



Complete Summary

GUIDELINE TITLE

Evidence based clinical practice guideline for management of post transplant lymphoproliferative disease (PTLD) following solid organ transplant.

BIBLIOGRAPHIC SOURCE(S)

Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for management of post transplant lymphoproliferative disease (PTLD) following solid organ transplant. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2003 Feb 4. 14 p. [187 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [September 11, 2008, Rituxan \(Rituximab\)](#): Genentech informed healthcare professionals of revisions to prescribing information for Rituxan regarding a case of progressive multifocal leukoencephalopathy (PML) leading to death in a patient with rheumatoid arthritis who received Rituxan in a long-term safety extension clinical study.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

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SCOPE

DISEASE/CONDITION(S)

Post transplant lymphoproliferative disease (PTLD) following solid organ transplant

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Risk Assessment
Treatment

CLINICAL SPECIALTY

Family Practice
Hematology
Infectious Diseases
Pediatrics
Surgery

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses
Patients
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

These guidelines are offered to establish some consistency and provide scientific evidence, where evidence is available, in the management of post transplant lymphoproliferative disease (PTLD)

TARGET POPULATION

Post solid organ transplant patients from birth to 18 years of age

These guidelines are not intended for use in the following:

- Non-transplant patients
- Patients with Epstein Barr Virus (EBV)-negative post transplant lymphoproliferative disease (PTLD).

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Assessment

1. Laboratory evaluation of serum Epstein-Barr virus (EBV) VCA IgG (Viral Capsid Antigen IgG) and IgM antibodies of recipient and donor at the time of transplantation to assess risk
2. Monitoring of all patients for evidence of EBV replication at regular intervals for six months after transplantation
3. Clinical assessment through high vigilance and evaluation of symptoms that would indicate EBV infection or post transplant lymphoproliferative disease (PTLD)
4. Biopsy of organ/site once symptoms of PTLD are assessed and identified
5. In situ hybridization by Epstein Barr early response (EBER) on the biopsy specimen
6. Additional diagnostic tests to determine extent of disease, including bone marrow, lumbar puncture, and/or radiologic evaluation

Note: Routine use of imaging is not recommended to screen for PTLD.

7. Contrast enhanced computed tomography (CT)
8. Complete survey of head and neck, chest, abdomen, and pelvis

Treatment

1. Reduction of immunosuppression following diagnosis of PTLD
2. Anti-CD 20 monoclonal antibody (Rituximab) if there is evidence of persistent or progressive PTLD without evidence of allograft rejection
3. Low-dose cyclophosphamide and corticosteroids
4. In patients with evidence of allograft rejection, restarting of prior immunosuppression dosing
5. Restarting of calcineurin inhibitors
6. Surgical resection of tumor masses for those in the small bowel

MAJOR OUTCOMES CONSIDERED

- Morbidity and mortality due to allograft rejection secondary to reduced immunosuppression
- Progression or regression of post transplant lymphoproliferative disease

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic and critical literature reviews, using a grading scale, and examined current local clinical practices.

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.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines have been reviewed and approved by clinical experts not involved in the development process, senior management, Risk Management & Corporate Compliance, the Institutional Review Board, other appropriate hospital committees, and other individuals as appropriate to their intended purposes.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each recommendation is followed by evidence grades (A-X) identifying the type of supporting evidence. Definitions of the evidence grades are presented at the end of the "Major Recommendations" field.

Screening

Laboratory evaluation

1. It is recommended that serum Epstein Barr Virus (EBV) VCA IgG (Viral Capsid Antigen IgG) and IgM antibodies be obtained and evaluated in the recipient and donor at the time of transplantation to assess risk (see Table 1 in the original guideline document Straus et al. 1993 [S].) (Ho et al.,1988 [D];Walker et al., 1995b [D]; Aris et al.,1996 [D]; Local Expert Consensus [E])

EBV-naive is an individual with no known or demonstrable serologic evidence of prior infection with EBV.

Primary EBV Infection is the detection of serum anti-VCA IgM antibodies followed by a rise in the VCA-IgG or a positive EBV polymerase chain reaction (PCR) in a previously EBV-naive (unexposed) individual.

EBV Reactivation is the detection of anti-VCA IgM antibodies or positive serum EBV PCR in a patient with previous latent infection.

Latent (Long Past) EBV Infection is the detection of serum anti-VCA IgG antibodies and anti-Epstein Barr nucleus antigen (EBNA) in the absence of IgM antibody titer and/or a positive EBV PCR in a patient who has not received passive immunoglobulin in the previous three months.

2. It is recommended that all patients be monitored for evidence of EBV viral replication (McDiarmid et al., 1998 [C]) by measuring whole blood quantitative EBV PCR (Baldanti et al., 2000 [C]; Rowe et al., 1997 [C]; Local Expert Consensus [E]) at regular intervals for six months after transplantation (Swerdlow et al., 2000 [D]) (see Table 2 in the original guideline document) (Local Expert Consensus [E]). The time intervals may vary depending on identified risk factors. Patients with a significant persistent increase of circulating EBV from baseline have an increased risk for post transplant lymphoproliferative disease (PTLD) (Baldanti et al., 2000 [C]; Rowe et al. 1997 [C]; Swerdlow et al., 2000 [D]).

Note 1: The positive predictive value of this PCR assay in the absence of symptoms is yet to be defined.

Note 2: It is recognized that the absolute copy number varies by assay type, making comparison of specific values difficult (Vajro et al., 2000 [C]; Rogers et al., 1998 [D]; McDiarmid et al., 1998 [C]; Rowe et al., 1997 [C]; Local Expert Consensus [E]).

Note 3: The quantitative PCR assay used at Children's Hospital Medical Center Cincinnati is a whole blood assay that specifically amplifies the region of the EBV genome that encodes nuclear antigen (EBNA) (Groen & Witte, 2001 [D]).

Note: The frequency of testing is based upon risk and those frequencies used in studies (Local Expert Consensus [E]). There are no studies designed to confirm testing frequency. These recommendations may change based on results collected.

Clinical Assessment

No symptom is pathognomonic for EBV disease or PTLN. Therefore, a high index of suspicion and clinical vigilance must be maintained at all times allowing for timely evaluation for disease.

1. It is recommended EBV infection and/or PTLN be considered if a patient presents with any of the following:
 - Fever, which is the most frequently reported symptom, alone or with other symptoms. (Srivastava et al., 1999 [C]; Markin, 1994 [S]; Harwood et al., 1999 [C]; Smets et al., 2000 [C]; Cao et al., 1998 [D]; Green et al., 1999 [S,E]; Shapiro et al., 1988 [D]; Quintanilla-Martinez et al., 2000 [C]; Cacciarelli et al., 1998 [C])
 - Gastrointestinal (GI) disturbances: diarrhea, abdominal pain, GI bleeding, vomiting, protein losing enteropathy, weight loss (Smets et al., 2000 [C]; Cao et al., 1998 [D]; Green et al., 1999 [S,E]; Cacciarelli et al., 1998 [C]; Shapiro et al., 1988 [D]; Kingma et al., 1996 [O]). bowel obstruction/perforation (Cohen, 1991 [S])
 - Lymphadenopathy (Srivastava et al., 1999 [C]; Markin, 1994 [S]; Harwood et al., 1999 [C]; Green et al., 1999 [S, E]; Cao et al., 1998 [D]; Cacciarelli et al., 1998 [C])
 - Tonsillar hypertrophy, upper respiratory obstruction/sleep apnea (Broughton et al., 2000 [D]; Cao et al., 1998 [D]; Cacciarelli et al., 1998 [C]; Lattyak et al., 1998 [D]) adenoidal hypertrophy (Srivastava et al., 1999 [C])
 - Infectious mononucleosis syndrome: sore throat, fatigue, anorexia, headache (Markin, 1994 [S]; Broughton et al., 2000 [D]) rash (Cao et al., 1998 [D])
 - Hepatic or splenic enlargement (Green et al., 1999 [S, E]; Smets et al., 2000 [C]; Quintanilla-Martinez et al., 2000 [C])
 - Anemia, pancytopenia, hemophagocytosis (Okano & Gross, 1996 [S]; Quintanilla-Martinez et al., 2000 [C])
 - Allograft dysfunction (Srivastava et al., 1999 [C]; Randhawa et al., 1996 [D])

Note: Allograft dysfunction may often be mistaken for rejection.

- Other symptoms related to the site of organ involvement or mass effects including lung, liver, GI, and central nervous system (CNS)

Diagnosis

Laboratory and Radiologic Evaluation

1. It is recommended that a biopsy of the involved organ/site be performed once symptoms of PTLD are assessed and identified. The use of the World Health Organization (WHO) criteria may be considered for biopsy assessment and evaluation (Harris et al., 1999 [E]) (See Table 3 in the original guideline document).
2. It is recommended that in situ hybridization by Epstein Barr early response (EBER) staining be performed on the biopsy specimen (Randhawa et al., 1992 [D]).
3. It is recommended that additional diagnostic tests be considered, when clinically indicated, to determine the extent of disease once diagnosis of PTLD is confirmed. This may include bone marrow biopsy, lumbar puncture, and/or radiologic evaluation described below (Pickhardt et al., 2000 [S]).

No publications describe the use of imaging in a population followed with EBV viral replication as an indicator of possible PTLD. The recommendations in this section are based on studies that used either a surveillance protocol or the presence of clinical symptoms to direct imaging.

4. Routine use of imaging is not recommended to screen for PTLD. Imaging appearance is not specific for PTLD, so it is recommended that histologic evaluation be considered to confirm the diagnosis (Strouse et al., 1996 [D]; Pickhardt & Siegel, 1998 [D]; Pickhardt & Siegel, 1999 [D]; Donnelly et al., 1998 [D]).
5. If PTLD has been detected, it is recommended that a contrast enhanced computed tomography (CT) be the modality of choice for further evaluation. Chest radiographs, ultrasound, CT, and magnetic resonance imaging (MRI) have been used to detect PTLD (Dodd et al., 1992 [D]; Pickhardt et al., 1998 [D]; Pickhardt & Siegel, 1998 [D]).

Note 1: CT scanning detects more thoracic disease than chest radiographs (Dodd et al., 1992 [D]; Pickhardt et al., 1998 [D]).

Note 2: Lung parenchyma cannot be evaluated by ultrasound or MRI.

Note 3: CT better demonstrates the full extent of disease in the abdomen (Pickhardt & Siegel, 1998 [D]). If intravenous contrast cannot be administered due to renal failure, MRI may better identify and define PTLD in the abdomen than noncontrast CT (Lopez-Ben et al., 2000 [D]).

6. A complete survey that includes the head and neck, chest, abdomen, and pelvis is recommended when PTLD is suspected (Local Expert Consensus [E]).

Note: Although PTLD is more common in area of transplant, particularly with lung and liver transplantation (Pickhardt & Siegal, 1999 [D]; Donnelly et al., 1998 [D]), our center has found biopsy-proven lymphoproliferative disease (LPD) in the CNS, pleural fluid, epiglottis, nasopharynx, and bone marrow in liver transplant recipients.

Treatment

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. (Green et al., 1999 [S,E]) Although antivirals have been shown to inhibit EBV deoxyribonucleic acid (DNA) replication in vitro and in vivo, there is inconclusive data regarding their efficacy to treat PTLD in this pediatric population. Similarly, there is inconclusive data supporting the use of intravenous immunoglobulin (IVIG), cytomegalovirus (CMV)-hyperimmune globulin. There is evidence that alpha-interferon is efficacious in treatment of PTLD, but due to concerns of toxicity and the availability of newer agents, it is not currently recommended as first line therapy (Morrison et al., 1994 [D]; Green et al., 1999 [S,E]).

1. It is recommended that immunosuppression be decreased in patients following the diagnosis of PTLD (Green et al., 1999 [S,E]; Praghakaran et al., 1999 [D]; Shapiro et al., 1988 [D]; Dror et al., 1999 [D]; Birkeland et al., 1999 [D]; Cacciarelli et al., 1998 [C]) and be monitored for evidence of persistent or progressive EBV disease and allograft rejection (Green et al., 1999 [S,E]).

Note 1: Decrease the dose of immunosuppression to achieve levels 1/3 of target range for patients without PTLD (Praghakaran et al., 1999 [D]; Shapiro et al., 1988 [D]; Dror et al., 1999 [D]; Cacciarelli et al., 1998 [C]).

Note 2: It is important to take into account the relative risk of morbidity and/or mortality due to rejection, secondary to decreased immunosuppression on overall outcome for each specific organ type (Local Expert Consensus[E]).

Note 3: Persistent disease is defined as ongoing clinical, histologic or radiologic evidence despite intervention (Local Expert Consensus [E])

Note 4: Progressive disease is defined as increased involvement at the primary site or development of PTLD lesions at new sites (Local Expert Consensus [E]).

2. In patients with evidence of persistent or progressive PTLD, without evidence of allograft rejection, despite reduced immunosuppression, it is recommended that treatment with anti-CD 20 monoclonal antibody (Rituximab®) be considered (Milpied et al., 2000 [D]; Haddad et al., 2001 [D]; Yang et al., 2000 [D]).

Note 1: Usual dosing of Rituximab® is 375 mg/m² weekly for 4 weeks (Rituxan package insert [O]). Premedication is recommended to decrease

incidence of reactions; these, however, have not been reported in post transplant patients receiving Rituximab®.

Note 2: It is recommended that patients who are receiving Rituximab® have serum IgG levels monitored at monthly intervals (Local Expert Consensus [E]) as hypogammaglobulinemia has been reported during therapy with Rituximab®.

3. In patients with evidence of persistent or progressive PTLD and evidence of allograft rejection, or patients refractory to Rituximab®, treatment with low-dose cyclophosphamide and corticosteroids may be considered (Gross, 2002 [S]).
4. In patients who have responded to therapy but have evidence of allograft rejection, it is recommended that prior immunosuppression dosing be restarted (Local Expert Consensus [E]).

Note: Use of T-cell antibody therapy such as OKT3 or antithymocyte globulin (ATG) should be used with extreme caution in patients with PTLD or history of PTLD (Local Expert Consensus [E]).

5. In patients who have successfully responded to therapy and without evidence of allograft rejection, it is recommended that calcineurin inhibitors be restarted at doses to achieve 50% of standard target level for the organ type and time since transplant. (Local Expert Consensus [E])
6. It is recommended that surgical resection of tumor masses be performed, particularly for those in the small bowel (Hanto, 1995 [E,S]; Starzl et al, 1984 [D]; Hanto, 1983 [D])

Definitions

Evidence Based Grading Scale:

- A: Randomized controlled trial: large sample
- B: Randomized controlled trial: small sample
- C: Prospective trial or large case series
- D: Retrospective analysis
- E: Expert opinion or consensus
- F: Basic laboratory research
- S: Review article
- M: Meta-analysis
- Q: Decision analysis
- L: Legal requirement
- O: Other evidence
- X: No evidence

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window](#)

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is identified and classified for each recommendation (see "Major Recommendations") using the following scheme:

Evidence Based Grading Scale:

- A: Randomized controlled trial: large sample
- B: Randomized controlled trial: small sample
- C: Prospective trial or large case series
- D: Retrospective analysis
- E: Expert opinion or consensus
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- S: Review article
- M: Meta-analysis
- Q: Decision analysis
- L: Legal requirement
- O: Other evidence
- X: No evidence

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Effective medical management of post transplant lymphoproliferative disease (PTLD) following solid organ transplant in patients from birth to 18 years of age.

Groups at highest risk for PTLD include:

- Epstein-Barr virus naive transplant recipients
- Children younger than 5 years of age
- Transplant recipients during the first 12 months after transplantation
- Transplant recipients receiving certain types of immunosuppression

POTENTIAL HARMS

- Hypogammaglobulinemia has been reported during therapy with Rituximab®.
- It is important to take into account the relative risk of morbidity and/or mortality due to rejection, secondary to decreased immunosuppression on overall outcome for each specific organ type.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Appropriate companion documents have been developed to assist in the effective dissemination and implementation of the guideline.

The implementation process for each Cincinnati Children's Hospital Medical Center (CCHMC) guideline is a phase in a larger process of Guideline Development. This process is utilized for every guideline but is not addressed in the content of every guideline.

At the start of each guideline, a projected implementation date is determined. Reservations for education are then made (Grand Rounds, Patient Services Inservices). When the guideline is complete and enters into the Approval Process, education planning begins. Changes created by the guideline are outlined as well as anticipated outcomes. The implementation date is confirmed. Education is provided. The guideline is implemented and pilot information collection started. The Guideline Coordinator makes daily rounds and eligible children are followed to document the use of the guideline. The implementation phase aids in finding areas for improvement or question. When issues identified are improved, the guideline progresses to the monitoring phase.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for management of post transplant lymphoproliferative disease (PTLD) following solid organ transplant. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2003 Feb 4. 14 p. [187 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Feb 4

GUIDELINE DEVELOPER(S)

Cincinnati Children's Hospital Medical Center - Hospital/Medical Center

SOURCE(S) OF FUNDING

Cincinnati Children's Hospital Medical Center

GUIDELINE COMMITTEE

Clinical Effectiveness Team for Management of Post Transplant Lymphoproliferative Disease (PTLD).

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cincinnati Children's Hospital Medical Center Web site](#).

For information regarding the full-text guideline, print copies, or evidence based practice support services contact the Children's Hospital Medical Center Health Policy and Clinical Effectiveness Department at HPCEInfo@chmcc.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on March 11, 2004. This summary was updated by ECRI on January 12, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Rituxan (Rituximab). This summary was updated by ECRI Institute on October 8, 2008 following the U.S. Food and Drug Administration advisory on Rituxan (rituximab).

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Date Modified: 10/6/2008

