Viral Diseases of the Liver

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Abbreviations

CMV	Cytomegalovirus
EBV	Epstein–Barr virus
HHV	Human herpes virus
HSV	Herpes simplex virus
IM	Infectious mononucleosis
PCR	Polymerase chain reaction
PTLD	Post-transplant lymphoproliferative disorder
VZV	Varicella zoster virus
XLP	X-linked lymphoproliferative disorder

Key Points (6–12)

1. A variety of viruses in addition to the classic hepatitis viruses A to E can affect the liver. These include Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV), human herpes viruses 6, 7, and 8, human parvovirus B19, adenoviruses, and others.
2. The clinical presentation of infections with these viruses may be indistinguishable from that associated with the "classic" hepatotropic viruses and can range from transient elevation of aminotransferases to liver failure.
3. Both the innate and adaptive arms of the immune system play a role in the pathogenesis of virally mediated target organ involvement.
4. In most immune-competent patients an asymptomatic or mild disease occurs, while immune-suppressed patients

and organ transplant recipients are at high risk for the development of severe systemic infection.
5. Antiviral agents have a role in the treatment of immune-compromised patients and in immune-competent patients who present with severe life-threatening disease.
6. EBV may be associated with increased risk of malignancy and post-transplant lymphoproliferative disorders (PTLDs).

Introduction

Viruses other than the classic hepatotropic viruses, hepatitis A through E, may cause hepatic injury [1]. Among these are Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV), human herpes viruses (HHV) 6, 7, and 8, human parvovirus B19, and adenoviruses (Table 12.1). The clinical presentation of infections with these viruses may be indistinguishable from that associated with infection with classic hepatotropic viruses. The presentation ranges from a mild and transient elevation of aminotransferases to acute hepatitis and liver liver failure [1]. These viruses should be considered as possible etiologic agents in patients who have acute liver injury and whose serologic markers for the classic hepatotropic viruses are not indicative of an active infection [1]. In the present chapter, we review the clinical manifestations and the potential for immune-mediated liver injury associated with several of these viruses (see summary Table 12.2).

Epstein–Barr Virus

EBV Infection

EBV is a double-stranded DNA virus that is a member of the gamma herpes virus family [1]. Its genome consists of a linear DNA molecule that encodes nearly 100 viral proteins. Expression of different combinations of these proteins allows

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Table 12.1 Non-hepatotropic viruses that may affect the liver

Herpes viruses: Cytomegalovirus, Epstein–Barr virus, varicella zoster virus, human herpes virus 6, human herpes virus 7, and human herpes virus 8
Adenoviruses
Arenaviruses: Guanarito virus, Junín virus, Lassa fever virus, Machupo virus, and Sabiá virus
Bunyaviruses: Crimean-Congo hemorrhagic fever virus, Dobrava virus, Hantaan virus, Puumala virus, Rift Valley fever virus, and Seoul virus
Coronavirus: Severe Acute Respiratory Syndrome Virus
Erythrovirus: Parvovirus B19
Filoviruses: Ebola virus and Marburg virus
Flaviviruses: Dengue, Lujo virus, Kyasanur Forest disease virus, Omsk hemorrhagic fever virus, and yellow fever virus
Orthomyxoviruses: Influenza
Picornaviruses: Echovirus
Reovirus: Colorado tick fever virus, Reovirus 3

the virus to establish different forms of infection [2]. Cell entry and translocation of EBV particles to the nucleus is confirmed by detection of the EBV genome in isolated nuclei [3]. While B cells in the oropharynx may be the primary site of infection, resting memory B cells are thought to be the site of persistence of EBV throughout the body. EBV has evolved several strategies to evade immune system recognition and to establish latent infection in memory B cells, where it resides lifelong without any consequence in the majority of individuals [4]. After infecting B lymphocytes, the linear EBV genome becomes circular, forming an episome, which usually remains latent in these B cells. Only ten of the viral proteins are expressed in latently infected B cells in vitro. Limited gene expression during latency ensures successful escape from cytotoxic T lymphocyte (CTL) recognition [2]. EBV shares the tendency of establishing latency in the host with other herpes viruses [2]. Viral replication is spontaneously activated in only a small percentage of latently infected B cells [5].

EBV infection is a common and lifelong infection affecting over 90 % of humans worldwide. The virus replicates in nasopharyngeal epithelial cells, and seropositive persons actively shed the virus in saliva [1, 6]. Transmission of EBV usually occurs by contact with oral secretions.

Diagnosis of EBV infection is based on clinical features and on laboratory and serological findings indicative of a recent infection. The most common is leukocytosis, which appears in 70 % of cases, predominantly as lymphocytosis and monocytosis, as well as mild thrombocytopenia in up to 50 % of affected individuals. EBV-specific IgG and IgM antibodies directed against the viral capsid antigens (VCA), the early antigens (EBV anti-D and anti-R), the nuclear antigen (EBVNA), and soluble complement-fixing antigens (anti-S) are used for viral detection [1]. The "monospot" test that detects heterophil antibodies is sensitive but not specific.

In the vast majority of cases, there is no indication for liver biopsy, but when performed there may be portal and sinusoidal mononuclear cell infiltration with focal hepatic necrosis or fatty infiltration [1, 7]. Specifically, the diagnosis of EBV hepatitis is established based on the combination of elevated aminotransferases, serology compatible with active EBV infection, typical findings on liver biopsy, and demonstration of the presence of the viral genome in liver tissue by various molecular methods.

The Role of the Immune System in EBV Infection

Imbalances in the equilibrium between the virus and the host's immune system lead to the development of liver damage in EBV-infected patients. EBV can also be involved in the development of tumors such as lymphoproliferative disorders, Hodgkin's lymphoma, Burkitt's lymphoma, and nasopharyngeal carcinoma [4]. The demonstration that immunotherapeutic approaches are effective for some of these cancer patients further supports a role for the immune system in disease pathogenesis [4]. In the context of EBV-related tumors, the expression of viral antigens by malignant cells makes them suitable targets for immune therapy. Infusion of EBV-specific CTLs has proved to be safe and effective and induces protective antiviral immunity, which is lacking in EBV-associated malignancy [4].

Both the innate and the adaptive arms of the immune system play a role in anti-EBV immunity [4, 8]. EBV interacts with NK cells, neutrophils, monocytes, and macrophages, as well as with epithelial cells that are relevant to viral resistance [4]. The tonsils are the primary site for EBV infection. EBV triggers monocyte TLRs, inducing maturation of DCs, which activate CD16–CD56 bright NK cells via IL12. NK cells hamper pathogen entry at mucosal sites, thus restricting EBV infection until the adaptive immunity establishes viral immune control [9]. IFN-γ secreted by DC-activated NK cells is associated with delayed latent EBV antigen expression. It inhibits B-cell transformation, decreasing their proliferation during the first week following infection [4, 10]. IFN-γ also promotes an EBV-specific adaptive immune response by favoring a Th1-polarization.

Early after primary viral infection, NK cells are thought to limit the viral burden until virus-specific T cells are able to eliminate the infection or maintain viral titers at low levels. Innate immunity uses several "pattern recognition" receptors to sense pathogen-associated molecular patterns (PAMPs) [4]. Toll-like receptor (TLR) activation has downstream effects during primary EBV infection that favor viral latency or reactivation and facilitate immune control. Intact viral particles are recognized by the membrane surface receptor TLR2 [11]. Following viral entry into cells, viral DNA is

Table 12.2 Clinical features, diagnosis, and treatment summary table

Virus	Population at risk	Clinical and laboratory features	Acute liver failure	Unique complications	Diagnostic tests	Treatment	Effective antiviral medication
EBV	IC	Lymphocytosis	Rare	Splenic rupture	Monospot	ICP: only if severe complications	Ganciclovir
	Age >30 (esp. >60)	Monocytosis	More common in immunosuppressed patients (60 % in patients with XLP)	PTLD	EBV VCA IgM	Steroids	Valganciclovir
	XLP	Splenomegaly		HLH	PCR (blood and tissue)	Antivirals (if steroid refractory)	Valacyclovir
	Solid organ transplant recipients (especially pediatric)	Gradually rising liver enzymes		AIH exac.	Liver biopsy—rarely needed (portal and sinusoidal mononuclear cell infiltration with focal hepatic necrosis or fatty infiltration)	IC: anti-EBV CTLs antivirals	Famciclovir Foscarent
CMV	IC	Hepatosplenomegaly	Rare	Graft rejection and loss	CMV IgM	ICP—only in severe end organ disease	Ganciclovir
	Solid organ transplant recipients	Aminotransferases lower than in "classic viral hepatitis"	More common in IC	encephalitis, pneumonitis, hepatitis, uveitis, retinitis, colitis	PCR (blood and tissue)	IC—antivirals±IVIG	Valganciclovir
	Neonates (congenital CMV)	Leukopenia			Liver biopsy—important (giant multinucleated cell reaction with an inflammatory response, multifocal necrosis, biliary stasis. Large nuclear inclusions in hepatocytes or bile duct epithelium)	Organ transplant recipients— prophylactic vs. preemptive treatment	Foscarnet
	IBD	Thrombocytopenia			Immuno-histochemistry		Cidofovir CMV hyperimmune globulin Leflunomide
HSV	IC	Leukopenia, thrombocytopenia, relatively mild elevation in bilirubin	Rare	Esophagitis	HSV PCR (blood and tissue) Liver biopsy—essential (focal—extensive, hemorrhagic, or coagulative hepatocyte necrosis, limited inflammatory response). Typical intranuclear inclusions (Cowdry type A) at the margins of the foci of necrosis	Early high-dose acyclovir	Acyclovir
	Pregnancy (third trimester) Neonates	Mucocutaneous lesions (50 %)	More common in pregnancy, IC, and neonates	Pneumonitis			
VZV	Adults	Cutaneous rash	Rare	Graft loss	Viral isolation from skin lesions	Early therapy with acyclovir in severe disease or IC patients	Acyclovir
	IC		More common in immunocompromised individuals		HSV PCR (blood and tissue)		
	Liver transplant recipients				Liver biopsy (foci of coagulative necrosis and intranuclear inclusions with an inflammatory response)		

IC immunocompromised, *ICP* immunocompetent, *XLP* X-linked lymphoproliferative disorder, *PTLD* post-transplant lymphoproliferative disorder, *HLH* hemophagocytic lymphohistiocytosis, *AIH* autoimmune hepatitis, *CTLs* cytotoxic T lymphocytes

recognized by TLR9. Dual interactions through TLR2 on the cell membrane and intracellular TLR9 lead to a rapid production of IL-8, initiating an effective antiviral immunity.

Innate lymphocytes also play a role in resistance to EBV-associated malignancies. Mutations in SAP (signaling-lymphocyte activation-molecule-(SLAM)-associated protein) are associated with loss of EBV-specific immune control [4]. During EBV latency, the virus develops mechanisms of immune escape from innate immunity-dependent mechanisms, including the inhibition of NK cell activation through EBV-induced gene 3 (EBI3) [4]. EBV-transformed B lymphocytes express high levels of EBI3 protein, which has immunosuppressive activity [12].

The EBV genome is also detected in non-B cells, including phagocytes. Monocytes and macrophages are involved in the uptake of small vesicles called exosomes that contain viral mRNA. Exosomes play a role during the early phases of EBV infection and also involve innate immunity-related cell types that are not targeted by the virus [4]. An increase in neutrophils is observed during the initial phases of EBV infection, whereas a transient episode of acute neutropenia is often observed in infectious mononucleosis (IM) during the third week of illness [13]. Infected neutrophils rapidly die by apoptosis [14]. Secretion of various cytokines and chemokines (e.g., IL-1, IL-8, MIP-1α, LTB4, and reactive superoxide anion) promotes the development of EBV-specific immunity, while upregulation of IL-1R and induction of apoptosis in neutrophils inhibit anti-EBV immune responses [12].

Episodes of monocytopenia are observed during the acute phase of IM [4]. Patients with EBV-associated malignancy show a deficiency in monocyte-mediated ADCC, suggesting that monocyte functions are affected during the course of EBV infection. This is also demonstrated by the reduced phagocytic activity observed in EBV-infected monocytes [3]. EBV infection inhibits the functional ability of macrophages to respond to bacterial challenge by reducing their phagocytic potential [15]. By inhibiting the differentiation of monocytes into mature DCs, EBV temporarily halts the onset of immune responses during primary infection, enabling efficient viral replication. This permits the accumulation of a large pool of virus-infected B lymphocytes, allowing access of the virus to the memory B-cell compartment, interfering with the functions of DCs during the initiation of virus-specific immunity, and modifying the profile of secreted cytokines, thus creating a favorable environment for viral propagation [3, 4].

CTLs are major determinants in the control of acute EBV infection and are directed against both lytic and latent antigens [16]. About half of the total CD8+ T cells in acute infection are specific for a single lytic EBV epitope, and most of these epitope-specific cells have an activated/memory phenotype. In the late stages of infection, the frequency of epitope-specific CD8+ T cells directed against latent EBV proteins selectively increases, confirming that CTLs are the most important cells for limiting infection in the convalescent phase of virus infection.

In lytic infections, the virus expresses a full complement of immediate-early, early, and late lytic cycle proteins and is capable of replicating within the host cell [16]. In latent infection, the virus expresses fewer proteins, does not replicate, and is able to persist within the host cell. EBV has developed the ability to rapidly promote the expression of its own genes while simultaneously shutting down the transcriptional program of its host cell [4]. TNF-α levels are increased in IM patients, indicating its importance in ongoing antiviral response. However, the entire virus inhibits TNF-α secretion by monocytes and macrophages [3]. EBV downregulates TNF-α mRNA transcripts via suppressive action at the transcriptional level [4]. EBV proteins can also modulate IFN signaling. This effect promotes viral persistence and may also contribute to tumor development [4, 17].

EBV reactivation associated with increased specific CTL-response to a lytic EBV epitope can lead to EBV-associated chronic hepatitis [18]. EBV reactivation in these patients is based on an increased percentage of terminally differentiated CD28-CD27-CD8+ T cells, suggestive of chronic antigen stimulation [18]. Diminished expression of the co-stimulatory molecules CD28 and CD27 compromises CD8+ reactivation, making cells more resistant to apoptosis [19]. A T-cell pool with low expression of CD28 and CD27 has low ability to control reactivation of virus and is a typical finding in an elderly group. Similar changes were found in younger patients under chronic CMV and EBV antigen stimulation [2, 20].

While cellular immunity is fundamental for controlling both the primary and persistent phases of EBV propagation, the humoral response controls viral spread in late phases of infection [21]. EBV stimulates strong humoral responses to lytic cycle proteins. IgM and developing IgG responses to nucleocapsid and envelope proteins are detectable in primary EBV infection [4]. IgG responses to immediate-early and early lytic cycle proteins and to the latent proteins EBNA1 and 2 are also detectable, together with neutralizing antibodies directed against gp350 [21].

Clinical Manifestations of Acute Liver Involvement in EBV Infection

Various clinical conditions have been associated with EBV, including infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease, peripheral T-cell lymphoma, and post-transplant lymphoproliferative disorder (PTLD) [22, 23].

Primary EBV infection takes place in the oropharyngeal region, to which the virus is conveyed by saliva droplets from infected individuals. Primary infection leads to transient viremia followed by a strong T-cell adaptive immune response that holds the infection latent in immunocompetent individuals [22, 24]. If infection is delayed to adolescence or adulthood, it can cause infectious mononucleosis (IM), a self-resolving lymphoid disorder largely resulting from an uncontrolled T-cell reaction directed against EBV-infected cells. In IM patients, EBV is exclusively found in B blasts that proliferate under the influence of latent genes [4]. Following resolution of the primary infection, EBV establishes a lifelong persistence in memory B cells in which the virus remains clinically silent. In this B-cell reservoir, viral expression is entirely repressed, a process described as "true latency." Short episodes of spontaneous reactivation and consequent viral replication normally occur in healthy individuals [24]. Manifestations of liver involvement in immunocompetent hosts range from mild self-limiting acute hepatitis to occasional reports of fatal acute fulminant hepatitis. Abnormal liver blood tests are common in EBV infection and occur in up to 90 % of patients, but symptomatic hepatitis is rare [23]. Jaundice is present in only 5–10 % of cases. Typically, the rise in aminotransferases is gradual, reaching a peak that is lower than that encountered in acute viral hepatitis [1]. The diagnosis is suggested by the presence of a lymphocytosis and/or splenomegaly [23].

Compared with IM, which usually affects young patients, EBV hepatitis usually affects an older age group. In a recent review of nearly 2,000 cases in England, 10/17 patients (59 %) were aged >30, and 7/17 (41 %) were ≥60 years [23]. While 88 % had clinical or biochemical jaundice, 100 % had lymphocytosis, and 88 % had splenomegaly, only 12 % had the classic symptoms of IM. Symptoms lasted for a median of 8 weeks, and only 3/17 patients required a brief hospitalization. Severe cholestatic jaundice and right upper quadrant abdominal pain, which could be mistaken for bile duct obstruction, may occur in elderly patients [25]. In this setting, indirect hyperbilirubinemia resulting from EBV-associated autoimmune hemolytic anemia is more commonly the cause of jaundice than viral-induced cholestasis. Other occasional clinical settings for EBV liver involvement include posttransfusion hepatitis, granulomatous hepatitis, and fatal fulminant hepatitis [1, 26]. EBV superinfection may occur in patients with preexisting autoimmune hepatitis, resulting in severe hepatic decompensation [27]. Cases of liver failure were described both in immunocompromised and immunocompetent hosts [26, 28, 29].

Viral replication may cause significant clinical entities and severe complications in patients with diminished cell-mediated immunity [2, 30].

EBV-Mediated Chronic Liver Damage

Chronic EBV hepatitis in immune-competent patients was suggested in several studies [31]. However, EBV was not detected in human hepatocytes [2]. Specific latent antigens, as well as EBER transcripts, were detected in infiltrating CD8+ CTLs, implying that hepatocytes suffer from "collateral" damage [2]. Chronic hepatitis might also be induced by a soluble Fas-ligand, TNF-α, and IFN-γ. Activated CD8+ cells are trapped in the liver via specific adhesive molecules expressed by Kupffer cells and sinusoidal endothelial cells [32–34]. It is suggested that reactivation leading to liver damage can occur whether the infected lymphocytes are incidentally or intentionally in the liver.

Chronic active EBV infection (CAEBV) may result from a disturbance in the host–virus balance and Th1/Th2 misbalance, and may be associated with an aggressive clinical course. CAEBV is defined by chronic severe illness, which begins as a primary EBV infection associated with elevated transaminases, abnormal EBV serology, suggestive histopathological features, and detection of viral genome in the liver tissue. Evidence of recurrent EBV reactivations, increased circulating EBV-specific CTLs, and increased CD38 B-cell expression, along with increased LDH levels, mild splenomegaly, and thrombocytopenia, can support the diagnosis [2, 31]. CAEBV may also progress to a chronic or recurrent IM-like disease [35]. In Western countries, CAEBV is milder than in Asian countries [2]. The mild form is characterized by intact immune control of B cells, relatively low viremia, and EBV-specific CTL expansion comparable to those of seropositive donors. Patients with iatrogenic, congenital, or acquired immunodeficiency are at increased risk for EBV-associated lymphomas and CAEBV. Immune senescence in the elderly is also associated with both reactive and neoplastic EBV-driven lymphoproliferative disorders. EBV may also trigger autoimmune hepatitis [36], chronic granulomatous hepatitis [37], and vanishing bile duct syndrome [38]. While the existence of acute mononuclear hepatitis during primary EBV infection is accepted, skepticism has been expressed as to the hypothesis that EBV causes chronic liver disease in immune-competent patients. EBV in this setting may be referred to as an "incidental virus," reflecting a co-infection with other hepatotropic viruses that are a more likely cause of chronic liver disease or amplification of the EBV genome in circulating B cells that turn up in the liver [2].

In some patients with chronic liver disease caused by a major hepatotropic virus, a co-EBV infection was suggested. In a cohort of patients with chronic hepatitis B and C, patients with reactivated EBV infection had lower levels of HBV DNA and higher mean values of serum hepatitis C virus (HCV) RNA, respectively, compared to EBV patients without reactivation [2]. EBV reactivations may precede HBV flares.

Reactivation of EBV-specific T cells promotes production of several cytokines such as interferon-γ (IFN-γ), interleukin (IL)-1, IL-2, and IL-10. EBV BCRF1 shares high sequence homology with IL-10, and exogenous IL-10 enhances HCV replication. EBNA1 can promote HCV replication. IFN-γ inhibits HBV replication in the absence of cell necrosis. T-cell cross-activation may also explain HBV or HCV reactivation [2].

Post-transplant Lymphoproliferative Disorder

PTLD is a spectrum of lymphoproliferative diseases occurring in the post-transplantation setting. EBV infection is the main cause of PTLD. The incidence of PTLD ranges from 0.5 to 30 % [72, 73]. Risk factors for the development of PTLD include EBV-seronegativity at the time of transplantation, the type of organ transplanted, being highest in lung and heart and lowest in liver and kidney recipients, and the level and type of immune suppression (specifically anti-T-cell immunosuppression) [39]. PTLD complicates up to 10 % of pediatric liver graft recipients, with a mortality of up to 50 %. In the pediatric population, post-transplant primary infection within 3 months of OLT was associated with sustained EBV detection and increased the risk of the late occurrence of PTLD [40].

PTLD emerges as either of recipient or donor origin depending on the type of transplant. Bone marrow transplant (BMT) patients develop PTLD of donor origin when EBV-infected B cells derived from the donor marrow proliferate into lymphoma. Conversely, solid organ transplant patients develop PTLD of recipient origin when EBV released from the transplanted organ infects the recipient's B cells [4, 39].

The spectrum of PTLD ranges from polymorphic lymphocyte proliferation to high-grade life-threatening monoclonal lymphoma [39]. The interplay between the EBV life cycle and latency and non-viral factors determines the histology and clinical presentation of the disease. The majority of PTLD is of B-cell origin. EBV's in vitro transforming abilities, distinctive latency, and clonality within the malignant cells determine the biology of the disease [39]. Measurement of viral load by quantitative polymerase chain reaction (PCR) can assist in the surveillance and diagnosis of PTLD, although its specificity for the diagnosis is only 50 % [39]. Post-transplantation patients should be monitored by EBV PCR levels in the peripheral blood with the purpose of detecting active EBV infection early and instituting preemptive therapy prior to the development of overt PTLD.

Management options for PTLD include reduction of immune suppression, biological therapy with anti-B cell antibodies, combination chemotherapy, and adoptive immunotherapy using EBV-specific CTLs [41]. Surgery may be considered for localized PTLDs. Reduction of immune suppression alone results in clinical remission in 25–63 % of adults and in 40–86 % of pediatric PTLD patients by restoring EBV-specific immunity [39]. These patients should be monitored closely for acute allograft rejection. Newer immunosuppressants, including mycophenolate mofetil and sirolimus, appear to be associated with fewer post-transplant malignancies.

Of patients with X-linked lymphoproliferative disorder (XLP), approximately 60 % may develop a severe form of IM with hemophagocytic lymphohistiocytosis and fulminant hepatitis. Treatment consists of etoposide-based chemotherapy and hematopoietic stem cell transplantation. Early treatment of primary EBV infection in these patients (prior to development of HLH) may be comprised of treatment with anti-CD20 antibodies in combination with antivirals (acyclovir or ganciclovir), IVIG, or steroids.

EBV-Mediated Liver Cancer

EBV has been considered a major factor in the development of a wide range of cancers both in immunocompetent and immunocompromised individuals [2]. EBV or infected cell clones can promote the replication of HCV and have been suggested to be involved in the development of hepatocellular carcinoma (HCC). EBV-infected cells support HCV replication better than uninfected cells, suggesting that EBV may act as a helper virus to promote HCV replication in HCV-positive HCCs. A greater amount of EBV DNA was reported in HCV-positive HCC compared to HBV-associated HCC. In some studies, up to 30 % of liver cancers were found to harbor EBV DNA [42]. This finding, however, was not confirmed in other studies. A possible source of detected EBV DNA might be the infiltrating lymphocytes [2]. The weak positivity of EBV DNA in some liver tissues was explained by others as possible amplification of EBV DNA in the lymphoid infiltrate or blood, reflecting a high EBV DNA load in these patients.

Treatment of EBV Hepatitis

Primary EBV infection is subclinical in the majority of immunocompetent individuals; it may lead to IM in adolescents and adults. It is generally self-limiting; therefore, in immunocompetent individuals, symptomatic treatment alone is recommended. This includes rest, adequate hydration and nutrition, and analgesics or antipyretics as needed. In patients suffering from IM, avoidance of exertion and participation in sports is recommended for at least 3 weeks due to the rare risk of splenic rupture. Rare patients suffering from severe complications of acute EBV are usually treated with corticosteroids even though there is little evidence to support their

use [43, 44]. The dose used varies in different reports. The use of antivirals in the management of severe EBV infections in immunocompetent hosts is debatable. However, it is suggested as an adjunct to steroid treatment [45], especially in cases of refractory disease [46]. Several antiviral drugs, including acyclic nucleoside and nucleotide analogues and pyrophosphate analogues, inhibit replication of EBV in cell culture via inhibition of EBV DNA polymerase. Acyclovir inhibits in vitro EBV replication and transiently reduces viral shedding in the oropharynx but does not reduce viremia or symptoms. Ganciclovir was effective in the treatment of EBV hepatitis in a small number of children and in adults [47]. Valganciclovir, the oral pro-drug of ganciclovir, has been successfully used in the treatment of severe acute EBV hepatitis (900 mg×2/daily for 15 days) [46]. Additional drugs with antiviral activity against EBV include valacyclovir, famciclovir, and foscarnet. Patients with acute liver failure should be considered for urgent liver transplantation, as the likelihood of spontaneous recovery is small [48]. Patients with immunodeficiencies are at increased risk of liver failure and the development of lethal lymphoproliferative diseases. The major pathogenic causes thought to be important in the development of lymphoproliferative disorders/lymphomas are primary immunodeficiency (XLP, ataxia telangiectasia, Wiskott-Aldrich syndrome, Chediak-Higashi syndrome, SCID, CVID, and others), immunosuppressive therapy, and HIV/AIDS. In these patients, primary EBV infection should be treated preemptively with ex vivo-generated EBV-specific CTLs or effective antiviral medication. In seronegative patients with XLP, monthly prophylaxis with IVIG is recommended. Patients who have developed EBV-associated lymphoproliferative disease may benefit from chemotherapy, radiation therapy, or biological therapy with monoclonal antibodies or EBV-specific CTLs. Hematopoetic stem cell transplantation is the only potentially curative therapy for many patients but is usually recommended only in children [49].

Cytomegalovirus

CMV Infection and Diagnosis

Human CMV is a double-stranded DNA virus that is the largest member of the beta herpesviridae family. The cellular response to CMV infection is characterized by cytomegaly and a spectrum of prominent clinical syndromes. The spectrum of clinical syndromes associated with CMV disease ranges from asymptomatic infection to life-threatening congenital CMV syndrome in neonates to infectious mononucleosis syndrome in young adults to severe pulmonary, retinal, neurological, gastrointestinal, and hepatic diseases in immunocompromised hosts [1]. Infection can be acquired either in the perinatal period and infancy or in adulthood through sexual contact, blood transfusions, or organ transplantation [1].

Serologic studies of CMV-IgM antibodies are helpful for the diagnosis of primary infections. Viral culture techniques use the "shell vial" assay and CMV early antigens. Molecular techniques to detect CMV early antigen or CMV DNA increase sensitivity for detecting CMV infection in blood and end organ tissue. To clearly establish the diagnosis of active CMV infection, it is necessary to have histological evidence of cellular injury associated with infection. Distinct pathologic findings on liver biopsy are important for the diagnosis of CMV hepatitis, especially in immunocompromised hosts. Giant multinucleated cell reaction with an inflammatory response, multifocal necrosis, and biliary stasis are common. Large nuclear inclusion-bearing cells, the so-called owl's eye inclusions, are detected in hepatocytes or in bile duct epithelium.

CMV Infection in the Immunocompetent Host

The seroprevalence for CMV worldwide ranges from 60 to 100 % [50]. Most primary CMV infections in immunocompetent adults are asymptomatic or associated with a mild IM syndrome. Symptomatic CMV infection in non-immunocompromised hosts has traditionally been considered to display a benign self-limited course of a disease that resembles EBV-IM syndrome. Similar to other herpes viruses, all primary infections resolve and enter into lifelong latency in which live viruses are sequestered in a non-replicative state. Persons with latent infection and intact immune systems have no symptoms but exhibit antibodies to CMV. Circulating lymphocytes, monocytes, and polymorphonuclear leukocytes may serve as the reservoir site of viral latency. The risk for intermittent reactivation is increased with immunosuppression [1].

Liver dysfunction is commonly associated with CMV mononucleosis. It is usually mild and rarely symptomatic in the immunocompetent patient. Hepatosplenomegaly and laboratory evidence of mild to moderate elevation of liver enzymes are the predominant features, with increased aminotransferases and alkaline phosphatase in the majority of cases, but the levels of these are lower than are encountered in acute hepatitis due to "classic" hepatitis viruses [1, 51]. Rare manifestations of CMV hepatitis include tender hepatomegaly, granulomatous hepatitis, anicteric or icteric cholestatic hepatitis, and acute hepatitis with massive necrosis [88].

The morbidity and mortality that CMV infection may cause in immunocompetent hosts were recently reviewed in 290 patients [52]. Severe CMV infections affected almost every system. The gastrointestinal tract (gastroenteritis, duodenitis, ileitis, colitis, proctitis) and the central nervous system (meningitis, encephalitis, transverse myelitis, nerve

palsies, myeloradiculopathy) were the most frequent sites [52, 53]. In addition, hematological manifestations (hemolytic anemia and thrombocytopenia), ocular (uveitis, retinitis), liver (hepatitis), pulmonary (pneumonitis), and thrombosis of the arterial and venous system (deep venous thrombosis, portal vein thrombosis, pulmonary embolism) have been described [52, 54]. Several cases were treated with ganciclovir or with valganciclovir, some with fatal outcome despite therapy.

A special population afflicted by CMV disease consists of patients with preexisting inflammatory bowel disease [55]. TNF-α and IFN-γ are frequently elevated in these patients and may promote reactivation of a latent CMV infection, which further promotes additional cytokine release, particularly of IL-6. This in turn leads to a vicious circle of exacerbation of the inflammatory bowel disease. This sequence of events may be observed in patients with inflammatory bowel disease who have not recently received any steroid treatment. CMV colitis in patients with underlying inflammatory bowel disease has the potential to lead to severe complications including toxic megacolon, colovesical fistula, perforation, and peritonitis.

CMV Infection in the Immunocompromised Host

In immunocompromised patients, CMV disease results either from a primary infection or, more commonly, from reactivation of a latent infection [1, 52]. Disseminated CMV infections in immunocompromised patients with impaired cell-mediated immunity, including HIV-infected patients, transplant recipients, and congenitally infected patients, are associated with increased morbidity and mortality. Anti-CMV antibodies are detected during episodes of reactivation. However, the incidence and severity of CMV disease closely parallels the degree of cellular immune dysfunction, characterized by decreased numbers of CTLs and natural killer cells [56]. The clinical syndromes observed in these patients include encephalitis, pneumonitis, hepatitis, uveitis, retinitis, colitis, and graft rejection. CMV infection affecting the human embryo, a host with immature immunologic responses, may lead to serious complications such as microcephaly, mental retardation, spastic paralysis, hepatosplenomegaly, anemia, thrombocytopenia, deafness, and optic nerve atrophy leading to blindness [52].

CMV is the most common opportunistic viral infection in AIDS patients, causing retinitis, central nervous system infections, esophagitis, and colitis. CMV may also invade the hepatobiliary tract in AIDS patients, causing hepatitis, pancreatitis, and acute acalculous cholecystitis [57]. The presence of CMV retinitis, gastrointestinal disease, or viremia in AIDS patients increases the risk for a cholestatic syndrome caused by papillary stenosis and sclerosing cholangitis (AIDS cholangiopathy), which does not usually respond to antiviral therapy. Hepatitis is the most frequent organ-specific complication of CMV infection after liver transplantation, affecting 10 % of recipients and with a higher incidence among seronegative recipients than seropositive patients (26 % vs. 9 %, respectively). In these cases, infection occurs as a consequence of reactivation rather than primary infection [1].

Treatment of CMV Infection

The current opinion is that CMV infection in immunocompetent patients does not require treatment [52]. Data on a need for antiviral treatment in immunocompetent patients with severe CMV infection is conflicting. The improvement observed in some treated patients may have been related to the typically self-limiting course of the disease and thus cannot be attributed with certainty to a treatment effect [45].

For severe cases, particularly in patients with impaired cell-mediated immunity, therapy can be life-saving [1]. Drugs approved for treatment of CMV disease include ganciclovir, valganciclovir, foscarnet, and cidofovir. Ganciclovir is considered the antiviral agent of choice against CMV. The duration of therapy is guided by repeated measurements of CMV in blood samples. Emerging strains resistant to ganciclovir pose a therapeutic challenge for which foscarnet or cidofovir may become alternative antiviral agents [58]. Valganciclovir has recently been evaluated among liver transplant recipients with CMV disease [1, 56]. Ganciclovir can lead to myelosuppression, central nervous system disorders, hepatotoxicity, irreversible infertility, or teratogenesis, whereas foscarnet can cause disturbances in mineral and electrolyte homeostasis and nephrotoxicity. Long-term administration of these agents may lead to the emergence of resistant viral strains [45].

CMV in Liver Transplant Recipients

CMV infection is a common complication following liver transplantation and contributes to morbidity and mortality in these patients [56]. CMV evades the immune system resulting in a state of latency in several types of host cells. Cellular sites of viral latency become reservoirs of reactivation during periods of stress and cytokine release and serve as vehicles for transmission to susceptible hosts. Pharmacologically induced impairment of immune response to "endogenously reactivated" or "allograft-transmitted" CMV leads to febrile and tissue-invasive diseases in liver transplant recipients [56].

Overall, 18–29 % of liver transplant recipients will develop CMV disease [59]. A lack of preexisting CMV-specific

immunity in CMV-seronegative recipients of liver allograft from CMV-seropositive donors (CMV D+/R−) exposes these patients to the highest risk of CMV disease and its complications (44–65 % in CMV D+/R− vs. 8–19 % in CMV-seropositive recipients, CMV R+) [60]. The incidence is reduced in liver transplant recipients who receive antiviral prophylaxis with valganciclovir or oral ganciclovir for the first 3 months following liver transplantation. CMV disease rates of 12–30 % in high-risk CMV D+/R− and less than 10 % in CMV R+ were reported in patients who received antiviral prophylaxis [59, 61]. A recent randomized control trial showed that 200 days of prophylaxis are more effective than 100 days of therapy in high-risk (D+/R−) patients; however, this has yet to become a standard recommendation due to safety and cost [62]. In individuals who received antiviral prophylaxis, CMV disease may occur 3–6 months after completing antiviral prophylaxis; hence, the term "delayed-onset" or "late-onset" CMV disease [56].

The use of highly potent pharmacologic immune suppression severely impairs the ability of liver transplant recipients to mount an effective immune response against reactivating CMV, thereby predisposing them to increased risk of CMV disease [60]. The severity of immune dysfunction is strongest with lymphocyte-depleting drugs such as anti-CD3 and antithymocyte globulin [56].

Defects in innate and in CMV-specific cell-mediated immunity predispose these patients to severe infections. Mutations in innate immunity-associated genes increase the risk of CMV disease after liver transplantation. TLR2 expressed in innate immune cells senses the glycoprotein B of CMV, thereby signaling immune cells to produce cytokines and antiviral peptides. In a study of 92 liver transplant recipients, a genetic polymorphism in the TLR-2 gene was associated with a higher degree of CMV replication and a higher incidence of CMV disease. This polymorphism decreased the cellular recognition of CMV by TLR2-expressing cells. Programmed death-1 receptor expression and immune evasion genes have also been assessed as prognostic indicators of CMV disease following liver transplantation.

CMV disease in liver recipients manifests with fever, bone marrow suppression, and organ-invasive disease. These direct clinical effects are classified as CMV syndrome (fever with myelosuppression) or as tissue-invasive CMV disease, which most often involves the gastrointestinal tract (CMV gastritis, esophagitis, enteritis, and colitis), although any organ may be involved. CMV hepatitis is common in liver transplant recipients compared to other solid organ transplant recipients and manifests with symptoms indistinguishable from acute allograft rejection [56]. The availability of sensitive tests for the rapid detection of CMV in the blood may obviate the need for a liver biopsy to differentiate CMV infection from rejection. However, in many cases, a liver biopsy is required to differentiate or demonstrate a coexistence of CMV disease and allograft rejection.

Several indirect outcomes in these patients are mediated by the ability of the virus to modulate the immune system [56]. CMV is known to be a potent up-regulator of alloantigens, thereby increasing the risk of acute rejection and chronic allograft dysfunction. CMV is associated with vanishing bile duct syndrome and ductopenic rejection, leading to chronic cholestasis and allograft failure and with a higher incidence of hepatic artery thrombosis. The immunomodulatory effects of CMV predispose to other opportunistic infections including fungi, other viruses, and bacteria such as *Nocardia*. CMV-infected transplant recipients are more likely to develop EBV-associated PTLD or to develop coinfections with other viruses such as human herpes virus HHV6 and HHV7 [63]. An association between CMV and an accelerated course of HCV recurrence was described [64]. Forty-eight percent of HCV-transplanted patients who developed CMV disease had allograft loss or died within 3 years of transplantation, compared to 35 % of patients with asymptomatic CMV infection and 17 % of those who did not develop CMV infection [64].

CMV infection is an independent predictor of mortality after solid organ transplantation. The use of anti-CMV drugs, either through antiviral prophylaxis or preemptive therapy, led to reduction in the overall mortality after solid organ transplantation. An analysis of 437 liver transplant recipients demonstrated that CMV disease occurred in 8.5 % of the patients and that its occurrence was independently associated with a fivefold increased risk of all-cause mortality and an 11-fold increased risk of infection-related mortality [65].

Allograft rejection can promote CMV reactivation and is a significant risk factor for CMV disease following liver transplantation [56]. Cytokines released during acute rejection, particularly TNF-α, are potent activators of latent CMV. Therapy for allograft rejection, which involves intensification of the immunosuppressive regimen, further increases the risk of CMV disease. The risk of CMV disease after liver transplantation is associated in direct proportion with the degree of CMV replication, which is partly a function of "over-immunosuppression" [66].

There are two strategies for CMV disease prevention after liver transplantation: preemptive therapy and antiviral prophylaxis [56]. For preemptive therapy, CMV reactivation is monitored by sensitive assays; upon detection, antiviral drugs are administered early to halt progression of the asymptomatic infection to full-blown clinical disease [67]. Preemptive therapy with oral ganciclovir or intravenous ganciclovir or valganciclovir resulted in reduction of CMV disease by 70 % [68], and, unlike antiviral prophylaxis, was not associated with late-onset CMV disease. Valganciclovir is currently the most commonly used drug for preemptive therapy.

Preemptive therapy may not be completely effective in CMV D+/R− liver transplant recipients because the replication kinetics of CMV in immune deficient individuals is very rapid [66].

For antiviral prophylaxis, antiviral drugs such as ganciclovir and valganciclovir are administered to patients at risk of CMV disease after liver transplantation [61, 69–73]. While there is no clear consensus regarding antiviral prophylaxis, it is administered by the majority of transplant centers for prevention of primary CMV disease in high-risk CMV D+/R− transplant recipients [74]. Prophylaxis is recommended in all CMV D+/R− liver recipients [75]. Several clinical trials have demonstrated its effectiveness in preventing the direct and indirect effects of CMV after liver transplantation [68]. Compared to placebo, patients who received antiviral prophylaxis had a 58–80 % reduction in CMV disease and a 40 % reduction in CMV infection [68]. The use of acyclovir as anti-CMV prophylaxis after liver transplantation has been supplanted by ganciclovir and valganciclovir because of their superior efficacy [71, 76, 77]. Prophylactic versus preemptive therapy for intermediate- and low-risk groups (D+/R+, D−/R+, and D−/R−, respectively) is based on the local expertise of each transplant center. However, the general approach for D−/R− patients is that only seronegative blood products are used and no prophylaxis is administered. D+/R+ or D−/R+ patients are monitored for CMV reactivation and treated preemptively for 7 days. Where available, "protective matching" of donor and recipient based on CMV serological status is advocated because it has been shown to reduce the risk of post-transplant CMV disease [69]. The current recommendation for antiviral treatment of CMV disease after liver transplantation is intravenous ganciclovir along with a reduction in the degree of pharmacologic immunosuppression [78]. Valganciclovir is a possible oral treatment for mild to moderate disease [78]. In cases of ganciclovir-resistant CMV disease, treatment options include foscarnet, cidofovir, CMV hyperimmune globulins, or leflunomide [69]. Compartmentalized CMV disease refers to clinical syndromes wherein the virus is detected in the affected tissues but is minimally detectable or undetectable in the blood [56, 69]. In the gastrointestinal system, "compartmentalized" CMV disease in the form of gastritis, esophagitis, enteritis, or colitis constitutes the vast majority of tissue-invasive conditions [60].

Herpes Simplex Virus

Herpes simplex viruses, HSV-1 and HSV-2, commonly infect humans and produce a wide variety of illnesses. The clinical manifestations and course of HSV infections depend on the site involved and patient's age and immune status [1]. HSV viremia results in visceral involvement, affecting mainly the esophagus, lungs, and liver. Liver involvement occurs in neonatal infections, pregnancy, and immunocompromised hosts, where it is frequently a fulminant disease [1].

HSV is an uncommon cause of hepatitis in immunocompetent patients. A mild asymptomatic elevation of aminotransferase levels can be detected in 14 % of healthy adults with genital infection [79]. Fulminant hepatitis with more than 100-fold rise in aminotransferases was reported and associated with a favorable outcome after antiviral therapy [80]. The incidence of HSV hepatitis was reported to be up to 6 % of fulminant hepatitis cases.

In immunocompromised hosts, HSV hepatitis has occurred during primary and, rarely, during recurrent infection, with a triad of fever, leukopenia and markedly elevated liver enzymes, as well as thrombocytopenia and a relatively mild increase in bilirubin [1]. Liver biopsy is essential to establish the diagnosis of HSV hepatitis. It shows focal, sometimes extensive, hemorrhagic, or coagulative, necrosis of the hepatocytes with limited inflammatory response. Typical intranuclear inclusions (Cowdry type A) are often identified at the margins of the foci of necrosis. The diagnosis is confirmed by detection of HSV DNA sequences by molecular techniques [1].

In neonates, hepatitis occurs with multi-organ involvement and carries a high mortality rate. In pregnant women, it is observed in the context of disseminated primary infection during the third trimester and presenting as fulminant hepatitis. Mucocutaneous lesions are present in only half of cases; thus, many cases are not diagnosed until autopsy. Early diagnosis and treatment with antiviral therapy may reverse an otherwise fatal process [1].

The treatment of choice in these patients is early high-dose acyclovir [81, 82]. Recurrence was not observed, suggesting that disseminated HSV infection should not be an absolute contraindication for transplantation in certain clinical settings [1, 83, 84].

The importance of additional human herpes viruses (HHV6 and 7) has been debated in recent years. According to some series, HHV6-infected patients have higher rates of acute and chronic allograft rejection, bacterial and opportunistic infections, a higher risk for CMV disease, and shorter graft survival [85]. While HHV6 reactivation is common after solid organ transplantation, clinical disease is rare, manifesting as fever, myelosuppression, and end organ disease including encephalitis and hepatitis. Treatment is indicated for end organ disease and includes foscarnet, ganciclovir, and cidofovir [86].

Varicella Zoster Virus

Primary varicella infection is usually benign with mild transient elevation in liver enzymes in up to 25 % of children; however, it can cause severe acute hepatitis and even ALF in immune-competent adults. In transplanted patients, primary

infection can present with an aggressive liver disease [1]. Such infection may occur in the immediate postoperative period or up to several months after liver transplantation and is usually associated with rapid onset and fatal hepatitis [87]. Serologic testing is of little value in immunocompromised patients. Confirmation of diagnosis is made through isolation of VZV from skin lesions or from the affected organs. Liver biopsy often shows foci of coagulative necrosis and intranuclear inclusions with an inflammatory response [1]. Early administration of intravenous acyclovir is critical in the setting of VZV hepatitis, especially in immunocompromised patients [1, 88].

Parvovirus (B19)

Parvovirus (B19), a small DNA virus, is a member of the parvoviridae family. Its clinical manifestations include erythema infectiosum, hydrops fetalis and fetal death in children, and arthritis in adults. Leucopenia, thrombocytopenia, and aplastic crisis in patients with chronic hemolytic anemia are additional features. Rare manifestations include neurological, cardiac, and hepatic end organ damage and vasculitis. Hepatic manifestations range from mild transient hepatitis to acute liver failure with or without associated aplastic anemia. Infection is usually benign and self-limiting, and symptomatic therapy alone is recommended [1].

Adenoviruses

There are 50 different serotypes of adenoviruses that cause acute infections of the respiratory system, conjunctivae, and gastrointestinal tract and occasionally hemorrhagic cystitis, infantile diarrhea, intussusception, and central nervous system infections [1]. Multi-organ involvement has been reported in immunocompromised, and rarely in immunocompetent, patients, associated with increased mortality [89]. Fatal cases of adenovirus infection with fulminant hepatitis were reported in immunosuppressed adults [90]. No specific therapy for adenovirus hepatitis is currently available, and cidofovir has been recently suggested as an optional treatment [1].

Additional Viruses That May Cause Hepatitis

Several viruses may involve the liver as a part of an acute viral infection (Table 12.1). This infection may manifest as mild hepatitis and rarely as severe hepatitis and liver failure, along with other severe manifestations such as hemorrhagic fever. Therapy is supportive with anecdotal reports supporting antiviral therapy. Patients with liver failure should be considered for urgent liver transplantation; however, this may be hindered by concomitant damage to other organs.

References

1. Gallegos-Orozco JF, Rakela-Brodner J. Hepatitis viruses: not always what it seems to be. Rev Med Chil. 2010;138:1302–11.
2. Petrova M, Kamburov V. Epstein-Barr virus: silent companion or causative agent of chronic liver disease? World J Gastroenterol. 2010;16:4130–4.
3. Savard M, Gosselin J. Epstein-Barr virus immunosuppression of innate immunity mediated by phagocytes. Virus Res. 2006;119: 134–45.
4. Martorelli D, Muraro E, Merlo A, Turrini R, Fae DA, Rosato A, Dolcetti R. Exploiting the interplay between innate and adaptive immunity to improve immunotherapeutic strategies for Epstein-Barr-virus-driven disorders. Clin Dev Immunol. 2012;2012: 931952.
5. Ressing ME, Horst D, Griffin BD, Tellam J, Zuo J, Khanna R, Rowe M, et al. Epstein-Barr virus evasion of CD8(+) and CD4(+) T cell immunity via concerted actions of multiple gene products. Semin Cancer Biol. 2008;18:397–408.
6. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. Nat Rev Cancer. 2004;4:757–68.
7. Markin RS. Manifestations of Epstein-Barr virus-associated disorders in liver. Liver. 1994;14:1–13.
8. Yamashita N, Kimura H, Morishima T. Virological aspects of Epstein-Barr virus infections. Acta Med Okayama. 2005;59: 239–46.
9. Strowig T, Brilot F, Munz C. Noncytotoxic functions of NK cells: direct pathogen restriction and assistance to adaptive immunity. J Immunol. 2008;180:7785–91.
10. Strowig T, Brilot F, Arrey F, Bougras G, Thomas D, Muller WA, Munz C. Tonsilar NK cells restrict B cell transformation by the Epstein-Barr virus via IFN-gamma. PLoS Pathog. 2008;4:e27.
11. Ning S. Innate immune modulation in EBV infection. Herpesviridae. 2011;2:1.
12. Levitsky V, Masucci MG. Manipulation of immune responses by Epstein-Barr virus. Virus Res. 2002;88:71–86.
13. Kagoya Y, Hangaishi A, Takahashi T, Imai Y, Kurokawa M. High-dose dexamethasone therapy for severe thrombocytopenia and neutropenia induced by EBV infectious mononucleosis. Int J Hematol. 2010;91:326–7.
14. Larochelle B, Flamand L, Gourde P, Beauchamp D, Gosselin J. Epstein-Barr virus infects and induces apoptosis in human neutrophils. Blood. 1998;92:291–9.
15. Lin YL, Li M. Human cytomegalovirus and Epstein-Barr virus inhibit oral bacteria-induced macrophage activation and phagocytosis. Oral Microbiol Immunol. 2009;24:243–8.
16. Mautner J, Bornkamm GW. The role of virus-specific CD4+ T cells in the control of Epstein-Barr virus infection. Eur J Cell Biol. 2012;91:31–5.
17. Shah KM, Young LS. Epstein-Barr virus and carcinogenesis: beyond Burkitt's lymphoma. Clin Microbiol Infect. 2009;15: 982–8.
18. Petrova M, Muhtarova M, Nikolova M, Magaev S, Taskov H, Nikolovska D, Krastev Z. Chronic Epstein-Barr virus-related hepatitis in immunocompetent patients. World J Gastroenterol. 2006; 12:5711–6.
19. van Baarle D, Tsegaye A, Miedema F, Akbar A. Significance of senescence for virus-specific memory T cell responses: rapid ageing during chronic stimulation of the immune system. Immunol Lett. 2005;97:19–29.
20. Wills MR, Okecha G, Weekes MP, Gandhi MK, Sissons PJ, Carmichael AJ. Identification of naive or antigen-experienced human CD8(+) T cells by expression of costimulation and chemokine receptors: analysis of the human cytomegalovirus-specific CD8(+) T cell response. J Immunol. 2002;168:5455–64.

21. Hislop AD, Taylor GS, Sauce D, Rickinson AB. Cellular responses to viral infection in humans: lessons from Epstein-Barr virus. Annu Rev Immunol. 2007;25:587–617.

22. Cohen JI. Epstein-Barr virus infection. N Engl J Med. 2000;343:481–92.

23. Vine LJ, Shepherd K, Hunter JG, Madden R, Thornton C, Ellis V, Bendall RP, et al. Characteristics of Epstein-Barr virus hepatitis among patients with jaundice or acute hepatitis. Aliment Pharmacol Ther. 2012;36:16–21.

24. Klenerman P, Hill A. T cells and viral persistence: lessons from diverse infections. Nat Immunol. 2005;6:873–9.

25. Shaukat A, Tsai HT, Rutherford R, Anania FA. Epstein-Barr virus induced hepatitis: an important cause of cholestasis. Hepatol Res. 2005;33:24–6.

26. Okano M, Gross TG. Acute or chronic life-threatening diseases associated with Epstein-Barr virus infection. Am J Med Sci. 2012;343:483–9.

27. Koay LB, Tsai SL, Sun CS, Wu KT. Chronic autoimmune hepatitis with Epstein-Barr virus superinfection: a case report and review of literature. Hepatogastroenterology. 2008;55:1781–4.

28. Ader F, Chatellier D, Le Berre R, Morand P, Fourrier F. Fulminant Epstein-Barr virus (EBV) hepatitis in a young immunocompetent subject. Med Mal Infect. 2006;36:396–8.

29. Chiba T, Goto S, Yokosuka O, Imazeki F, Tanaka M, Fukai K, Takahashi Y, et al. Fatal chronic active Epstein-Barr virus infection mimicking autoimmune hepatitis. Eur J Gastroenterol Hepatol. 2004;16:225–8.

30. Babel N, Schwarzmann F, Prang N, Jaeger M, Wolf H, Kern F, Volk HD, et al. Association between Epstein-Barr virus infection and late acute transplant rejection in long-term transplant patients. Transplantation. 2001;72:736–9.

31. Drebber U, Kasper HU, Krupacz J, Haferkamp K, Kern MA, Steffen HM, Quasdorff M, et al. The role of Epstein-Barr virus in acute and chronic hepatitis. J Hepatol. 2006;44:879–85.

32. Mehal WZ. Intrahepatic T, cell survival versus death: which one prevails and why? J Hepatol. 2003;39:1070–1.

33. Mehal WZ, Azzaroli F, Crispe IN. Immunology of the healthy liver: old questions and new insights. Gastroenterology. 2001;120:250–60.

34. Crispe IN, Dao T, Klugewitz K, Mehal WZ, Metz DP. The liver as a site of T-cell apoptosis: graveyard, or killing field? Immunol Rev. 2000;174:47–62.

35. Straus SE. The chronic mononucleosis syndrome. J Infect Dis. 1988;157:405–12.

36. Vento S, Cainelli F. Is there a role for viruses in triggering autoimmune hepatitis? Autoimmun Rev. 2004;3:61–9.

37. Biest S, Schubert TT. Chronic Epstein-Barr virus infection: a cause of granulomatous hepatitis? J Clin Gastroenterol. 1989;11:343–6.

38. Kikuchi K, Miyakawa H, Abe K, Fujikawa H, Horiuchi T, Nagai K, Kako M. Vanishing bile duct syndrome associated with chronic EBV infection. Dig Dis Sci. 2000;45:160–5.

39. Kamdar KY, Rooney CM, Heslop HE. Posttransplant lymphoproliferative disease following liver transplantation. Curr Opin Organ Transplant. 2011;16:274–80.

40. D'Antiga L, Del Rizzo M, Mengoli C, Cillo U, Guariso G, Zancan L. Sustained Epstein-Barr virus detection in paediatric liver transplantation. Insights into the occurrence of late PTLD. Liver Transpl. 2007;13:343–8.

41. Kataoka K, Seo S, Sugawara Y, Ota S, Imai Y, Takahashi T, Fukayama M, et al. Post-transplant lymphoproliferative disorder after adult-to-adult living donor liver transplant: case series and review of literature. Leuk Lymphoma. 2010;51:1494–501.

42. Li W, Wu BA, Zeng YM, Chen GC, Li XX, Chen JT, Guo YW, et al. Epstein-Barr virus in hepatocellular carcinogenesis. World J Gastroenterol. 2004;10:3409–13.

43. Luzuriaga K, Sullivan JL. Infectious mononucleosis. N Engl J Med. 2010;362:1993–2000.

44. Candy B, Hotopf M. Steroids for symptom control in infectious mononucleosis. Cochrane Database Syst Rev. 2006;CD004402.

45. Rafailidis PI, Mavros MN, Kapaskelis A, Falagas ME. Antiviral treatment for severe EBV infections in apparently immunocompetent patients. J Clin Virol. 2010;49:151–7.

46. Pisapia R, Mariano A, Rianda A, Testa A, Oliva A, Vincenzi L. Severe EBV hepatitis treated with valganciclovir. Infection. 2013;41:251–4.

47. Adams LA, Deboer B, Jeffrey G, Marley R, Garas G. Ganciclovir and the treatment of Epstein-Barr virus hepatitis. J Gastroenterol Hepatol. 2006;21:1758–60.

48. Feranchak AP, Tyson RW, Narkewicz MR, Karrer FM, Sokol RJ. Fulminant Epstein-Barr viral hepatitis: orthotopic liver transplantation and review of the literature. Liver Transpl Surg. 1998;4:469–76.

49. Okano M, Gross TG. Advanced therapeutic and prophylactic strategies for Epstein-Barr virus infection in immunocompromised patients. Expert Rev Anti Infect Ther. 2007;5:403–13.

50. Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988–1994. Clin Infect Dis. 2006;43:1143–51.

51. Kunno A, Abe M, Yamada M, Murakami K. Clinical and histological features of cytomegalovirus hepatitis in previously healthy adults. Liver. 1997;17:129–32.

52. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME. Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. Virol J. 2008;5:47.

53. Galiatsatos P, Shrier I, Lamoureux E, Szilagyi A. Meta-analysis of outcome of cytomegalovirus colitis in immunocompetent hosts. Dig Dis Sci. 2005;50:609–16.

54. Karakozis S, Gongora E, Caceres M, Brun E, Cook JW. Life-threatening cytomegalovirus colitis in the immunocompetent patient: report of a case and review of the literature. Dis Colon Rectum. 2001;44:1716–20.

55. Al-Zafiri R, Gologan A, Galiatsatos P, Szilagyi A. Cytomegalovirus complicating inflammatory bowel disease: a 10-year experience in a community-based, university-affiliated hospital. Gastroenterol Hepatol (N Y). 2012;8:230–9.

56. Razonable RR. Cytomegalovirus infection after liver transplantation: current concepts and challenges. World J Gastroenterol. 2008;14:4849–60.

57. Roulot D, Valla D, Brun-Vezinet F, Rey MA, Clavel F, Degott C, Guillan J, et al. Cholangitis in the acquired immunodeficiency syndrome: report of two cases and review of the literature. Gut. 1987;28:1653–60.

58. Balfour Jr HH. Antiviral drugs. N Engl J Med. 1999;340:1255–68.

59. Singh N. Optimal prevention of late-onset cytomegalovirus (CMV) disease and other sequelae of CMV infection in organ transplant recipients. Clin Infect Dis. 2008;47:296–7; author reply 297.

60. Arthurs SK, Eid AJ, Pedersen RA, Dierkhising RA, Kremers WK, Patel R, Razonable RR. Delayed-onset primary cytomegalovirus disease after liver transplantation. Liver Transpl. 2007;13:1703–9.

61. Sun HY, Wagener MM, Singh N. Prevention of posttransplant cytomegalovirus disease and related outcomes with valganciclovir: a systematic review. Am J Transplant. 2008;8:2111–8.

62. Arthurs SK, Eid AJ, Deziel PJ, Marshall WF, Cassivi SD, Walker RC, Razonable RR. The impact of invasive fungal diseases on survival after lung transplantation. Clin Transplant. 2010;24:341–8.

63. Mendez JC, Dockrell DH, Espy MJ, Smith TF, Wilson JA, Harmsen WS, Ilstrup D, et al. Human beta-herpesvirus interactions in solid organ transplant recipients. J Infect Dis. 2001;183:179–84.

64. Burak KW, Kremers WK, Batts KP, Wiesner RH, Rosen CB, Razonable RR, Paya CV, et al. Impact of cytomegalovirus infection,

year of transplantation, and donor age on outcomes after liver transplantation for hepatitis C. Liver Transpl. 2002;8:362–9.

65. Limaye AP, Bakthavatsalam R, Kim HW, Randolph SE, Halldorson JB, Healey PJ, Kuhr CS, et al. Impact of cytomegalovirus in organ transplant recipients in the era of antiviral prophylaxis. Transplantation. 2006;81:1645–52.

66. Emery VC, Sabin CA, Cope AV, Gor D, Hassan-Walker AF, Griffiths PD. Application of viral-load kinetics to identify patients who develop cytomegalovirus disease after transplantation. Lancet. 2000;355:2032–6.

67. Walker JK, Scholz LM, Scheetz MH, Gallon LG, Kaufman DB, Rachwalski EJ, Abecassis MM, et al. Leukopenia complicates cytomegalovirus prevention after renal transplantation with alemtuzumab induction. Transplantation. 2007;83:874–82.

68. Hodson EM, Jones CA, Webster AC, Strippoli GF, Barclay PG, Kable K, Vimalachandra D, et al. Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid-organ transplants: a systematic review of randomised controlled trials. Lancet. 2005;365:2105–15.

69. Eid AJ, Razonable RR. New developments in the management of cytomegalovirus infection after solid organ transplantation. Drugs. 2010;70:965–81.

70. Badley AD, Seaberg EC, Porayko MK, Wiesner RH, Keating MR, Wilhelm MP, Walker RC, et al. Prophylaxis of cytomegalovirus infection in liver transplantation: a randomized trial comparing a combination of ganciclovir and acyclovir to acyclovir. NIDDK Liver Transplantation Database. Transplantation. 1997;64:66–73.

71. Gane E, Saliba F, Valdecasas GJ, O'Grady J, Pescovitz MD, Lyman S, Robinson CA. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. The Oral Ganciclovir International Transplantation Study Group [corrected]. Lancet. 1997;350:1729–33.

72. Lautenschlager I. CMV infection, diagnosis and antiviral strategies after liver transplantation. Transpl Int. 2009;22:1031–40.

73. Watt K, Veldt B, Charlton M. A practical guide to the management of HCV infection following liver transplantation. Am J Transplant. 2009;9:1707–13.

74. Singh N, Wannstedt C, Keyes L, Wagener MM, Gayowski T, Cacciarelli TV. Indirect outcomes associated with cytomegalovirus (opportunistic infections, hepatitis C virus sequelae, and mortality) in liver-transplant recipients with the use of preemptive therapy for 13 years. Transplantation. 2005;79:1428–34.

75. Opelz G, Dohler B, Ruhenstroth A. Cytomegalovirus prophylaxis and graft outcome in solid organ transplantation: a collaborative transplant study report. Am J Transplant. 2004;4:928–36.

76. Limaye AP. Ganciclovir-resistant cytomegalovirus in organ transplant recipients. Clin Infect Dis. 2002;35:866–72.

77. Paya C, Humar A, Dominguez E, Washburn K, Blumberg E, Alexander B, Freeman R, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant. 2004;4:611–20.

78. Asberg A, Hansen CN, Reubsaet L. Determination of ganciclovir in different matrices from solid organ transplanted patients treated with a wide range of concomitant drugs. J Pharm Biomed Anal. 2007;43:1039–44.

79. Minuk GY, Nicolle LE. Genital herpes and hepatitis in healthy young adults. J Med Virol. 1986;19:269–75.

80. Peters DJ, Greene WH, Ruggiero F, McGarrity TJ. Herpes simplex-induced fulminant hepatitis in adults: a call for empiric therapy. Dig Dis Sci. 2000;45:2399–404.

81. Glorioso DV, Molloy PJ, Van Thiel DH, Kania RJ. Successful empiric treatment of HSV hepatitis in pregnancy. Case report and review of the literature. Dig Dis Sci. 1996;41:1273–5.

82. Kaufman B, Gandhi SA, Louie E, Rizzi R, Illei P. Herpes simplex virus hepatitis: case report and review. Clin Infect Dis. 1997;24:334–8.

83. Pinna AD, Rakela J, Demetris AJ, Fung JJ. Five cases of fulminant hepatitis due to herpes simplex virus in adults. Dig Dis Sci. 2002;47:750–4.

84. Norvell JP, Blei AT, Jovanovic BD, Levitsky J. Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. Liver Transpl. 2007;13:1428–34.

85. Sampaio AM, Guardia AC, Milan A, Sasaki AN, Andrade PD, Bonon SH, Stucchi RS, et al. Co-infection and clinical impact of human Herpesvirus 5 and 6 in liver transplantation. Transplant Proc. 2012;44:2455–8.

86. Lautenschlager I, Razonable RR. Human herpesvirus-6 infections in kidney, liver, lung, and heart transplantation: review. Transpl Int. 2012;25:493–502.

87. Patti ME, Selvaggi KJ, Kroboth FJ. Varicella hepatitis in the immunocompromised adult: a case report and review of the literature. Am J Med. 1990;88:77–80.

88. Alford CA. Acyclovir treatment of herpes simplex virus infections in immunocompromised humans. An overview. Am J Med. 1982;73:225–8.

89. Rothenberg M, Cheung R, Ahmed A. Adenovirus-induced acute liver failure. Dig Dis Sci. 2009;54:218–21.

90. Carmichael Jr GP, Zahradnik JM, Moyer GH, Porter DD. Adenovirus hepatitis in an immunosuppressed adult patient. Am J Clin Pathol. 1979;71:352–5.