Journal of the Pediatric Infectious Diseases Society

SUPPLEMENT ARTICLE

A Focused Review of Epstein-Barr Virus Infections and PTLD in Pediatric Transplant Recipients: Guidance From the IPTA and ECIL Guidelines

Masaki Yamada,[1,†] Arnaud G. L'Huillier,[2,3,†] and Michael Green[4,5]

[1]Division of Infectious Diseases, Department of Medical Subspecialties, National Center for Child Health and Development, Tokyo, Japan, [2]Pediatric Infectious Diseases Unit, Department of Woman, Child and Adolescent Health, Geneva University Hospitals, Pittsburgh, Pennsylvania, USA, [3]Department of Pediatrics Gynecology and Obstetrics, Faculty of Medicine, Geneva, Switzerland, [4]Departments of Pediatrics and Surgery, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, USA and [5]Departments of Pediatrics and Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Epstein-Barr Virus (EBV) diseases, including EBV-associated post-transplant lymphoproliferative disorder (PTLD) remain important causes of morbidity and mortality in children undergoing solid organ transplantation (SOT) and hematopoietic cell transplantation (HCT). Despite progress in the prevention of EBV disease including PTLD (EBV/PTLD) in HCT, key questions in the prevention, and management of these infectious complications remain unanswered. The goal of this manuscript is to highlight key points and recommendations derived from the consensus guidelines published by the International Pediatric Transplant Association and the European Conference on Infections in Leukemia for children undergoing SOT and HCT, respectively. Additionally, we provide background and guidance on the use of EBV viral load measurement in the prevention and management of these children.

Key words. Epstein-Barr virus; hematopoietic cell transplantation; pediatrics; post-transplant lymphoproliferative disorders; review; solid organ transplantation.

INTRODUCTION

Epstein-Barr Virus (EBV) is an important cause of morbidity and mortality in children undergoing solid organ transplantation (SOT) and hematopoietic cell transplantation (HCT). While there has been substantial progress on prevention of EBV disease in the HCT population and some progress in the SOT setting, many key clinical questions relating to EBV and post-transplant lymphoproliferative disorder (PTLD) remain unanswered. A recent consensus conference convened by the International Pediatric Transplant Association (IPTA) has published evidence-based guidelines addressing EBV disease and PTLD in pediatric SOT recipients [1–5]. Similarly, the Sixth European Conference on Infections in Leukemia (ECIL-6) published guidelines relating to EBV in HCT recipients [6]. The goal of this manuscript is to highlight key points and recommendations from these guidelines. Of note, for both the IPTA and ECIL-6 guidelines, the strength of many of the recommendations is weakened by the quality of data informing them.

Received 27 June 2023; editorial decision 18 October 2023; accepted 8 November 2023

[†]Co-first authors.

Corresponding Author: Michael Green, MD, MPH, Professor of Pediatrics, Surgery and Clinical and Translational Science, Division of Pediatric Infectious Diseases, University of Pittsburgh School of Medicine, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, USA. E-mail: Michael.green@chp.edu.

Journal of the Pediatric Infectious Diseases Society 2024;13(S1):S31–8

https://doi.org/10.1093/jpids/piad097

EPIDEMIOLOGY AND CLINICAL SPECTRUM OF EBV DISEASE

Prior EBV infection and immunity of both the donor and recipient are key parameters associated with risk for EBV disease including PTLD (EBV/PTLD). However, the risk associated with various donor (D)/recipient (R) combinations differ between SOT and HCT recipients. Prior infection status is defined serologically, though the presence of passive antibody from either an infant's mother or blood products can confound the ability to accurately assess risk. For SOT, primary infection typically derived from the donor (D+/R−) is the major risk factor for severe disease and PTLD. However, community-acquired primary EBV infection is also associated with increased risk (D−/R− or D+/R−). In contrast, except for intestinal transplant recipients, R+ patients rarely develop EBV/PTLD [7–9]. Additional risk factors in SOT recipients include young age (infants and toddlers), organ transplanted (with intestine and lungs being at highest risk), and treatment with anti-lymphocyte antibodies. For HCT, the ECIL guidelines identify T-cell depletion (either in vivo or ex vivo), HLA mismatch, splenectomy, second HCT, severe acute/chronic graft vs host disease, high or rising EBV viral load (EBV VL), treatment with mesenchymal stem cells, any D/R mismatch (D+/R−and D−/R+) and cord blood transplantation amongst key risk factors for EBV/PTLD. Accordingly, the ECIL-6 guidelines recommend matching HCT D/R whenever possible [6]. For HCT, the increased risk is attributed to the absence of donor-derived EBV T-cell immunity even after engraftment and immune reconstitution [6, 10].

The clinical presentation of EBV ranges from asymptomatic infection to symptomatic disease with a spectrum that includes a nonspecific febrile syndrome, end-organ disease (eg, hepatitis and enteritis), and life-threatening PTLD. Definitions for EBV disease not meeting published criteria for PTLD have been previously proposed [1–3, 11], but not widely accepted and these clinical syndromes were not addressed by the IPTA Guidelines. A histological diagnosis is required to confirm PTLD and is classified based on the 2017 WHO Classification scheme (Table 1) [12]. This classification applies to tissue obtained from any transplant recipient and characterizes PTLD lesions as nondestructive, polymorphic lesions, monomorphic lesions, and classic Hodgkin lymphoma. Its international acceptance has improved the ability to compare incidence and outcomes among centers and studies.

ROLE OF EBV SEROLOGIC SCREENING IN EBV DISEASE RISK ASSESSMENT

History of prior EBV infection of donor and recipient forms the basis for risk assessment for post-transplant infection. Thus, EBV serologic screening is strongly recommended for all HCT and SOT donors and recipients, even if the EBV serologic screening is not required in some policy. Screening is accomplished using a combination of antiviral capsid antigen (VCA) IgG, VCA IgM, and anti-EBV nuclear antigen (EBNA) IgG. While the presence of a positive anti-VCA IgM with negative anti-VCA/anti-EBNA IgG may identify early EBV infection, it may also represent a false positive result. The use of quantitative EBV VL measurement in the blood in this setting should be informative as early EBV infection is typically associated with DNAemia.

To optimize the accuracy of these assessments, the IPTA Guidelines recommend rescreening of EBV-negative SOT candidates on the waitlist every 6–12 months and at the time of transplantation. However, this was not discussed in the ECIL guidelines. Notably, the presence of passive antibodies (whether due to transplacental acquisition for candidates <12 months or from blood products in candidates of any age) can confound the interpretation of these results. To avoid the latter, screening tests should be performed remote from blood products administration whenever possible. In case of candidates <12 months or with recent administration of blood products, most experts recommend considering the scenario at the highest risk. For SOT, the recipient is considered negative while a donor with passive antibody exposure would be considered positive. For HCT, the recipient would be assumed to be EBV positive if the donor were EBV negative and negative if the donor were EBV positive. Passive antibody exposure in HCT donors is not expected except for cord blood donors which places HCT recipients at risk regardless of recipient status.

USE OF EBV VL

Use of EBV VL determined through quantitative nucleotide amplification testing of peripheral blood is considered standard-of-care practice for pediatric transplant recipients and is recommended in both Guidelines [3, 6, 9]. An understanding of the technical and biological aspects of VL monitoring is essential to optimizing the use of these tests in the care and management of pediatric transplant recipients experiencing EBV infection.

Table 1. PTLD Categorization According to the 2017 World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues [11]

Pathological type of PTLD	Histopathology; Major Findings and Presence of EBV	Genetics IGH/TR Clonal Rearrangements Cytogenetic/oncogene Abnormalities
Nondestructive PTLDs; Plasmacytic hyperplasia	Predominantly small lymphocytes and plasma cells; EBV+	Polyclonal or very small monoclonal B-cell populations; may have clonal/oligoclonal TR genes Cytogenic abnormalities; none
Nondestructive PTLDs; Infectious mononucleosis	Admixed small lymphocytes, plasma cells, and immunoblasts; EBV+	Polyclonal or very small monoclonal B-cell population(s) Cytogenic abnormalities; rare
Nondestructive PTLDs; Floid follicular hyperplasia	Prominent hyperplastic germinal centers; EBV±	Monoclonal B cells, non-clonal T cells Cytogenic abnormalities; simple abnormalities present
Polymorphic	Full spectrum of lymphoid maturation seen, not fulfilling criteria for NHL; most EBV+	Clonal B cell and/or T cells except for rare NK-cell cases Cytogenic abnormalities; somatic mutations present
Monomorphic	Fulfills criteria for an NHL or plasma cell neoplasm; EBV more variable than in other categories	IGH not easily demonstrated Cytogenic abnormalities; variable
Classic Hodgkin lymphoma (CHL)	Fulfills criteria for CHL; EBV+	Cytogenic abnormalities; Unknown

Abbreviations: CHL, classic Hodgkin lymphoma; mcl, monoclonal; IGH, immunoglobulin heavy chain; TR, T-cell receptor, NHL, non-Hodgkin lymphoma; PTLD, post-transplant lymphoproliferative disorder.

Monoclonality and polyclonally are only inferred when finding monotypic or polytypic light chain expression.

What Is Measured in an EBV VL?

EBV DNA is predominantly found within circulating EBV-infected B-lymphocytes rather than as EBV virions in plasma. Intracellular EBV replicates along with human DNA during the proliferation of EBV-infected B-lymphocytes. In this setting, infection does not progress to lytic viral replication as EBV typically remains in type III latency. However, recent single-cell-based studies indicate that EBV-infected cells show heterogeneous gene expression patterns, with a mixture of latency and lytic gene expressions even from infected cells not progressing to full lytic infection (unpublished data). The IPTA Guidelines highlight that VL measured from plasma does not represent viremia but rather fragments of cell-free DNA [3, 13]. While the biology of EBV infection and proliferation of EBV-infected cells are believed to be similar in recipients of different types of transplantation, a variety of signatures in host immunity skewed by different types of organ transplantation have been reported and likely play another role in the development of PTLD [14].

Technical Issues Related to Quantification of EBV VL

The WHO Expert Committee on Biological Standardization approved the first international standard for EBV DNA as a common assay calibrator in 2011 to minimize differences in test results between centers [15]. EBV VL measurements calibrated to this standard are expressed as $\log_{10}$ IU/ml and widely used [3]. Unfortunately, despite the use of this standard, results obtained using different assays are still not reliably comparable [16]. Accordingly, the IPTA Guidelines recommend monitoring patients using the same sample type and laboratory whenever possible. For measurements done at the same lab, results of VL that differ by at least 0.5 $\log_{10}$ IU/ml (3-fold) should be considered significantly different [3].

Specimen Type for Quantitative EBV VL

VL measurement in the peripheral blood is the preferred approach to EBV surveillance in transplant recipients. While both whole blood (WB) and plasma are used for VL measurement, which of these is the most optimal remains undetermined. While the ECIL Guidelines do not endorse a preference between WB and plasma [6], the IPTA Guidelines suggest that the best choice varies based on the purpose of the test. Quantification of VL in WB is more sensitive [3, 13] than in plasma, but the latter may be a more specific marker for EBV disease. Leveraging these differences, they suggest that WB may be preferred for patients undergoing VL surveillance to inform preemptive interventions to prevent progression to EBV/PTLD, while plasma may be preferable when evaluating symptomatic patients with possible EBV disease [3, 17].

Interpretation of EBV VL Value and Kinetics

Both the IPTA and ECIL Guidelines endorse the use of VL measurement to inform prevention strategies in patients at risk for EBV/PTLD as well as to diagnose patients with symptomatic EBV disease in combination with histologic assessment [1, 3, 6]. While the identification of symptomatic EBV disease might be accomplished with a single load measurement, the identification of patients at risk for EBV/PTLD requires sequential measurement of VL over time. Unfortunately, available evidence did not support the endorsement of a specific monitoring protocol in the IPTA guidelines (though an example was provided [3]) and this was not addressed in the ECIL guidelines. Additionally, neither guideline provides specific thresholds or rates of rise of VL where intervention is indicated as values that are applicable across laboratories, assays or specimen types have not been identified. Accordingly, clinicians must become familiar with their center's assay's performance to optimally use results in the care of their patients [6]. Uncertainty can also arise from the presence of persistent EBV high-load carrier states which are associated with different levels of risk of progression to disease in different organ recipients [18] and have not been described in HCT recipients. The IPTA Guidelines recommend against the use of VL alone to monitor response to PTLD treatment, though use in combination with imaging and clinical follow-up was endorsed. Notably, VL results may be misleading for children receiving anti-B cell monoclonal therapies as treatment for PTLD.

Role of Immunological Assay and Other Potential Biomarkers

The lack of VL specificity has led to the evaluation of other immunological assays to inform EBV risk. To date, none have shown reliable clinical utility and the IPTA Guidelines recommend against their use for surveillance, diagnosis, or informing prognosis of PTLD. Examples of potential assays include those measuring ATP release by stimulated CD4+ or CD3+ EBV-specific T cells, functional or phenotypic assays of NK cells, lymphocyte subpopulation assessments, and monitoring for orphan viruses in serum or tissue. Interest has focused on the measurement of EBV-specific cell-mediated responses in combination with EBV VL. However, the IPTA Guidelines recommended against use based on limited available data and called for further studies to help define its value.

PREVENTION

Effective prevention strategies can focus on either preventing primary EBV infection or progression from asymptomatic EBV infection to EBV/PTLD. Potential approaches to accomplish this include the use of immunoprophylaxis, chemoprophylaxis, and preemptive interventions informed by elevations of EBV VL, summarized in Table 2.

Immunoprophylaxis

Vaccines.

There are no currently marketed EBV vaccines. Amongst potential candidates, vaccines targeting gp350, the main target of

Table 2. Guideline-Endorsed Recommendations for the Prevention of EBV Disease and PTLD [1, 6].

	SOT[a1]	HCT[b2]
Prophylaxis		
Chemoprophylaxis—Antivirals	Not recommended *(weak/moderate to prevent EBV infection)* *(strong/moderate to prevent EBV disease)*	Not recommended *(DII)*
Immunoprophylaxis		
Vaccines	Unavailable	
IVIG	Not recommended *(weak/moderate)*	Not recommended *(DIII)*
Anti-CD20	Not recommended *(strong/low)*	Marginally recommended *(CII)*
VSTs	Not recommended	Marginally recommended *(CII)*
Preemptive therapy		
Reduction of immunosuppression	Recommended *(strong/moderate for liver)* *(weak/low for other organs)*	Recommended when combined with anti-CD20 *(AII)*
Chemoprophylaxis—Antivirals	Not recommended *(weak/low)*	Not recommended *(DIII)*
Immunoprophylaxis		
Anti-CD20	Not recommended *(weak/very low)*	Recommended, alongside RIS whenever possible *(AII)*
VSTs	Not recommended *(weak/low)*	Marginally recommended *(CII)*

Abbreviations: EBV, Epstein-Barr virus; HCT, hematopoietic cell transplanation; IVIG, intravenous immunoglobulin; PTLD, post-transplant lymphoproliferative disorder, SOT, solid organ transplantation; VSTs, virus-specific T cells.

[a]Grading recommendations for SOT: (x/y); x = strength of recommendation; y = quality of evidence.
[b]Grading recommendations for HCT: A = strong; B = moderate; C = marginal; D = against; I = at least 1 RCT; II = at least from one clinical trial; III = expert opinion, descriptive studies.

EBV-specific neutralizing antibodies, have been the most widely studied. Published studies in immune-competent volunteers have not shown benefit in preventing infection, though some suggested reduced likelihood of symptomatic disease [19]. The development of effective EBV vaccines was endorsed as an important research goal by the IPTA Guidelines [1].

Intravenous Immunoglobulin.

Two randomized controlled studies evaluated intravenous immunoglobulin (IVIG) in this context. The first showed a decreasing, yet nonsignificant trend in the incidence of EBV/PTLD in pediatric liver recipients receiving CMV-IVIG compared with placebo [11]. The second failed to demonstrate any difference in incidence, time of onset, or peak EBV VL between IVIG and placebo in EBV-mismatched adults and pediatric SOT recipients [20]. Both the IPTA and ECIL guidelines recommended against the use of IVIG to prevent EBV/PTLD [1, 6].

Monoclonal Antibodies.

Data evaluating use of anti-CD20 antibodies (eg, rituximab) to prevent primary EBV infection are lacking in both SOT and HCT recipients. Potential indirect evidence comes from a study of SOT recipients receiving rituximab at induction for ABO incompatibility who were noted to be less likely to develop PTLD [21]. More recently, a randomized controlled trial showed that pediatric lung recipients who received rituximab had less EBV VL detection than the placebo group, even though the study was underpowered to document an effect on PTLD rates [22]. Given the limited data and known side effects (eg, hypogammaglobulinemia), use for prophylaxis was not recommended by the IPTA Guidelines [1]. In contrast, the ECIL Guidelines note that prophylactic rituximab might reduce the risk of DNAemia and provides a marginal recommendation for its use to prevent PTLD in HCT [6].

Virus-Specific T Cells.

Virus-specific T cell (VST) is used to augment the cellular immune response against viral pathogens when the IS attenuates the cellular immune response after HCT and SOT [23, 24]. Use of VST therapy against EBV infection has been shown to be effective in both the prevention and treatment of EBV/PTLD in HCT recipients [25]. Accordingly, the ECIL Guidelines recommend considering the use of VSTs for the prevention of EBV in HCT recipients when available [6] However, the use of VSTs for prophylaxis against primary EBV infection was not recommended by the IPTA Guidelines due to insufficient data in SOT recipients.

Antiviral Chemoprophylaxis

Antiviral chemoprophylaxis refers to the use of antiviral agents to prevent EBV primary infection or reactivation. Evidence assessing the benefit of antivirals for the prevention of EBV

infection and disease is limited. Animal studies provide some supportive data but clinical data in humans is unconvincing. Acyclovir and its prodrug valacyclovir have no apparent effect on the incidence of EBV/PTLD. However, several studies of ganciclovir and valganciclovir report a protective effect within the limitations of the study design. One prospective study of EBV D+/R− pediatric kidney transplant recipients found patients receiving ganciclovir or valganciclovir for cytomegalovirus prevention had a decreased incidence of primary EBV infection, delayed onset of DNAemia, and lower VL compared with those not receiving prophylaxis [26]. However, the limited number of observed PTLD events hinders assessing the possible benefit on PTLD prevention. In contrast, a systematic review and meta-analysis concluded that antiviral prophylaxis in mismatched SOT recipients had no effect on PTLD [27]. Both IPTA and ECIL Guidelines recommend against the use of antivirals to prevent PTLD in pediatric transplant recipients [1] though the IPTA Guidelines call for prospective studies to clarify the potential role of antivirals.

Preemptive Strategies

Preemptive strategies involve monitoring VL at regular intervals to detect subclinical infection to inform starting an intervention to avoid progression to clinical disease. The IPTA Guidelines recommend VL monitoring for all D+/R− pediatric SOT recipients and suggest considering it for all pediatric EBV R− recipients as well as R+ children <1 year of age at the time of transplantation as seropositivity likely reflects maternal antibodies [1]. VL monitoring of R+ intestinal transplant recipients should also be considered given their increased risk of PTLD even in case of previous EBV seropositivity [1]. Along the same lines, the ECIL recommends EBV VL monitoring after high-risk allogeneic HCT [6].

Reduction of Immunosuppression.

Reduction of immunosuppression (RIS) can contribute to control of EBV replication and help in reversing lymphoproliferative lesions [28]. For HCT recipients, the ECIL Guidelines recommend RIS in combination with rituximab as a first-line preemptive intervention [6]. For SOT, several studies demonstrated that low-immunosuppression protocols were associated with reduced incidence of EBV/PTLD in pediatric liver transplant recipients [29, 30]. Moreover, the incidence of PTLD was lower in a cohort of pediatric liver transplant recipients with EBV VL-driven RIS compared with historical controls, without an increase in rejection rates [31]. Consequently, the IPTA guidelines recommend preemptive RIS whenever possible for elevated or rising VL to prevent the development of EBV/PTLD in pediatric liver transplant recipients [1]. However, until more data are available for other organs, they provide a weaker recommendation to consider RIS for non-liver recipients with an elevated or rising VL [1]. An important limitation is the absence of specific recommendations addressing how to decrease each of the different immunosuppressive agents. For tacrolimus, many centers will aim to achieve a level of <5 ng/ml. Similarly, data addressing how long to maintain low immunosuppression are lacking. In the absence of rejection, many experts recommend maintaining low immunosuppression until there is either evidence of reduced EBV VL or progression to EBV disease.

Antiviral Therapy.

Most studies evaluating the role of antivirals in patients with elevated or rising VL have not shown a benefit in the incidence of PTLD in SOT [1], which was confirmed in a systematic review and meta-analysis [27]. Both the IPTA and ECIL Guidelines recommend against the use of antivirals to prevent EBV disease and PTLD in patients with elevated or rising VL [1, 6].

Monoclonal Antibodies.

The ECIL Guidelines recommend preemptive use of weekly rituximab until the resolution of EBV DNAemia combined with RIS whenever possible for HCT recipients with a positive VL [6]. However, as there is only limited data for SOT [1, 32], the IPTA Guidelines do not recommend the routine preemptive use of rituximab in pediatric SOT recipients [1], though they do call for well-designed randomized controlled trials to assess potential benefits vs risks for preemptive use in pediatric SOT recipients.

VSTs.

The ECIL Guidelines recommend considering the use of VSTs as an alternative to rituximab in HCT with an elevated VL [6]. Several studies report the use of autologous VSTs in SOT recipients [1]. Despite limitations of small sample size and absence of control groups, the studies suggest that VSTs are well tolerated and achieved a reduction or clearance of VL in most patients, with no patient developing PTLD. However, given the limited data in SOT, the IPTA Guideline recommended against the routine preemptive use of VSTs to prevent EBV/PTLD but called for additional studies to define their potential role in this setting. Several studies evaluating preemptive VST therapy for pediatric SOT recipients with elevated or rising EBV VL refractory to RIS are currently enrolling. (NCT0326653, NCT04364178, and NCT02580539).

MANAGEMENT OF EBV-PTLD

The confirmed presence of EBV/PTLD warrants consultation with both infectious diseases and oncology to collectively recommend treatment options as part of a multi-disciplinary team. While the IPTA Guidelines suggest a stepwise approach to management with exceptions made for certain types of PTLD (Figure 1), the ECIL Guidelines recommend rituximab monotherapy as the preferred first-line therapy for EBV CD20+ PTLD after

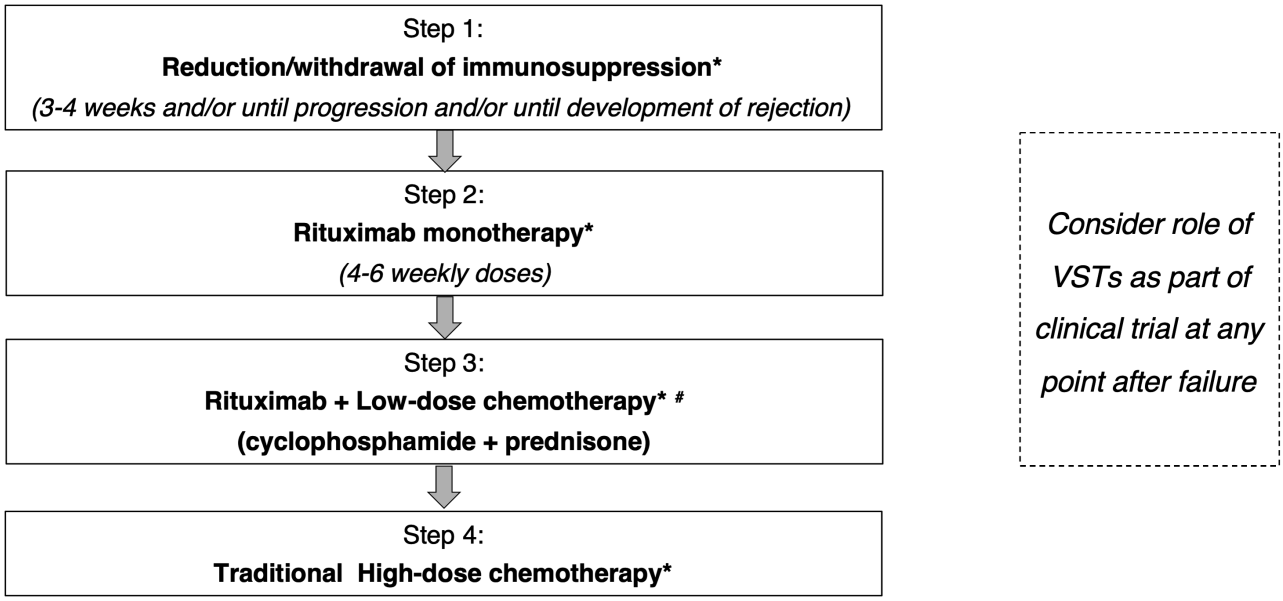

Figure 1. International Pediatric Transplant Association PTLD Consensus Conference proposed stepwise approach to the treatment of EBV + PTLD in children after SOT(ref). CNS: central nervous system; EBV, Epstein-Barr virus; NK, natural killer; PTLD, post-transplant lymphoproliferative disorder; VSTs, virus-specific T cells. *Potential exceptions to standard algorithm include: Burkitt PTLD, Hodgkin PTLD, T/NK cell lymphomas (monomorphic type), CNS PTLD, and plasmacytoma.

Table 3. Recommendation for Therapy of EBV-PTLD in HCT According to ECIL-6 Guidelines [6]

First-line therapy in EBV-PTLD	Grade of recommendation
1. Rituximab	AIIu
2. Reduction of immunosuppressive therapy (if possible) combined with rituximab	AIIu
3. EBV-specific cytotoxic T lymphocytes (generated from HCT or third-party donor) if available	CIIu
Second-line therapy in EBV-PTLD	
1. EBV-specific-CTLs or donor lymphocyte infusion	BIII
Third-line therapy in EBV-PTLD	
1. Chemotherapy ± rituximab after failure of other methods	CIIh
CNS EBV disease	
Therapeutic options in EBV-PTLD in central nervous system include;	
1. Rituximab ± chemotherapy	BIIh
2. Rituximab systemic or intrathecal monotherapy	CIII
3. Anti-EBV T-cell therapy	CIII
4. Radiotherapy	CIII
Strategies that are NOT recommended for treatment of EBV-PTLD: Surgery, IVIG, interferon, and antiviral agents are not recommended for therapy of PTLD	DIII

Abbreviations: CNS, central nervous system; EBV, Epstein-Barr virus; ECIL-6, sixth European conference on infections in leukemia; IVIG, intravenous immunoglobulin; PTLD, post-transplant lymphoproliferative disorder.
Grading recommendations for HCT: A = strong; B = moderate; C = marginal; D = against; I = at least 1 RCT; II = at least from one clinical trial; III = expert opinion, descriptive studies, h = historical controls. u = uncontrolled clinical trials.

HCT with the use of second-line therapies reserved for those failing treatment with this agent (Table 3) [4, 6]. Differences in recommendations between SOT and HCT are primarily based on both differences in supportive data and differential tolerability of treatments. A discussion of available treatments for EBV/PTLD follows.

RIS

RIS is generally the recommended initial approach to PTLD management for both HCT and SOT recipients [3, 4, 6] though recommendations vary by type of transplantation and histologic character of the lesion. For management of EBV/PTLD, immune suppression is often completely discontinued but this may vary by organ type and depend on which immunosuppressive agents are being used. Reported response rates vary widely, likely reflecting the heterogeneity and size of the populations, variability in lesions studied, and non-standardized approach to RIS. RIS may not be a practical choice early after transplantation or during an episode of rejection/GVHD.

Anti-CD20 Monoclonal Antibodies

Rituximab is very effective in reducing the burden of EBV-infected B cells. The ECIL Guidelines recommend rituximab as first-line therapy for HCT recipients with CD20+ EBV/PTLD while the IPTA Guidelines recommend rituximab alone or in combination with chemotherapy, for patients not responding to RIS as well as for specific lesions including lymphoma (see Figure 1). The fact that rituximab is only used for CD20+

EBV/PTLD further highlights the importance of histological diagnosis.

VSTs

VSTs derived from the HCT or a third-party donor have been used successfully for the treatment of EBV-PTLD in allogeneic HCT recipients and in a smaller number of SOT recipients [4, 24]. The ECIL Guidelines recommend the use of VST when available; its limited availability likely underlies their recommendation to use it as a second-line therapy for those not responding to rituximab. Data in SOT is limited and the IPTA Guidelines recommend use of VST be limited to participation in clinical trials. The studies open for preemptive VST therapy for pediatric SOT recipients are also open to SOT recipients with EBV/PTLD (NCT0326653, NCT04364178, and NCT02580539).

Other Therapies

For pediatric SOT recipients, use of cytotoxic chemotherapy is reserved for those failing to respond to other therapies or for patients presenting with specific monoclonal lesions including lymphomas (Figure 1). The ECIL guidelines recommend that use be limited to those with refractory or relapsed PTLD given the poor tolerability of these treatments in the HCT population. A variety of potential combination chemotherapies regimens have been used (eg, CHOP, ACVBP, often accompanied by rituximab). Complete or partial surgical resection, as well as local radiotherapy, have been used as adjunctive therapy along with reduced immunosuppression. However, their efficacy as monotherapy is rarely assessed and accordingly not well investigated except in tonsillar/adenoid PTLD where resection is often used as an isolated curative measure [33].

CONCLUSIONS

EBV infections and associated diseases remain an important problem in children undergoing SOT and HCT. Efforts to develop strategies to optimize their prevention and management have improved outcomes and begun to limit their impact in children undergoing transplantation. While Consensus Guidelines from the IPTA and the ECIL provide much-needed guidance in the management of EBV, more data and better studies are needed.

Note

Supplement sponsorship. This article appears as part of the supplement "Advances in Pediatric Transplant Infectious Diseases," sponsored by Eurofins Viracor.

REFERENCES

1. Green M, Squires JE, Chinnock RE, et al. The IPTA Nashville consensus conference on post-transplant lymphoproliferative disorders after solid organ transplantation in children: II-consensus guidelines for prevention. Pediatr Transplant **2022**; Nov 11:e14350.
2. Wilkinson JD, Allen U, Green M, et al; IPTA Pediatric PTLD Consensus Guidelines Conference. The IPTA Nashville consensus conference on post-transplant lymphoproliferative disorders after solid organ transplantation in children: I-methodology for the development of consensus practice guidelines. Pediatr Transplant **2022**; Nov 11:e14333.
3. Preiksaitis J, Allen U, Bollard CM, et al. The IPTA Nashville consensus conference on post-transplant lymphoproliferative disorders after solid organ transplantation in children: III - consensus guidelines for Epstein-Barr virus load and other biomarker monitoring. Pediatr Transplant **2023**; Jun 9:e14471.
4. Allen UD, L'Huillier AG, Bollard CM, et al. The IPTA Nashville consensus conference on post-transplant lymphoproliferative disorders after solid organ transplantation in children: management of post-transplant lymphoproliferative disorders in children and adolescents. Pediatr Transplant **2023**. in press.
5. Webber SA, Chinnock RE, Danziger-Isakov L, et al. The IPTA Nashville consensus conference on post-transplant lymphoproliferative disorders after solid organ transplantation in children: V – definitions and diagnostic evaluation of suspected PTLD. Pediatr Transplant **2023**. in press.
6. Styczynski J, van der Velden W, Fox CP, et al; Sixth European Conference on Infections in Leukemia, a Joint Venture of the Infectious Diseases Working Party of the European Society of Blood and Marrow Transplantation (EBMT-IDWP), the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG), the International Immunocompromised Host Society (ICHS) and the European Leukemia Net (ELN). 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**; 101:803–11.
7. Green M, Webber S. Posttransplantation lymphoproliferative disorders. Pediatr Clin North Am **2003**; 50:1471–91.
8. Dharnidharka VR. Epidemiology of PTLD after SOT. In: Dharnidharka VR, Green M, Webber SA, Trappe RU, eds. *Post-Transplant Lymphoproliferative Disorders*. Cham: Springer International Publishing; **2021**. p. 111–27.
9. Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant **2019**; 33:e13652.
10. Uhlin M, Wikell H, Sundin M, et al. Risk factors for Epstein-Barr virus-related post-transplant lymphoproliferative disease after allogeneic hematopoietic stem cell transplantation. Haematologica **2014**; 99:346–52.
11. Green M, Michaels MG, Katz BZ, et al. CMV-IVIG for prevention of Epstein Barr virus disease and posttransplant lymphoproliferative disease in pediatric liver transplant recipients. Am J Transplant **2006**; 6:1906–12.
12. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. France: International Agency for Research on Cancer (IARC); **2017**.
13. Fournier B, Boutboul D, Bruneau J, et al. Rapid identification and characterization of infected cells in blood during chronic active Epstein-Barr virus infection. J Exp Med **2020**; 217:e20192262.
14. Yamada M, Macedo C, Louis K, et al. Distinct association between chronic Epstein-Barr virus infection and T cell compartments from pediatric heart, kidney, and liver transplant recipients. Am J Transplant **2023**; 23:1145–58.
15. Fryer JF, Heath AB, Wilkinson DE, Minor PD, Collaborative Study G. A collaborative study to establish the 1st WHO International Standard for Epstein-Barr virus for nucleic acid amplification techniques. Biologicals **2016**; 44:423–33.
16. Hayden RT, Preiksaitis J, Tong Y, et al. Commutability of the first World Health Organization international standard for human cytomegalovirus. J Clin Microbiol **2015**; 53:3325–33.
17. Kanakry JA, Hegde AM, Durand CM, et al. The clinical significance of EBV DNA in the plasma and peripheral blood mononuclear cells of patients with or without EBV diseases. Blood **2016**; 127:2007–17.
18. Yamada M, Nguyen C, Fadakar P, et al. Epidemiology and outcome of chronic high Epstein-Barr viral load carriage in pediatric kidney transplant recipients. Pediatr Transplant **2018**; 22:e13147.
19. Sokal EM, Hoppenbrouwers K, Vandermeulen C, et al. Recombinant gp350 vaccine for infectious mononucleosis: a phase 2, randomized, double-blind, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of an Epstein-Barr virus vaccine in healthy young adults. J Infect Dis **2007**; 196:1749–53.
20. Humar A, Hebert D, Davies HD, et al. A randomized trial of ganciclovir versus ganciclovir plus immune globulin for prophylaxis against Epstein-Barr virus related posttransplant lymphoproliferative disorder. Transplantation **2006**; 81:856–61.
21. Walti LN, Mugglin C, Sidler D, et al; Swiss Transplant Cohort Study (STCS). Association of antiviral prophylaxis and rituximab use with posttransplant lymphoproliferative disorders (PTLDs): a nationwide cohort study. Am J Transplant **2021**; 21:2532–42.
22. Sweet SC, Armstrong B, Blatter J, et al. CTOTC-08: a multicenter randomized controlled trial of rituximab induction to reduce antibody development and

improve outcomes in pediatric lung transplant recipients. Am J Transplant **2022**; 22:230–44.
23. Rubinstein J, Green A, T GMP. Virus-specific T cells and their use in pediatric transplantation. J Pediatric Infect Dis Soc **2023**.
24. Leen AM, Bollard CM, Mendizabal AM, et al. Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation. Blood **2013**; 121:5113–23.
25. McLaughlin LP, Rouce R, Gottschalk S, et al. EBV/LMP-specific T cells maintain remissions of T- and B-cell EBV lymphomas after allogeneic bone marrow transplantation. Blood **2018**; 132:2351–61.
26. Hocker B, Bohm S, Fickenscher H, et al. (Val-)Ganciclovir prophylaxis reduces Epstein-Barr virus primary infection in pediatric renal transplantation. Transpl Int **2012**; 25:723–31.
27. AlDabbagh MA, Gitman MR, Kumar D, Humar A, Rotstein C, Husain S. The role of antiviral prophylaxis for the prevention of Epstein-Barr virus-associated posttransplant lymphoproliferative disease in solid organ transplant recipients: a systematic review. Am J Transplant **2017**; 17:770–81.
28. Starzl TE, Nalesnik MA, Porter KA, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. Lancet **1984**; 1:583–7.
29. Ganschow R, Schulz T, Meyer T, Broering DC, Burdelski M. Low-dose immunosuppression reduces the incidence of post-transplant lymphoproliferative disease in pediatric liver graft recipients. J Pediatr Gastroenterol Nutr **2004**; 38:198–203.
30. Narkewicz MR, Green M, Dunn S, et al; Studies of Pediatric Liver Transplantation Research Group. 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**; 19:730–40.
31. 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**; 5:2222–8.
32. San-Juan R, Manuel O, Hirsch HH, et al; ESGICH PTLD Survey Study Group. Current preventive strategies and management of Epstein-Barr virus-related post-transplant lymphoproliferative disease in solid organ transplantation in Europe Results of the ESGICH Questionnaire-based Cross-sectional Survey. Clin Microbiol Infect **2015**; 21:604.e1–9.
33. Trappe RU, Webber SA. Management of PTLD after SOT. In: Dharnidharka VR, Green M, Webber SA, Trappe RU, eds. *Post-Transplant Lymphoproliferative Disorders*. Cham: Springer International Publishing; **2021**. p. 167–90.