Prevention and Treatment of EBV-Related Complications

7

Sophie Caillard and Michael Green

7.1 Description of Pathogen

Epstein–Barr Virus (EBV) is a ubiquitous human γ-herpesvirus (HHV4) notable for its tropism for B-cell lymphocytes and its ability to establish lifelong infection through latency. Infection typically spreads via saliva, with the virus initially targeting oropharyngeal epithelial cells and subsequently mucosal B lymphocytes leading to dissemination throughout the body. Of note, EBV can also be transmitted from organ donors, serving as perhaps the most important source of EBV infection in individuals undergoing solid organ transplantation (SOT).

7.2 Definitions and Epidemiology

EBV infection occurs worldwide, with seropositivity rates exceeding 90% of the adult population. Data identifies an EBV seroprevalence rate of 83% by the age of 19 in the United States [1] and 95% by the age of 20 in a French population [2]. In seronegative transplant recipients, primary EBV infection is frequently acquired from the donor via passenger leucocytes accompanying the transplant organ. EBV infection can lead to various outcomes after SOT ranging from asymptomatic infection to severe lymphoproliferative disorders including true malignancies. Primary infections are typically associated with more significant clinical syndromes, while

S. Caillard
Nephrology Transplantation Department, INSERM UMR_S 1109, Strasbourg University Hospital, Strasbourg, France

M. Green (✉)
Department of Pediatrics and Surgery, Division of Infectious Diseases, University of Pittsburgh School of Medicine, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA
e-mail: Michael.green@chp.edu

O. Manuel, M. G. Ison (eds.), *Infectious Diseases in Solid-Organ Transplant Recipients*, https://doi.org/10.1007/978-3-030-15394-6_7

reactivation of the recipient strain present prior to transplant or reinfection with a new strain of EBV from the donor tends to be mild or even asymptomatic in SOT recipients. Since most adults are already EBV seropositive prior to transplant, primary infection and its associated more prominent disease states occur much more frequently in the pediatric SOT population [3].

Definitions developed to describe the range of EBV infection and diseases are shown in Table 7.1 [4]. Unfortunately, only limited data quantifying the relative frequencies of the full range of EBV disease has been published. Smets and colleagues reported that only 15% of pediatric liver transplant recipients presented with a symptomatic primary EBV infection [5]. Observed symptoms varied from isolated fever or a non-specific viral syndrome to presentation with classical infectious mononucleosis. Not uncommonly, transplant recipients manifest organ-specific symptoms associated with hepatitis, enteritis, pneumonitis, and, rarely, meningoencephalitis. On exceptional occasions, a primary infection can progress toward a life-threatening disease with acidosis, intravascular disseminated coagulopathy, and multi-organ failure.

Symptomatic EBV infection was defined as either seroconversion, development of a positive viral load ≥200 genome copies per 100,000 PBL [12], or histologic evidence of EBV infection (by EBER) in the presence of typical symptoms or laboratory findings (e.g., fever, leukopenia, atypical lymphocytosis, exudative tonsillitis, and/or adenopathy). EBV disease was further characterized as either "proven," "probable," or "possible." "Proven" EBV disease required histologic confirmation using the EBER stain. "Probable" symptomatic EBV infection was diagnosed if there was evidence of EBV infection in the presence of typical symptoms and in the absence of alternate explanation. "Possible" symptomatic EBV infection was made if there was evidence of EBV, the presence of typical symptoms, and an inability to exclude the diagnosis despite the presence of alternate explanation. Episodes of "probable" and "possible"

Table 7.1 EBV infection and disease definitions

EBV infections and diseases	Characteristics
Symptomatic infection	Seroconversion, or more likely the presence of a positive viral load in the range that EBV disease is seen on the assay used to perform the measurement, histological evidence of EBV infection (by EBER) in the presence of typical symptoms or laboratory findings. For probable or possible cases, this could be further classified as viral syndrome, mononucleosis, adenopathy, or adenitis. For proven disease, where biopsy identifies the presence of EBV but does not demonstrate the presence of PTLD, this could be classified by affected organ (e.g., EBV hepatitis, enteritis, adenitis, etc.)
Proven EBV disease	Histological evidence of EBV staining using EBER probe in the presence of signs and symptoms of disease
Probable EBV disease	Presence of typical symptoms, in the absence of alternate explanation
Possible EBV disease	Presence of typical symptoms and inability to exclude alternate explanation

EBV disease were further classified as viral syndrome, mononucleosis, or adenitis/adenopathy.

Patients experiencing primary EBV infection may experience neoplastic transformation of B lymphocytes leading to the development of posttransplant lymphoproliferative disorders (PTLD). PTLD represent a continuous spectrum of abnormal lymphoid proliferations, ranging from lymphoid hyperplasia to polyclonal proliferations to frank malignant monoclonal proliferations, including Hodgkin lymphomas and myelomas [6] (see Table 7.2). Rarely, EBV has also been associated with T- or NK-cell lymphomas, hemophagocytic lymphohistiocytosis, gastric carcinoma, and smooth cells tumors.

7.2.1 PTLD Incidence After SOT

PTLD incidence varies according to the transplanted organ, recipient's age at the time of transplantation, and EBV serostatus [7]. Data from the 2010 OPTN/SRTR annual report revealing the cumulative 1- and 5-year incidence of PTLD in pediatric and adult SOT recipients by transplanted organ is shown in Table 7.3. Results from additional published studies are consistent with these data (reviewed in [8]). For all organ types, PTLD incidence is higher in pediatric compared to adult transplant recipients due to the differential risk of being EBV seronegative at the time of transplantation.

Table 7.2 PTLD histological classification, World Health Organization 2016 (Ref. [5])

Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD[a]
Polymorphic PTLD
Monomorphic PTLD (B and T/NK cell types)
Classical Hodgkin lymphoma PTLD

[a]Changes from the 2008 classification

Table 7.3 Cumulative 1- and 5-year incidence of PTLD in pediatric and adult SOT recipients by transplanted organ as reported in the 2010 OPTN/SRTR annual report [7][a]

Organ	Pediatric 1 year (%)	Pediatric 5 year(%)	Adult 1 year(%)	Adult 5 year(%)
Lung/heart-lung	4.0	16	1.0	1.5
Liver	2.1	4.7	0.25	1.1
Pancreas (isolated)	N/A	N/A	2.3	2.3
Heart	1.6	5.7	0.3	0.7
Kidney	1.3	2.4	<0.2	0.6

[a]Data for intestinal transplant recipients not broken down by pediatric versus adult and therefore not included

7.2.2 Risk Factors for PTLD

EBV seronegativity and the development of primary infection after transplant are the most important risk factors for PTLD [9, 10]. While primary infection usually occurs in the setting of an EBV-seronegative recipient receiving an organ from an EBV-seropositive donor, viral acquisition via usual transmission routes also occurs. Immunosuppression is another important risk factor impacting the development of EBV/PTLD. The impact of immunosuppression likely is dependent both on the "net state of immunosuppression" and exposure to specific agents. T-cell-depleting agents like OKT3 and polyclonal antithymocyte globulins have been associated with PTLD after SOT in most studies [11, 12]. An association between tacrolimus and PTLD was reported in adults and pediatric populations [12]. To date, MMF has not been found to impact PTLD [12]. Effects of mTOR inhibitors are unclear with experimental data suggesting inhibition of the lymphoblastoid cell proliferation, whereas clinical registry data showed an increased risk of PTLD in patients receiving these agents [13]. Finally, recent studies indicate that EBV-seronegative patients treated with belatacept, a drug inhibiting the costimulation pathway, are at higher risk of PTLD, especially CNS PTLD.

7.3 Diagnosis of EBV

The ability to quantify the EBV viral load (VL) in the peripheral blood using nucleic acid amplification testing (NAT) (e.g., PCR) has markedly enhanced the ability to monitor for and diagnose EBV infection and disease including PTLD (EBV/PTLD). EBV VL monitoring is routinely used to both identify those at risk of progression to and to diagnose patients presenting with EBV/PTLD. Data derived from multiple studies support the use of EBV VL to predict progression to EBV/PTLD, and published guidelines support the routine use of the viral load to guide therapeutic choices for EBV infection and disease [8]. Despite its widespread use, several areas of controversy around EBV load testing deserve discussion. The optimal component of peripheral blood to test is not fully defined with conflicting results for assays using peripheral blood lymphocytes, whole blood, or plasma [8, 14]. In fact, it is not completely clear exactly what is being measured within these different compartments. While is it presumed that one is measuring EBV-infected B lymphocytes when one measures the EBV load in peripheral blood lymphocytes, less is known about measurement of whole blood or plasma. For these compartments one may be amplifying EBV DNA fragments or lytic virions though at least some evidence argues against the latter. Another major limitation has been the fact that EBV load monitoring is not standardized between laboratories. While individual centers demonstrate a high level of internal reproducibility, substantial variability has been demonstrated between laboratories. This poor interlaboratory reproducibility contributes to a lack of consensus on threshold EBV VL which should trigger diagnostic and therapeutic interventions. It is hoped that the recently released WHO International Standard for EBV for Nucleic Acid Amplification Techniques will help to overcome these issues.

Viral load testing alone cannot be used to diagnose EBV/PTLD as the test can lack sensitivity and frequently lacks specificity. Rarely, the viral load will remain low in patients with EBV/PTLD, while patients with elevated EBV VL do not always have or develop EBV disease. Accordingly, aggressive use of imaging and performance of biopsies should be used when the diagnosis of EBV/PTLD is suspected. CT scanning of the neck, chest, and abdomen may identify lesions not apparent from symptoms or examination. Many if not most experts will now also use 18-FDG PET/CT in this scenario. Imaging of the brain is paramount if central nervous system symptoms are present. Biopsy of lesions or sites of disease is needed to definitively diagnose PTLD and rule out other opportunistic infections. Because the bowel can frequently be involved in PTLD, early endoscopic evaluation should be considered in patients with unexplained abdominal pain and diarrhea. Biopsy specimens should be evaluated by pathologists familiar with PTLD, and specific assays should be performed to characterize the involved cell including evaluating cell markers such as CD20 which may influence therapeutic options and in situ hybridization for EBER, a marker of EBV-infected cells.

7.4 Prevention of EBV Disease and PTLD

Increasing interest has focused on the prevention of EBV/PTLD in SOT recipients. Potential prevention strategies can be further categorized as immunoprophylaxis, chemoprophylaxis, and preemptive therapy.

Immunoprophylaxis Immunoprophylaxis can be categorized as active or passive. Active immunoprophylaxis would be accomplished through the use of an EBV vaccine. Unfortunately, no vaccine is currently available. Passive immunoprophylaxis is accomplished by providing anti-EBV antibody through the infusion of intravenous immune globulin (IVIG). Opelz showed in a retrospective analysis that SOT recipients receiving anti-CMV immunoglobulins for CMV prophylaxis did not develop PTLD during the first year (during the time of prophylaxis) [15]. These data were not confirmed in a randomized controlled trial using anti-CMV immunoglobulin prophylaxis vs. placebo in pediatric liver transplant recipients although a trend toward less EBV disease and PTLD was observed in patients receiving immunoglobulins [4]. Finally, the use of EBV-specific cytotoxic T lymphocytes (CTLs) as adoptive immunotherapy could serve as a third potential immunoprophylactic strategy. Unfortunately, although this approach has been proven to be efficacious in stem cell transplant recipients, efforts to translate these benefits to the prevention of EBV/PTLD in SOT recipients have not succeeded as of this time (reviewed in [6]).

Chemoprophylaxis Chemoprophylaxis using antiviral agents, such as acyclovir and ganciclovir, represents another possible approach to preventing EBV/PTLD. Ganciclovir or its prodrug valganciclovir may be the preferred drug for EBV prophylaxis because of its higher in vitro antiviral activity. Nevertheless, these drugs are only effective against the lytic forms of EBV which explains their

inefficiency when the virus is in latent phase. Despite a US case-controlled study suggesting a potential role of ganciclovir given for CMV prophylaxis to reduce the PTLD incidence in kidney transplant recipients [16], other studies have not confirmed the efficacy of ganciclovir, valganciclovir, or acyclovir against EBV/PTLD in SOT recipients. A randomized prospective trial of 2 weeks of ganciclovir compared to 2 weeks of ganciclovir followed by 50 weeks of oral acyclovir in EBV-seronegative pediatric liver transplant patients did not establish any benefit to the extended use of antiviral therapy to prevent EBV disease [17]. A 2016 meta-analysis showed that the use of antiviral drugs (ganciclovir, valganciclovir, acyclovir, and valacyclovir) in mismatched EBV transplant recipients (D+/R) had no effect on PTLD incidence [18]. No significant differences were seen across all types of solid organ transplants, age groups, or antiviral use as prophylaxis or preemptive strategy.

Viral Load Monitoring and Preemptive Strategies of Prevention Surveillance monitoring of EBV loads to inform preemptive reductions in immunosuppression has resulted in a decreased incidence of EBV/PTLD compared to historical controls. McDiarmid reported a decreased incidence of PTLD from 10 to 5% using EBV viral load monitoring to guide the combined use of reduced immunosuppression and intravenous ganciclovir in pediatric liver transplant recipients with rising EBV loads [19]. Two other studies demonstrated decreased incidences of PTLD using decreased immunosuppression alone without ganciclovir in response to elevated EBV loads [20, 21]. Some centers have considered the preemptive use of the anti-CD20 monoclonal antibody rituximab for those with elevated EBV load though little published data is available. Martin reported encouraging results using EBV load monitoring to inform the preemptive use of rituximab in EBV D+/R− adult kidney transplant recipients [22]. However, the majority of treated patients actually had clinical evidence of EBV disease at the time of treatment. Accordingly, these data speak more to use rituximab for early treatment and not prevention of EBV disease. Additional experience is needed to confirm efficacy and long-term safety of rituximab in a prevention/preemption model against EBV.

Based upon available data, it appears that the strategy of using EBV load monitoring to inform preemptive reduction in immunosuppression to prevent EBV/PTLD is the optimal currently available preventive strategy, while more data evaluating the comparative safety and efficacy of rituximab with reduced immunosuppression alone in response to rising or elevated EBV loads are needed.

7.5 Treatment of EBV Disease and PTLD

The optimal treatment of the spectrum of EBV disease has not been well established. While reduction of immunosuppression is widely accepted, the role of additional therapies remains controversial. Therapeutic interventions encompass

different tools depending on histological features, disease stages, localization of the tumor, and comorbid conditions.

7.5.1 Immunosuppression (IS) Reduction

IS reduction is the first and most important treatment strategy since it allows for the development of EBV-specific cytotoxic immunity. IS reduction should be considered in patients, particularly in children, at the time of diagnosis of EBV/PTLD. In many cases, including those with polymorphic lymphoproliferations, restoration of cytotoxicity is sufficient to control the transformed B-cell population [23]. IS reduction is more effective if the tumor expresses LMP1 and EBNA2, two viral proteins which facilitate the interaction between transformed B cells and recipient cytotoxic T cells. Nevertheless, the precise IS drug blood concentrations which allow a sufficient antiviral activity while still protecting against graft rejection are not known. In practice, calcineurin inhibitors (CNI) are reduced or withdrawn; steroids may be reintroduced or increased. The role of reduction of other classes of immunosuppression is less well established and may vary by organ. Using this approach, alone or in combination with other strategies, successful regression of both polyclonal and monoclonal EBV/PTLD lesions was reported to occur in 45% of patients [23]. Response rates of IS reduction among adults are highly variable, with excellent results reported in some series and very poor results in others. A progressive stepwise reduction schedule, maintaining the lower therapeutic ranges of immunosuppressive drugs and adjusting dosage depending upon blood level monitoring, may avoid onset of acute rejection. While reduction of IS clearly carries the risk of rejection, graft function is preserved without development of rejection in some patients despite completely stopping IS suggesting the presence of acquired graft tolerance.

7.5.2 Antiviral Therapy

There is no evidence that antiviral inhibition of lytic EBV replication by intravenous ganciclovir or oral valganciclovir is beneficial to SOT recipients with high EBV loads in the presence or absence of EBV disease. The vast majority of EBV-infected cells within PTLD lesions have been shown to be transformed B cells that are not undergoing lytic infection. Nevertheless, some experts use these antivirals as an adjunct to the reduction of immunosuppression in order to lower de novo infection and recruitment of B cells into lymphoproliferation.

7.5.3 AntiCD20: Rituximab

Rituximab targets CD20-positive B lymphocytes including those infected with and transformed by EBV. Rituximab has become a standard element in the treatment of CD20-positive EBV/PTLD, alone or in combination with chemotherapy.

While some centers opt for the early use of rituximab even before a trial of reduced immunosuppression, most experts consider this to be a second-line treatment for patients who fail to respond to, or develop rejection during periods of, reduced immunosuppression. Despite its widespread use, published data defining the optimal timing and use of rituximab remains limited. The use of rituximab alone (without additional chemotherapeutic agents) appears to be effective for non-specific EBV disease and polyclonal proliferations. In aggressive PTLD forms, response rate after rituximab therapy alone was only 45%, and patient survival fell to 30% at 2 years [24]. Accordingly, the use of rituximab in combination with additional chemotherapy should be considered for patients with monomorphic PTLD, especially those with late-onset disease. Unfortunately, the optimal combination of chemotherapy and rituximab has not been established. In the randomized multicenter phase 2 prospective trial PTLD-1, patients who received four infusions of rituximab followed by four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone had a 67% rate of complete remission [25].

7.5.4 Chemotherapy

Chemotherapy represents the preferred strategy in the cases of monomorphic proliferations, myeloma, and Hodgkin diseases. Current protocols combine cyclophosphamide, adriamycine, vincristine, and steroids ("CHOP" or "ACVPB") with overall response rates of 60–75%, though the use of chemotherapy is associated with important toxicities in SOT recipients. Indeed, 15–30% of patient deaths were related to a toxic complication in the French Registry and PTLD-1 series. The use of dose-adjusted regimen, the systematic use of G-CSF, and the cures spacing are strongly recommended. Stopping IS during chemotherapy is also strongly encouraged [26]. In children, adapted protocols with low doses of cyclophosphamide and rituximab have been proposed in cases of malignant tumors [27]. Of note, none of the chemotherapy regimens have been directly compared to each other in controlled trials in the setting of PTLD.

7.5.5 Adoptive Cellular Therapy

Since the presence of EBV-specific CD8 CTL effectively controls EBV transformed B-cell proliferation in immunocompetent patients, the use of adoptive cellular therapy has been considered as a potential strategy in PTLD management in SOT. While the generation and use of EBV-specific CTL therapy have been well established for stem cell transplant recipients, this strategy has not translated easily to the SOT arena, where most PTLD are of host origin

requiring the presence of host EBV-specific CTLs to control the EBV-driven proliferation. Unfortunately, strategies using recipient cells have been tried, but the highest-risk recipients are EBV naïve prior to SOT and have dysfunctional T cells after transplantation due to iatrogenic immunosuppression. Of interest, the use of third party class 1 matched generated allogenic T cells coming from a donor bank for treatment of PTLD in SOT demonstrated a response rate greater than 50% in patients with refractory PTLD [28]. These procedures demonstrated an excellent safety profile but are currently restricted to few specialized teams.

In conclusion, treatment of PTLD remains challenging, and randomized controlled trials are still lacking. Immunosuppression lowering, rituximab, and chemotherapy are the cornerstones of transplant recipient's management, but the precise administration of these therapies should be adapted to each patient depending on its particular tumor and graft conditions.

General Approach Figure 7.1 provides an algorithmic approach to the diagnosis of EBV disease including PTLD. Figure 7.2 provides an algorithmic approach to the treatment of EBV disease including PTLD.

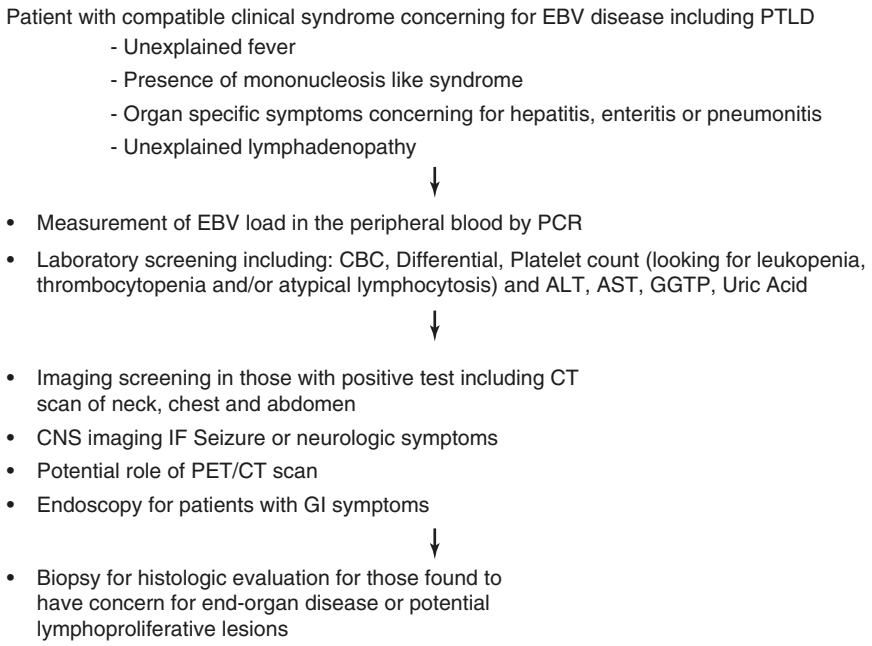

Fig. 7.1 Algorithmic approach to the diagnosis of EBV disease including PTLD

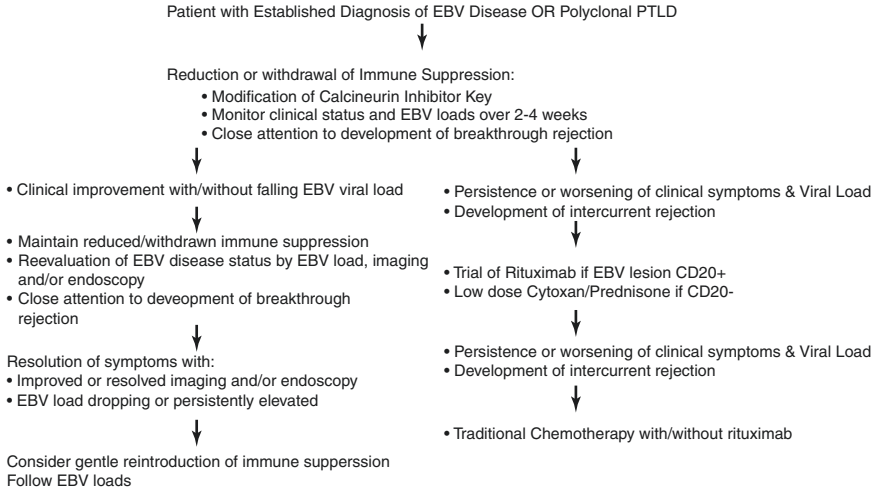

Fig. 7.2 Algorithm for the treatment of EBV disease including PTLD

References

1. Dowd JB, Palermo T, Brite J, McDade TW, Aiello A. Seroprevalence of Epstein-Barr virus infection in U.S. children ages 6-19, 2003-2010. PLoS One. 2013;8(5):e64921.
2. Fourcade G, Germi R, Guerber F, et al. Evolution of EBV seroprevalence and primary infection age in a French hospital and a city laboratory network, 2000-2016. PLoS One. 2017;12(4):e0175574.
3. Dharnidharka VR, Araya CE. Post-transplant lymphoproliferative disease. Pediatr Nephrol. 2009;24(4):731–6.
4. 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.
5. Smets F, Latinne D, Bazin H, et al. Ratio between Epstein Barr viral load and anti-Epstein Barr virus specific T-cell response as a predictive marker of post-transplant lymphoproliferative disease. Transplantation. 2002;73(10):1603–10.
6. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–90.
7. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant. 2004;4:222–30.
8. Green M, Michaels MG. Epstein-Barr virus infection and post-transplant lymphoproliferative disorder. Am J Transplant. 2013;13:41–54.
9. Caillard S, Lamy FX, Quelen C, Dantal J, Lebranchu Y, Lang P, et al. Epidemiology of post-transplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. Am J Transplant. 2012;12(3):682–93.
10. Kotton CN, Huprikar S, Kumar S. Transplant infectious diseases: a review of the scientific registry of transplant patients published data. Am J Transplant. 2017;17:1–8.
11. Opelz G, Naujokat C, Daniel V, Terness P, Döhler B. Disassociation between risk of graft loss and risk of non-Hodgkin lymphoma with induction agents in renal transplant recipients. Transplantation. 2006;81:1227–33.

12. Caillard S, Dharnidharka V, Agodoa L, Bohen E, Abbott K. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation. 2005;80(9):1233–43.
13. Sampaio MS, Cho YW, Qazi Y, Bunnapradist S, Hutchinson IV, Shah T. Posttransplant malignancies in solid organ adult recipients: an analysis of the U.S. national transplant database. Transplantation. 2012;94(10):990–8.
14. Allen U, Preiksaitis J. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplant recipients. Am J Transplant. 2013;13(S4):S107–20.
15. Opelz G, Daniel V, Naujokat C, Fickenscher H, Dohler B. Effect of cytomegalovirus prophylaxis with immunoglobulin or with antiviral drugs on post-transplant non-hodgkin lymphoma: a multicentre retrospective analysis. Lancet Oncol. 2007;8:212–8.
16. Funch DP, Walker AM, Schneider G, Ziyadeh NJ, Pescovitz MD. Ganciclovir and acyclovir reduce the risk of post-transplant lymphoproliferative disorder in renal transplant recipients. Am J Transplant. 2005;5:2894–900.
17. Green M, Kaufmann M, Wilson J, Reyes J. Comparison of intravenous ganciclovir followed by oral acyclovir with intravenous ganciclovir alone for prevention of cytomegalovirus and Epstein-Barr virus disease after liver transplantation in children. Clin Infect Dis. 1997;25(6):1344–9.
18. 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.
19. McDiarmid SV, Jordan S, Kim GS, et al. Prevention and preemptive therapy of postransplant lymphoproliferative disease in pediatric liver recipients. Transplantation. 1998;66:1604–11.
20. Lee TC, Savoldo B, Rooney CM, Heslop HE, Gee AP, Caldwell Y, 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.
21. 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(2):198–203.
22. Martin SI, Dodson B, Wheeler C, Davis J, Pesavento T, Bumgardner GL. Monitoring infection with Epstein-Barr virus among seromismatch adult renal transplant recipients. Am J Transplant. 2011;11(5):1058–63.
23. Reshef R, Vardhanabhuti S, Luskin MR, Heitjan DF, Hadjiliadis D, Goral S, et al. Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder. Am J Transplant. 2011;11:336–47.
24. Milpied N, Vasseur B, Parquet N, Garnier JL, Antoine C, Quartier P, et al. Humanized anti-CD20 monoclonal antibody (rituximab) in post transplant B-lymphoproliferative disorder: a retrospective analysis on 32 patients. Ann Oncol. 2000;11(Suppl 1):113–6.
25. Trappe RU, Dierickx D, Zimmermann H, Morschhauser F, Mollee P, Zaucha JM, et al. Response to rituximab induction is a predictive marker in B-cell post-transplant lymphoproliferative disorder and allows successful stratification into rituximab or R-CHOP consolidation in an international, prospective, multicenter phase II trial. J Clin Oncol. 2017;35(5):536–43.
26. Fohrer C, Caillard S, Koumarianou A, et al. Long term survival in post-transplant lymphoproliferative disorders with a dose-adjusted ACVBP regimen. Br J Haematol. 2006;134:602–12.
27. Gross TG, Orjuela MA, Perkins S, Park J, Lynch J, Cairo M, Smith L, Hayashi R. Low-dose chemotherapy and rituximab for post-transplant disease (PTLD): a children's oncology group report. Am J Transplant. 2012;12(11):3069–75.
28. Haque T, Wilkie GM, Jones MM, Higgins CD, Urquhart G, Wingate P, et al. Allogeneic cytotoxic T-cell therapy for EBV-positive posttransplantation lymphoproliferative disease: results of a phase 2 multicenter clinical trial. Blood. 2007;110(4):1123–31.