detection of post transplant lymphoproliferative disorder. *Haematologica 2013;*98(5):771-775.

Dierickx D, Tousseyn T, Sagaert X, et al. Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinic pathological characteristics and prognostic factors. *Leuk Lymphoma* 2013;54(11):2433-2440.

Gross TG, Savoldo B, Punnett A. Posttransplant lymphoproliferative diseases. *Pediatr Clin N Am* 2010;57(2):481-503.

Hayashi, R. J. et al.: Posttransplant lymphoproliferative disease in children: correlation of histology to clinical behavior. *J Pediatr Hematol Oncol* 2001;23(1):14-8.

McDiarmid SV, Jordan S, Kim GS et al. Prevention and preemptive therapy of post-transplant lymphoproliferative disease in pediatric liver recipients. *Transplantation* 1998;66(12):1604-1.

Opelz G, Döhler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant* 2004;4(2):222-230.
Panagiotidis E, Quigley AM, Pencharz D, et al. (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in diagnosis of post-transplant lymphoproliferative disorder. *Leuk Lymphoma* 2014;55(3):515-519.

Savoldo B, Goss JA, Hammer MM. Treatment of solid organ transplant recipients with autologous Epstein Barr virus-specific cytotoxic T lymphocytes (CTLs). *Blood* 2006;108(9): 2942-9.

Schober T, Framke T, Kreipe H. Characteristics of early and late PTLD development in pediatric solid organ transplant recipients. *Transplantation* 2013;95(1):240-6.

Stevens S, Verschuuren E, Verkuujlen S, et al. Role of Epstein-Barr virus DNA load monitoring in prevention and early detection of post-transplant lymphoproliferative disease. *Leuk Lymphoma* 2002;43(4):831-40.

Takehana CS, Twist CJ, Mosci C, Quon A, Mittra E, Iagaru A. (18)F-FDG PET/CT in the management of patients with post-transplant lymphoproliferative disorder. *Nucl Med Commun* 2014;35(3):276-281.

Trappe, R.: CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. *Haematologica* 2007;92(2):273-4.

Tsao L, Hsi ED. The clinicopathologic spectrum of post-transplantation lymphoproliferative disorders. *Arch Pathol Lab Med* 2007;131(8):1209-1218.

Urschel S, Altamirano-Diaz L and West L. Immunosuppression Armamentarium in 2010: Mechanistic and Clinical Considerations. *Pediatr Clin N Am* 2010;57:433-457.

Vali R, Punnett A, Bajno L et al. The value of 18F-FDG PET in pediatric patients with post-transplant lymphoproliferative disorder at initial diagnosis. *Pediatr Transplant* 2015;19(8):932-9.

Wistinghausen B, Gross TG, Bollard C. Post-transplant lymphoproliferative disease in pediatric solid organ transplant recipients. *Pediatr Hematol Oncol* 2013;30(6):520-31.

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