Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

38

Liver Disease Associated With Systemic Viral Infection

ALINA M. ALLEN AND JAYANT A. TALWALKAR

ABBREVIATIONS

AIDS acquired immunodeficiency syndrome
ALT alanine aminotransferase
AST aspartate aminotransferase
CMV cytomegalovirus
DHF dengue hemorrhagic fever
DSS dengue shock syndrome
EBV Epstein-Barr virus
ELISA enzyme-linked immunosorbent assay
HAART highly active antiretroviral therapy
HHV human herpesvirus
HIV human immunodeficiency virus
HSV herpes simplex virus
IgG immunoglobulin G
IgM immunoglobulin M
PTLD posttransplant lymphoproliferative disease
RT-PCR reverse transcription polymerase chain reaction
SARS severe acute respiratory syndrome
VZV varicella-zoster virus

Introduction

The liver can be affected as part of a generalized host infection with viruses that primarily target other tissues. Liver involvement in nonhepatotropic viral infections can range from mild derangement of liver biochemistry to fulminant liver failure. In most of these infections, liver inflammation is thought to be a consequence of an immune response to viral antigens rather than a direct hepatic infection. In this chapter we review liver diseases associated with opportunistic viral infections in immunocompromised hosts, common systemic viral infections, and viral hemorrhagic fevers.

Opportunistic Viral Infections (Table 38-1)

Epstein-Barr Virus

Epstein-Barr virus (EBV) is transmitted by contact with oral secretions and resides latently in the resting memory B cells.[1] Primary EBV infection affects 90% of the population and manifests as the classic triad of fever, sore throat, and lymphadenopathy, known as *infectious mononucleosis*. Gastrointestinal manifestations such as abdominal pain, nausea, and diarrhea are mild. EBV often causes a mild self-limited hepatitis, manifested as twofold to threefold elevations of the levels of serum aminotransferases and hepatosplenomegaly. A cholestatic biochemical pattern has been described in up to 65% of cases[2] but jaundice is rare (5% to 10 % of cases)[3] and vanishing bile duct syndrome is sporadic.[4] Severe hepatitis or acute liver failure requiring emergent liver transplantation is very rare (0.21% of acute liver failure cases in the United States) but has a high case-fatality rate.[5] Notably, these patients are young (younger than 30 years) and immunocompetent.[5-7] Clinically significant hepatic damage from EBV infection can occur in immunosuppressed patients, such as human immunodeficiency virus (HIV)-positive patients, transplant patients, or inflammatory bowel disease patients receiving immunosuppressive medications.[8,9] Chronic hepatitis potentially linked to EBV infection has been reported.[10] Some cases of autoimmune[11] or granulomatous[12] hepatitis have also been associated with EBV infection. Despite the definite oncogenic potential of EBV, there is no convincing evidence linking EBV and the development of liver cancer, with the exception of the lymphoepithelioma-like hepatocellular carcinoma[13] and lymphoepithelioma-like cholangiocarcinoma.[14] EBV infection after liver transplantation is a rare (3%) but feared complication because it can lead to posttransplant lymphoproliferative disease (PTLD). Because 90% of adults are EBV seropositive, the predominant pathophysiologic mechanism of active EBV infection after transplant is EBV reactivation.[15] High-dose steroid treatment of rejection is a strong predictor of PTLD.[16]

Although liver biopsy samples from EBV hepatitis patients exhibit a wide spectrum of histologic features, a moderate to marked lymphocytic infiltrate in the portal tracts with scattered foci of interface activity is the main finding. When a large number of atypical lymphocytes are present, exclusion of hepatosplenic T-cell lymphoma should be considered. A more characteristic feature of EBV hepatitis is the beaded sinusoidal lymphocytic infiltration in a single-file pattern[17] (Fig. 38-1). Additionally, a variable degree of bile duct damage can be seen in most cases, although the mechanism is unknown. Small epithelioid granulomas can be seen, which, together with the biliary histopathologic features and biochemical cholestatic pattern can mistakenly lead to a false diagnosis of primary biliary cholangitis. The diagnosis of EBV hepatitis requires a high index of suspicion and confirmation with ancillary tests, such as *in situ* hybridization and polymerase

TABLE 38-1 Summary of Opportunistic Viral Infections in Immunocompromised Hosts

Virus	Manifestations of Primary Infection	Manifestations in Immunocompromised State	Characteristic Features of Liver Disease	Diagnosis	Treatment
EBV	Fever, sore throat, lymphadenopathy (infectious mononucleosis); self-limited hepatitis	Severe hepatitis; PTLD	Beaded sinusoidal lymphocytic infiltration in a single-file pattern	*In situ* hybridization and PCR	Supportive; PTLD: reduction of immunosuppression, rituximab
CMV	Mononucleosis-like symptoms (10%)	Fever, neutropenia/ thrombocytopenia, end-organ disease (hepatitis, pneumonia, retinitis, central nervous system disease); AIDS cholangiopathy	Mononuclear portal and sinusoidal infiltrate	Quantitative PCR assays, histopathology, and CMV-specific immunostaining	Ganciclovir or valganciclovir; reduction in pharmacologic immunosuppression
HSV	Oral (HSV 1) or genital (HSV 2) vesicular lesions	Fulminant hepatitis	Hepatocyte necrosis, intranuclear inclusions detected by H&E staining	HSV DNA detected by PCR and histopathology	Acyclovir
VZV	Generalized rash (chickenpox)	Hepatitis, cutaneous lesions	Hepatocyte necrosis, intranuclear inclusions detected by H&E staining	PCR and histopathology	Acyclovir
HHV 6 and HHV 7	Roseola infantum (HHV 6); pityriasis rosea (HHV 7)	Fever, hepatitis, pneumonitis, encephalopathy, cytopenia	NA	PCR or shell-vial cultures	Ganciclovir, foscarnet, cidofovir
HHV 8	Fever, lymphadenopathy, rash	Kaposi sarcoma, body cavity lymphoma and multicentric Castleman's disease	Whorls of spindle-shaped cells with leukocytic infiltration and neovascularization with aberrant proliferation of small vessels	Viral DNA in serum or tissue detected by PCR	HAART in HIV infection; reduction of immunosuppressive regimen after transplant or switch of immunosuppression agent to an mTOR inhibitor (sirolimus, everolimus)
Adenoviruses	Pharyngitis, conjunctivitis	Hepatitis	Circumscribed foci of necrosis in the hepatic lobule with infiltration of monocytes	Immunohistochemical staining or viral culture	Cidofovir

AIDS, Acquired immunodeficiency syndrome; *CMV,* cytomegalovirus; *EBV,* Epstein-Barr virus; *HAART,* highly active antiretroviral therapy; *H&E,* hematoxylin and eosin; *HHV,* human herpesvirus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *mTOR,* mammalian target of rapamycin; *NA,* not available; *PCR,* polymerase chain reaction; *PTLD,* posttransplant lymphoproliferative disease; *VZV,* varicella-zoster virus.

chain reaction (PCR), which are equally sensitive. Immunohistochemical staining for EBV latent membrane proteins does not have a role in EBV diagnosis.[17]

Because a positive EBV PCR or *in situ* hybridization of the liver tissue cannot discriminate a relevant EBV infection from occasionally circulating EBV-positive lymphocytes, it is important to interpret these results in the context of histopathologic changes, EBV serologic findings (immunoglobulin M [IgM] and immunoglobulin G [IgG] to viral capsid antigen and Epstein-Barr nuclear antigen) and liver enzyme level alterations.

Treatment of EBV infection is supportive, as the infection self-resolves in 2 to 4 weeks. Corticosteroids and acyclovir do not have a clinical benefit.[18] Liver transplantation in EBV-related acute liver failure is effective.[5] Initial treatment of PTLD consists of reduction of immunosuppression,[19] followed by additional therapies such as anti-CD20 monoclonal antibodies (rituximab) if no response is observed.

Cytomegalovirus

Cytomegalovirus (CMV) is a ubiquitous herpesvirus that, depending on the population studied, infects 40% to 100% of humans.[20] Primary CMV infection in immunocompetent individuals presents most commonly as an asymptomatic illness or as a benign infectious mononucleosis-like syndrome in approximately 10% of cases. Subclinical self-limited serum aminotransferase elevation can be present.[21] Rare cases of thrombotic complications, such as portal vein thrombosis and Budd-Chiari syndrome, have been

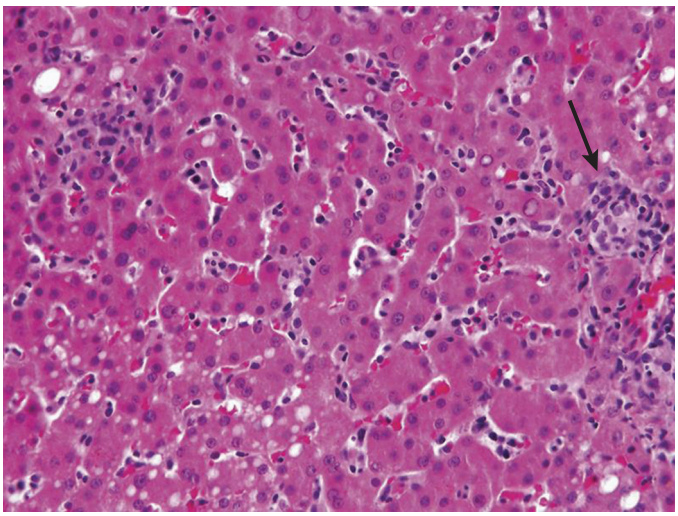
described.[22] Histologic findings are nonspecific and include mononuclear portal and sinusoidal infiltrates, increased hepatocellular mitotic activity, and minimal hepatocellular necrosis.[23] Typical CMV nuclear inclusions and CMV antigen by immunoperoxidase are rare. CMV has been described as a cause of acute granulomatous hepatitis in immunocompetent patients with fever of unknown origin.[24,25]

When CMV infection occurs in individuals with compromised immunity, such as liver transplant recipients, or individuals with HIV infection or malignancy, it is associated with substantial morbidity and mortality. Infection after liver transplantation is an important entity, as CMV is the most common viral pathogen that influences the outcome of liver transplantation. In these patients, CMV disease manifests as fever, neutropenia/ thrombocytopenia, and commonly end-organ disease, such as pneumonia, retinitis, central nervous system disease, or hepatitis. CMV infection (evidence of CMV replication regardless of symptom presence) and disease (evidence of CMV infection with attributable signs or symptoms) occurring after liver transplantation in high-risk recipients are associated with a significant increased risk of death and graft loss.[26,27] There is a bidirectional relationship between CMV infection and the risk of allograft rejection.[26,28]

CMV is an important etiologic agent of acquired immunodeficiency syndrome (AIDS) cholangiopathy, along with *Cryptosporidium parvum*. The most common cholangiogram findings are distal stenosis of the extrahepatic biliary ducts combined with diffuse irregularity of the intrahepatic bile ducts[29,30] (Fig. 38-2).

Diagnosis of primary CMV infection in immunocompetent hosts is usually made by serologic studies, either the detection of CMV-specific immunoglobulin (IgM) or a fourfold rise in the level of CMV-specific IgG. Serologic tests have no role in diagnosing CMV disease in immunocompromised patients, for which quantitative PCR assays and histopathology and CMV-specific immunostaining of tissue biopsy specimens should be used.

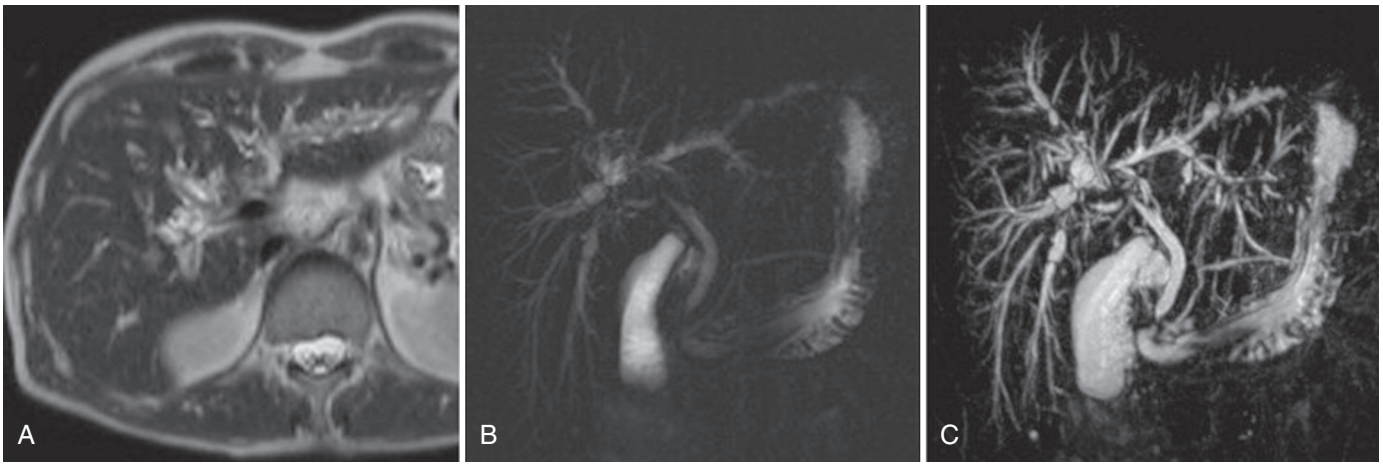
The standard treatment of CMV disease consists of intravenously administered ganciclovir or orally administered valganciclovir, and if feasible, reduction in pharmacologic immunosuppression. Antiviral prophylaxis or preemptive therapy is similarly effective in preventing CMV disease in modest-risk CMV-seropositive liver transplant recipients, whereas antiviral prophylaxis is the preferred strategy over preemptive therapy for the prevention of CMV disease in high-risk recipients (CMV-seronegative recipients of liver allografts from CMV-seropositive donors).[31]



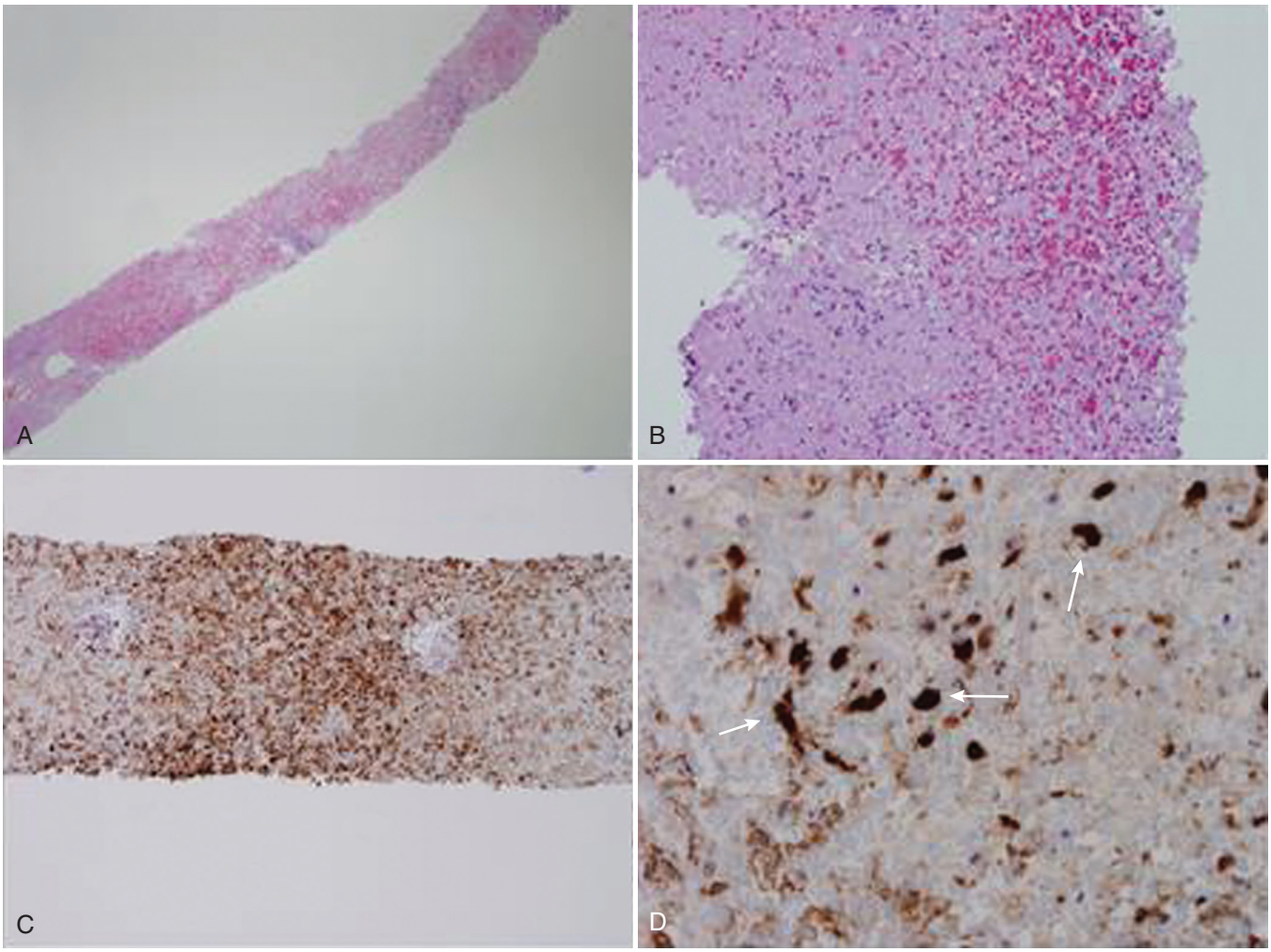
• **Fig. 38-1** Characteristic sinusoidal lymphocytic infiltration in Epstein-Barr virus hepatitis. A microgranuloma was present in the lobule (*arrow*) (original magnification ×400). (From Suh N, et al. Epstein-Barr virus hepatitis: diagnostic value of in situ hybridization, polymerase chain reaction, and immunohistochemistry on liver biopsy from immunocompetent patients. *Am J Surg Pathol* 2007;31:1403-1409.)

Herpes Simplex Virus

Herpes simplex virus (HSV) infections are common and manifest as characteristic oral (HSV 1) or genital (HSV 2) vesicular lesions, occasionally accompanied by fever and malaise. The virus persists



• **Fig. 38-2** Human immunodeficiency virus–related cholangiopathy. Magnetic resonance imaging (**A**) shows irregular intrahepatic ductal dilatation mainly involving the left liver lobe. *Magnetic resonance* cholangiopancreatography acquisitions (**B** and **C**) detect multiple alternating stenosis and saccular dilatations of segmental portions of the intrahepatic biliary tree. A poorly visualized common hepatic duct is consistent with a stricture, whereas the choledochus appears minimally dilated with terminal tapering (papillary stenosis). (From Tonolini M, Bianco R. HIV-related/AIDS cholangiopathy: pictorial review with emphasis on MRCP findings and differential diagnosis. *Clin Imaging* 2013;37:219-226.)



• **Fig. 38-3** Herpes simplex virus (HSV) hepatitis. **A,** Low-power micrograph (hematoxylin and eosin [H&E] stain, ×40) of the needle liver biopsy specimen showing a disruption of the overall architecture with patches of inflammatory cells. **B,** Higher magnification (H&E stain, ×200) reveals morphologic evidence of severe necrosis and hemorrhage. **C,** Immunohistochemistry for detection of HSV (×200) demonstrates extensive positive staining of necrotic hepatocytes, diffusely distributed throughout the tissue. **D,** Immunohistochemistry for detection of HSV (×400) emphasizes high-power magnification of the positive cells with characteristic intranuclear inclusions (*arrows*) seen with HSV. (From Pietrucha-Dilanchian P, et al. Fatal herpes simplex virus type 2 hepatitis in a heart transplant recipient: a case report and review of the literature. *Transplant Infect Dis* 2013;15:E87-E96.)

in a latent state in the ganglion neurons and can reactivate during episodes of immunosuppression or stress.

Hepatic involvement is rare but can be associated with 80% mortality.[32] Unlike the smoldering course of CMV infection, HSV hepatitis presents as a fulminant disease that is usually fatal if untreated.[33] It occurs most commonly in immunosuppressed settings, such as after transplant, in malignancies, in HIV infection, and during the neonatal period, but it has also been described in immunocompetent hosts.[34] Clinical manifestations include fever, abdominal pain, leukopenia, and coagulopathy. Typical vesicular lesions occur in 30% of cases; thus the diagnosis should not rely on their presence.[33]

Before the institution of antiviral prophylaxis, HSV hepatitis after solid-organ transplant was noted within 20 days after transplant (earlier than for CMV disease) and was associated with disseminated infection in most of the cases.[35,36] The serum aminotransferase levels can be elevated 10 to 100 times the normal range. In the absence of timely diagnosis and treatment, the clinical course can rapidly progress to multiorgan failure, disseminated intravascular coagulopathy, and death. The liver appears enlarged and necrotic. Microscopy reveals focal or diffuse hepatocyte necrosis, with characteristic intranuclear inclusions revealed by hematoxylin and eosin staining (Fig. 38-3).

The diagnosis should be established rapidly by measurement of serum HSV DNA by PCR. Serology has a limited role, as IgM presence can be falsely negative early in the disease course or in very ill patients.[37] Liver biopsy should be performed early in the course of the disease.

The role of liver transplantation in fulminant HSV hepatitis is controversial. Removal of the liver as a large HSV reservoir leads to significant decline of the level of viral DNA, but extrahepatic disease in the context of posttransplant immunosuppression can occur despite low or undetectable levels of HSV DNA. Mortality after liver transplantation for HSV-related acute liver failure

is 55%.[37] It is unclear if the mortality is attributed to direct viral effects or indirectly to the pretransplant morbidity or underlying disease that predisposed the individual to the initial HSV infection.

Fulminant liver failure secondary to HSV disease is an infectious disease emergency. Because of the potential for rapid progression to death or the need for liver transplantation, empiric acyclovir therapy for patients presenting with acute liver failure of unknown cause is recommended until HSV hepatitis has been excluded. Acyclovir reduces the risk of death or need for liver transplantation by 86% (odds ratio 0.14; 95% confidence interval 0.06 to 0.33).[32] With the routine use of acyclovir for prophylaxis, the incidence of HSV infections after solid-organ transplant has declined significantly. Acyclovir resistance is rare but it has been described in immunocompromised individuals.[38]

Varicella-Zoster Virus

Primary varicella-zoster virus (VZV) infection affects approximately one third of the U.S. population[39] and causes varicella (chickenpox), manifested as generalized rash. Persistence of virus in the sensory dorsal root ganglia can lead to reactivation, manifested as a painful vesicular rash in a dermatomal distribution (shingles). The risk of reactivation is higher in immunocompromised patients. Visceral organ involvement is rare but has been documented in immunocompromised patients because of HIV infection or immunosuppressive drugs (chemotherapy after transplant).[40-42] Cutaneous lesions eventually develop but their appearance may be delayed. Liver histologic features are similar to those in HSV hepatitis. Diagnosis is made by serum VZV PCR. Prompt institution of high-dose intravenously administered acyclovir has improved the prognosis of patients with this disease.[43] Live attenuated vaccines are licensed for prevention of varicella and zoster but are contraindicated in immunosuppressed individuals such as transplant recipients.[44]

Human Herpesviruses

Human herpesvirus (HHV) 6 and HHV 7 are ubiquitous lymphotropic viruses with genetic and biologic properties similar to those of CMV. Their effects are mediated by immunomodulatory properties and synergistic effects with other viruses. They are acquired during early childhood by 95% of the population.[45] Most primary infections are subclinical but the disease can manifest as fever and rash. HHV 6 causes roseola infantum. HHV 7 has been associated with pityriasis rosea. The viruses persist in a latent state and reactivate during periods of immunosuppression, such as after organ transplant or during critical illness–related stress.[46,47]

Similarly to CMV, HHV 6 can cause fulminant hepatitis in neonates and infants as a result of mother-to-child transmission.[48,49] It may also account for a large number of acute liver failure cases of unclear cause.[50] Timely diagnosis and valganciclovir therapy can potentially avoid the need for liver transplantation.[51] Half of the patients who received a transplant for HHV 6–related fulminant hepatitis showed HHV recurrence after liver transplantation, without long-term impact on graft or patient survival.[52]

The incidence of infection with HHV 6 and HHV 7 after transplant ranges from 32% to 48% and from 46% to 57%, respectively.[47] HHV 6 infections occur typically 2 to 4 weeks after transplant. The clinical manifestations can be divided into direct clinical manifestations, including febrile syndromes, pneumonitis, hepatitis, encephalopathy, and marrow suppression, and indirect effects resulting from the triggering of immunologic phenomena or transactivation of other herpesviruses such as CMV. Hepatitis from HHV 6 and HHV 7 has been described most commonly in liver transplant recipients. The liver test values are elevated in a mixed pattern.[53] HHV 6 may also be associated with liver allograft rejection[54] and increased mortality.[55] HHV 6 has been associated with reactivation of HHV 7, CMV,[56] and invasive fungal infections.[57]

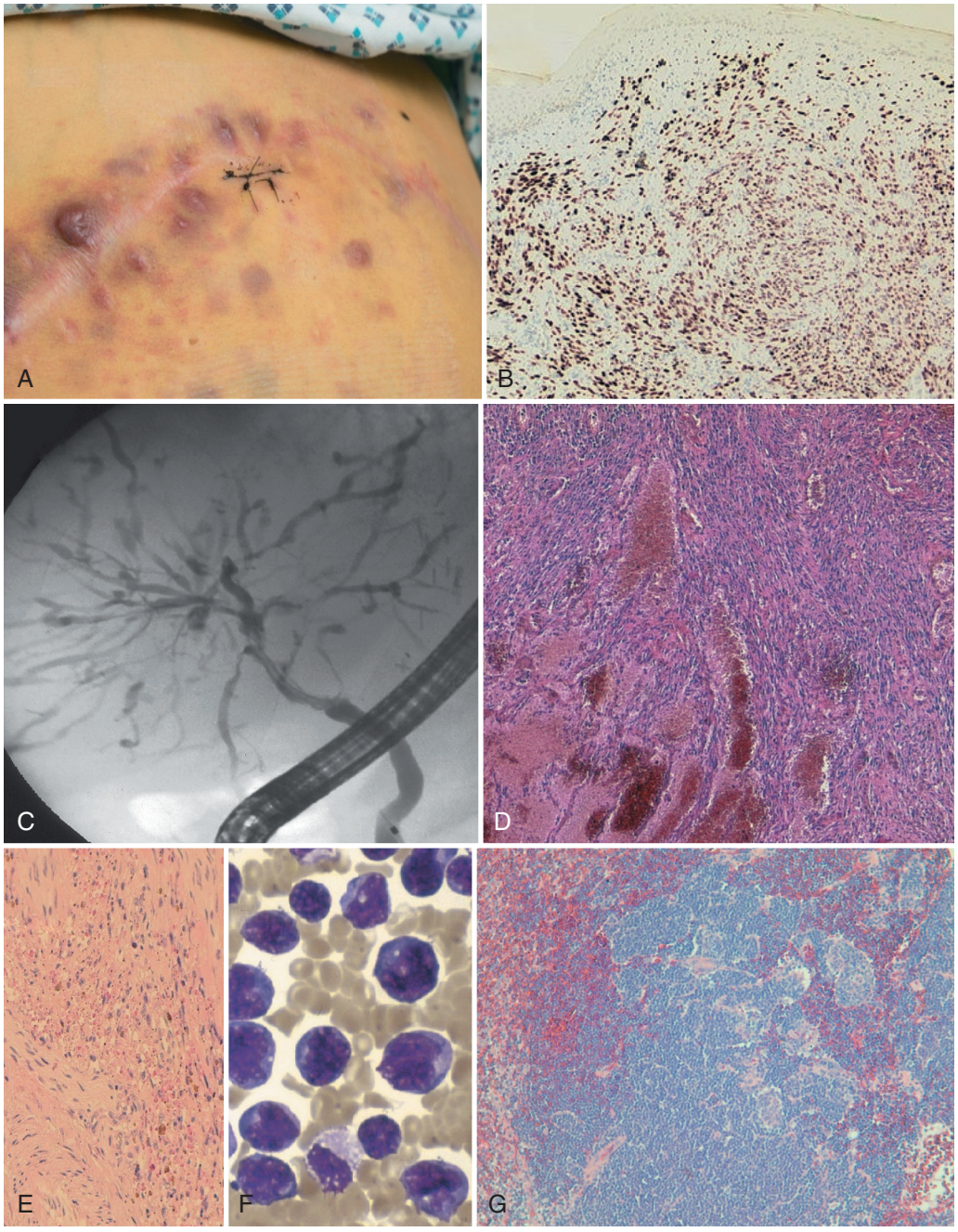
Diagnosis is best established by PCR techniques or shell-vial cultures. Serologic tests are of limited value because of high seroprevalence in the general population, cross-reactivity, and diminished serologic reactivity in immunosuppressed individuals.[58] Treatment includes active antiviral agents as in CMV infection, such as ganciclovir, foscarnet, and cidofovir.

HHV 8 (Kaposi sarcoma–associated herpesvirus) is part of the human gamma herpesviruses, which include EBV, similarly to which it plays an important role in cellular proliferation and the development of malignancies. HHV 8 is the etiologic agent of Kaposi sarcoma, body cavity lymphoma, and multicentric Castleman disease. The exact mode of transmission of HHV 8 remains unclear. Potential modes of transmission include saliva, sexual transmission, blood transfusions, and solid organ transplant. The prevalence of HHV 8 infection in the United States is unclear but recent studies estimate a rate of 30% in blood donors[59] and up to 56% in HIV-seropositive subjects.[60] Kaposi sarcoma is classically associated with AIDS, as it is 300 times more common in AIDS patients than in other immunosuppressed hosts. However, it is increasingly recognized as a complication of solid organ transplant (incidence of 0.4% in the United States),[61] with the highest rates in liver transplant recipients.[62] Kaposi sarcoma represents 5.7% of malignancies after transplant.[63]

Hepatic involvement is not common with primary infection, which typically manifests as a mild febrile illness, lymphadenopathy, and rash. However, liver nodules can be part of the multiorgan involvement of Kaposi sarcoma, or rarely the first manifestation of the disease.[64] The manifestations include characteristic dark-red nodules present on the skin and visceral organs. Whorls of spindle-shaped cells with leukocytic infiltration and neovascularization with aberrant proliferation of small vessels are characteristic microscopic findings[65] (Fig. 38-4).

Castleman disease is a rare lymphoproliferative disorder, which manifests as fever, splenomegaly, hepatomegaly, and massive lymphadenopathy. Primary effusion lymphoma (body cavity lymphoma) is a specific subtype of B-cell lymphoma related to HHV 8, and involves the peritoneal, pleural, and pericardial spaces.

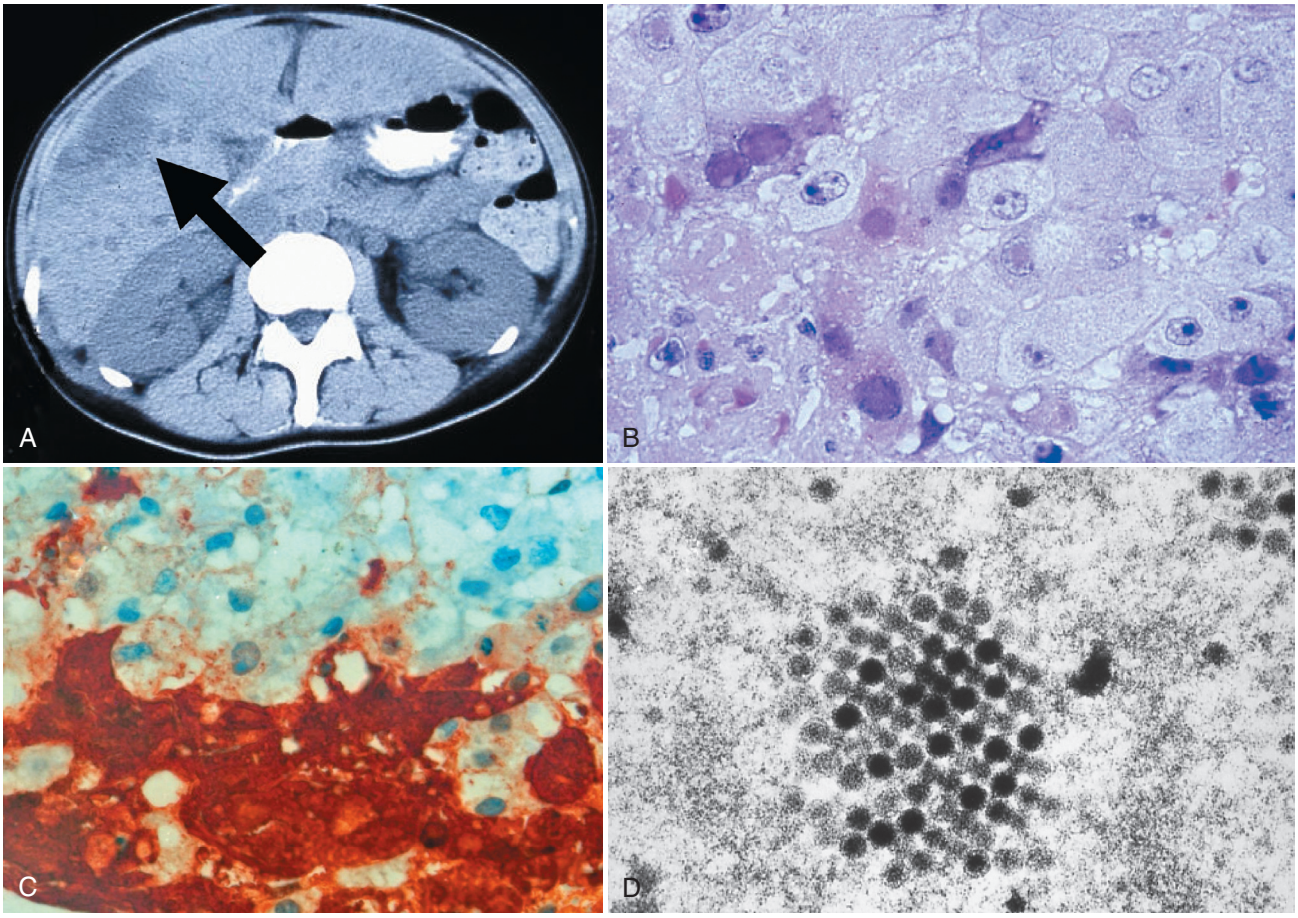
Diagnosis is based on identification of viral DNA in serum or tissue by PCR. In the setting of HIV infection, treatment of HHV 8–related disease consists of immune function restoration with highly active antiretroviral therapy (HAART). In transplant recipients with positive HHV 8 serologic findings or receiving an organ from a donor with positive HHV8 serologic findings, the monitoring of HHV 8 DNA after transplant is strongly recommended.[44] Management of Kaposi sarcoma in these patients consists of reduction of the immunosuppressive regimen or a switch of the immunosuppression agent to an inhibitor of mammalian target of rapamycin such as sirolimus or everolimus.[66] Ganciclovir, foscarnet, and cidofovir are effective *in vitro* but clinical studies showing benefit of targeted antiviral therapy are limited to valganciclovir.[67] For patients with visceral of Kaposi sarcoma or lymphoma, chemotherapy agents such as doxorubicin, daunorubicin, paclitaxel, or rituximab have been used with some success.[68-71]



• **Fig. 38-4** Human herpesvirus 8 (HHV 8)-associated manifestations. **A,** Cutaneous Kaposi sarcoma developing in a surgical scar 4 weeks after liver transplantation. **B,** Detection of HHV 8 latency-associated nuclear antigen 1 in a skin section from the patient in **A**. **C,** Endoscopic retrograde cholangiopancreatography demonstrates compressed and partially blocked biliary ducts as a result of multifocal hepatic tumor infiltration (same patient as in **A**). **D,** Liver histology illustrating typical Kaposi sarcoma with abundant spindle cells and dilated vascular spaces (same patient as in **A**). **E,** High-power field of hepatic Kaposi sarcoma. **F,** Multicentric Castleman disease in a perihepatic lymph node. Histology shows many atypical follicle-like structures and abnormal vessels. **G,** Plasma cell–like lymphoma cells in a human immunodeficiency virus–infected patient with HHV 8-associated body cavity lymphoma.

Adenoviruses

Adenoviruses are common etiologic agents of febrile disease in childhood. The most common form of presentation is acute upper respiratory tract infection, with pharyngitis and conjunctivitis, but pneumonia and enteritis have been described. Adenoviral hepatitis is rare but can present in immunocompromised hosts, particularly in pediatric liver transplant recipients. Approximately 2.5% of pediatric liver transplant recipients develop adenoviral hepatitis, which is the second most common infection, after CMV infection.[72] Of more than 50 serotypes, serotype 5 is most commonly associated with hepatitis. Transmission via the liver allograft seems to be more common that viral reactivation. Histologic features include circumscribed foci of necrosis in the hepatic



• **Fig. 38-5** Fulminant adenoviral hepatitis in a woman infected with human immunodeficiency virus. **A,** Computed tomography scan illustrating extensive focal necroses in the liver (*arrow*). **B,** Necrosis and enlarged hepatocytes with adenoviral inclusions. **C,** Immunohistochemistry demonstrates the presence of abundant adenoviral antigens. **D,** Intracellular adenoviral virions seen on electron microscopy.

lobule with infiltration of monocytes (Fig. 38-5). The case-fatality rate is as high as 50%, due to massive liver necrosis. Diagnosis is confirmed by immunohistochemical staining or viral culture. The most effective direct antiviral is cidofovir but treatment is limited by significant nephrotoxicity.[73]

Systemic Viral Infections (Table 38-2)

Human Immunodeficiency Virus

Liver test abnormalities in HIV-infected patients are common and can be explained by multiple factors, such as coinfection with hepatotropic viruses (hepatitis B and C), CMV, EBV, opportunistic infections, alcohol abuse, and exposure to hepatotoxic drugs, including HAART. Primary HIV infection rarely manifests as self-limited hepatitis, including abdominal pain, hepatomegaly, and elevated levels of serum aminotransferase levels.[74,75] Severe hepatitis has been more commonly described in children.[76] HIV has been detected in the liver, in the hepatocytes and Kupffer cells.[77] During accelerated viral replication in the context of a low CD4 count, the levels of serum aminotransferases can be highly elevated (>5 times the upper limit of normal) without any other apparent cause.[78] Liver histologic findings are nonspecific but steatohepatitis with a mononuclear/lymphocytic infiltrate is a common characteristic. Immune restoration with HAART and a decrease in HIV load results in normalization of liver test findings.

AIDS cholangiopathy is a rare condition characterized by abnormalities of the bile ducts in patients with advanced AIDS and low CD4 count. The hallmark of the disease is the cholangiographic abnormalities, which include papillary stenosis, sclerosing cholangitis, and rarely, biliary strictures, along with a cholestatic serologic pattern.[79] Opportunistic infections with *Cryptosporidium parvum*, *Microsporidium*, and CMV are the most common causes but do not account for all causes. Antimicrobial treatment targeted at these agents does not resolve the symptoms and anatomic abnormalities. Endoscopic treatment with ampullary sphincterotomy and balloon dilation of the biliary strictures, along with HAART, are the main therapies.

Influenza

Gastrointestinal symptoms are common during influenza but are usually mild and self-limited and do not prompt further evaluation. Thus the prevalence of liver test abnormalities is not known. During the Southeast Asian outbreak of the avian influenza A H5N1 infection, altered liver function test findings that resolved after viral clearance were noted in 60% of patients with

TABLE 38-2 Summary of Liver Diseases Caused by Systemic Viral Infections

Virus	Liver Disease Manifestations	Diagnosis	Treatment
HIV	Self-limited hepatitis in primary infection; severe elevation in serum aminotransferases during high viral replication; AIDS cholangiopathy	Nonspecific: steatohepatitis with a mononuclear/lymphocytic infiltrate	HAART; ampullary sphincterotomy and biliary duct dilation in AIDS cholangiopathy
Influenza virus	Abnormal liver test findings	Hepatic central lobular necrosis	Supportive
SARS coronavirus	Transaminitis	Marked mitotic activity, moderate lymphocytic infiltrates and hepatocyte apoptosis	Supportive
Parvovirus B19	Range from mild hepatitis to fulminant hepatic failure with aplastic anemia	Parvovirus B19 IgM in immunocompetent subjects; PCR in immunocompromised host	IVIG in chronic infection or reactivation; liver and bone marrow transplant
Measles virus	Self-resolving hepatitis; jaundice; chronic autoimmune hepatitis	Measles IgM; PCR in blood or secretions	Supportive. Vitamin A in children

AIDS, Acquired immunodeficiency syndrome*; HAART,* highly active antiretroviral therapy; *HIV,* human immunodeficiency virus; *IgM,* immunoglobulin M; *IVIG,* intravenous immunoglobulin; *SARS,* severe acute respiratory syndrome.

pneumonia.[80] There is evidence that influenza virus can trigger T cell–mediated hepatitis in the absence of viral antigens in the liver.[81] Liver histologic findings are therefore nonspecific. Extensive hepatic central lobular necrosis was among the autopsy findings in fatal cases of H5N1 outbreaks.[82]

Severe Acute Respiratory Syndrome Coronavirus

Severe acute respiratory syndrome (SARS) coronavirus was the etiologic agent of a severe respiratory disease outbreak in the Far East and Canada in 2003. The disease had a case-fatality rate of 9% to 12%. Laboratory abnormalities include elevated lactate dehydrogenase level (70%), lymphopenia (50% to 70%), thrombocytopenia (50%), and hypocalcemia (60%). Mild elevation of serum aminotransferase levels was found in almost 30% of patients on initial presentation and in 76% of patients during the subsequent clinical course and ribavirin treatment.[83] Fulminant hepatic failure has not been described. In patients with moderate to marked liver test elevation, liver biopsy findings include marked mitotic activity, moderate lymphocytic infiltrates, and hepatocyte apoptosis.[84] SARS coronavirus was detected in the liver tissue by reverse transcription PCR (RT-PCR), but not by electron microscopy; thus it is unclear if direct viral toxicity explains the hepatic abnormalities. No effective therapeutic strategies for SARS have been developed. Antiviral agents such as ribavirin and lopinavir/ritonavir were used because of their broad spectrum of activity against RNA viruses and HIV respectively, but their clinical efficacy has not been proven.

Parvovirus B19

Parvovirus B19 affects approximately 50% of the population. Manifestations are mild and include fever, myalgias, arthralgias, and rash (erythema infectiosum). Severe complications include aplastic anemia and arthropathy. Hepatic manifestations of parvovirus B19 infection range from liver chemistry abnormalities to fulminant hepatic failure with aplastic anemia, requiring liver and bone marrow transplant.[85-87] Infection during pregnancy can lead to abortion due to hydrops fetalis, which is associated with severe hepatitis.[88] In immunocompromised hosts (posttransplant, AIDS, congenital immunodeficiency) chronic infection has been described. This lacks typical immune-mediated symptoms such as rash and arthralgias, and manifests as refractory anemia and organ damage (hepatitis, pneumonitis, myocarditis).[89] Serologic diagnosis with parvovirus B19 IgM can be negative in 29% of cases because of failure to mount antibodies. Diagnosis relies on PCR assays, and intravenous immunoglobulin is the most commonly used treatment modality.[89]

Measles (Rubeola) Virus

Measles is a human virus of the genus *Morbillivirus* in the family *Paramyxoviridae*. Measles is a highly contagious infection acquired during childhood, which manifests as a characteristic rash. The symptoms are usually mild but pneumonia and encephalitis can complicate the disease course. Transient liver enzyme level elevations are common.[90] The hepatic manifestations are present in 80% of adults with measles, and it may manifest as jaundice.[91] The liver test values return to normal within 2 weeks to 3 weeks. Histologic changes show necrotic hepatocytes and portal inflammation, attributed to direct viral toxicity.[92] Persistent measles virus genome has been implicated in the pathogenesis of chronic autoimmune hepatitis.[93] Diagnosis is most commonly based on the serologic finding of anti-measles IgM, which is detectable between 3 days and 30 days from rash onset. Viral RNA can be detected by PCR in blood, respiratory secretions, or urine for 3 days after the rash has appeared. Measles vaccination usually leads to long-term immunity. The vaccine is live attenuated and thus is contraindicated in pregnant or immunocompromised hosts. Immunocompromised patients exposed to measles should receive postexposure prophylaxis with intravenous immunoglobulin (400 mg/kg) regardless of the immunologic or vaccination status. Treatment is supportive and in children should include administration of vitamin A.[94]

Rubella

Rubella virus belongs to the family *Togaviridae*. Rubella is a mild infection that manifests as a generalized rash, and rarely complicated by otitis media, encephalitis, or arthritis. Rubella is not

known to cause hepatic dysfunction, with the exception of one case of neonatal giant-cell hepatitis described in 1966.[95]

Enteroviruses

Enteroviruses, members of the family *Picornaviridae*, are transmitted via a fecal-oral route in the summer and autumn months. Members include polioviruses, Coxsackie A virus, Coxsackie B virus, echoviruses, and the numbered enteroviruses. Echovirus 9 and echovirus 18 have been associated with fulminant hepatitis in immunocompromised adults.[96,97] Liver histology reveals lymphocytic inflammatory infiltrates of the portal tracts and ballooned hepatocytes. Hepatitis secondary to Coxsackie B virus infection has been described as part of a multisystemic disease.[98] Diagnosis includes serology and RNA detection by PCR. Treatment is supportive, and effective vaccination is not yet available.

Viral Hemorrhagic Fevers (Table 38-3)

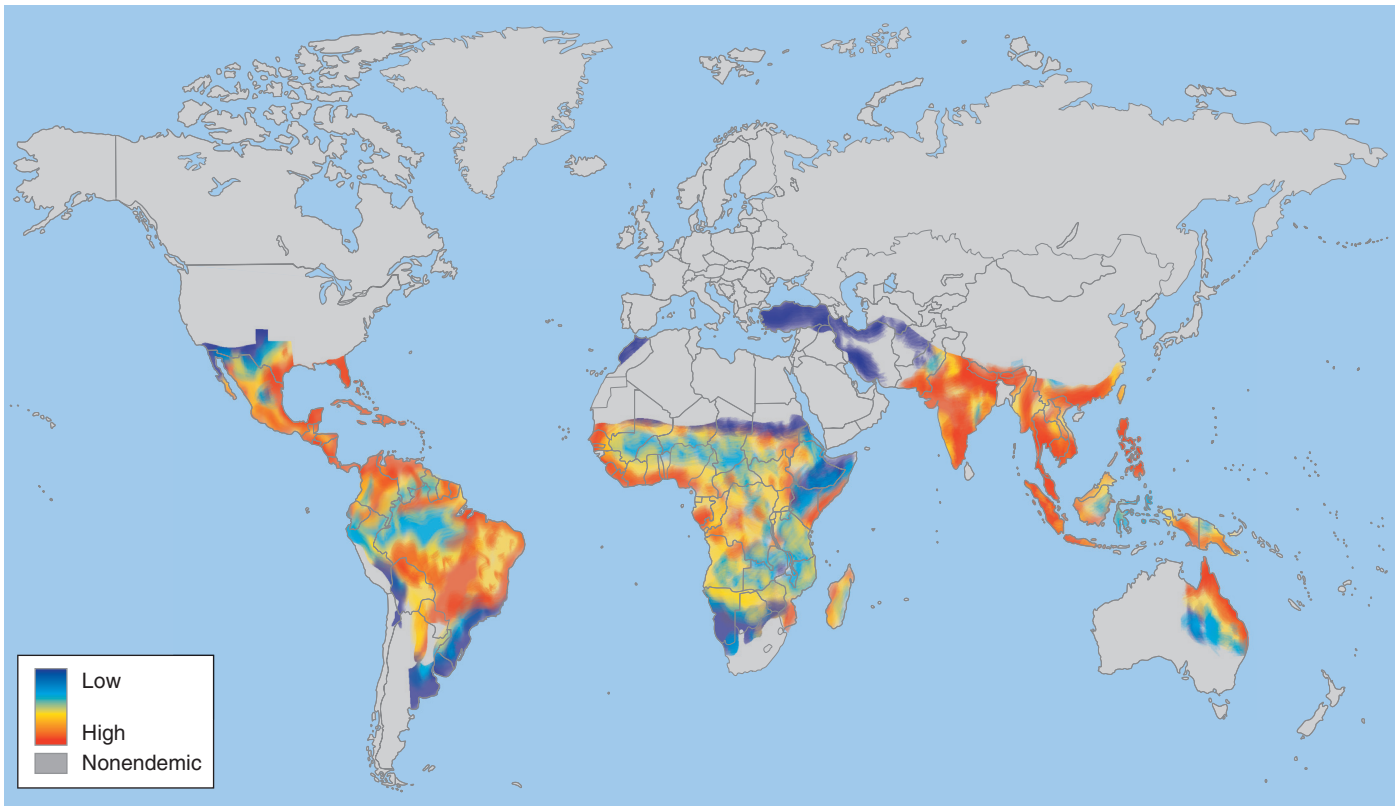
Dengue Fever

Dengue fever is the most prevalent mosquito-borne viral infection. Dengue virus belongs to the family *Flaviviridae* and consists of four serotypes. *Aedes aegypti* mosquitoes are the transmission vectors in the endemic areas of Asia, Africa, Central America, and South America (Fig. 38-6). More than 390 million infections

TABLE 38-3 Summary of Liver Diseases in Viral Hemorrhagic Fevers

Virus	Vector	Person-to-Person Transmission	Liver Manifestations	Mortality	Ribavirin	Vaccine
Dengue virus	*Aedes aegypti* mosquitoes	No	Mild elevation of aminotransferase levels; rarely hemorrhagic liver damage	Low (up to 50% in DSS)	No	No
Yellow fever virus	*Aedes* mosquitoes	No	Jaundice	Up to 50% in rare cases	No	Yes (live attenuated)
Lassa virus	*Mastomys natalensis* rodent	Rare (aerosols)	Mild-to-severe elevation of aminotranferases	1%	Yes	No
Ebola virus	Bats	Yes	Mild-to-severe elevation of aminotransferases	Up to 72%	No	No

DSS, Dengue shock syndrome.



• **Fig. 38-6** Distribution of global dengue fever risk.

are estimated to occur each year worldwide, of which 96 million are clinically evident.[99] Dengue fever is increasingly recognized as a frequent cause of hospitalization in travelers to endemic areas, second after malaria,[100] with approximately 3.4 to 5 cases per 1000 travelers, although the incidence is thought to be underestimated.[101]

Most infections are asymptomatic. When present, the clinical features of dengue fever vary and can be classified into five presentations: (1) nonspecific febrile illness, (2) classic dengue fever, (3) dengue hemorrhagic fever (DHF), (4) DHF with dengue shock syndrome (DSS), and (5) other unusual syndromes such as encephalopathy and acute liver failure. Onset of symptoms is typically 3 to 6 days after the mosquito bite. The incubation period lasts no longer than 14 days.

Classic dengue fever manifests as fever, rash, severe headache, joint and muscle pain ("break-bone fever"), and fatigue.[102] The infection self-resolves with supportive care in 5 to 7 days but the convalescent fatigue can last a few weeks. In a minority of cases (up to 3% in travelers) severe disease, such as DHF and DSS, can occur. The widespread hemorrhagic disease is likely due to a second infection with a different dengue virus type, leading to a heightened immune amnestic response. Petechial hemorrhages and multiorgan damage, including liver damage, is associated with high morbidity. Intensive supportive care is recommended, especially in DSS, where massive capillary leak and hypovolemic shock can lead to death in up to 50% of cases.

The hepatic manifestations vary with the clinical severity of dengue fever. In classic dengue fever, mild hepatomegaly and elevated levels of liver enzymes (mainly aspartate aminotransferase [AST]) can occur in most patients[103] and are is attributed to direct viral damage. Dengue virus antigens can be isolated in hepatocytes, Kupffer cells, and sinusoidal endothelial cells. In DHF and DSS, tender hepatomegaly has been reported in up to 40% of patients. Direct viral damage of hepatocytes and Kupffer cells leads to multifocal hemorrhage. Pathologic evaluation at autopsy shows hepatocellular necrosis with no or minimal inflammation. Liver biopsy should be avoided because of the increased risk of bleeding.

A confirmed diagnosis is established by culture of the virus, PCR tests, or serologic assays. However, there are significant limitations in sensitivity and availability at the time of presentation. Therefore the diagnosis is made by clinical symptoms and characteristic laboratory features (travel history, fever characteristics, positive tourniquet sign, low platelet counts, and increased aminotransferase levels). Early recognition and aggressive supportive management is the mainstay of care because vaccination against dengue virus is not available.

Yellow Fever

Yellow fever is a mosquito-borne viral hemorrhagic fever with a high case-fatality rate. Unvaccinated travelers to tropical regions of sub-Saharan Africa and South America are at risk of infection (1 in 1000) and death from yellow fever (1 in 5000).[104] In 2013 there were approximately 130,000 infections in Africa, including 78,000 deaths.[105]

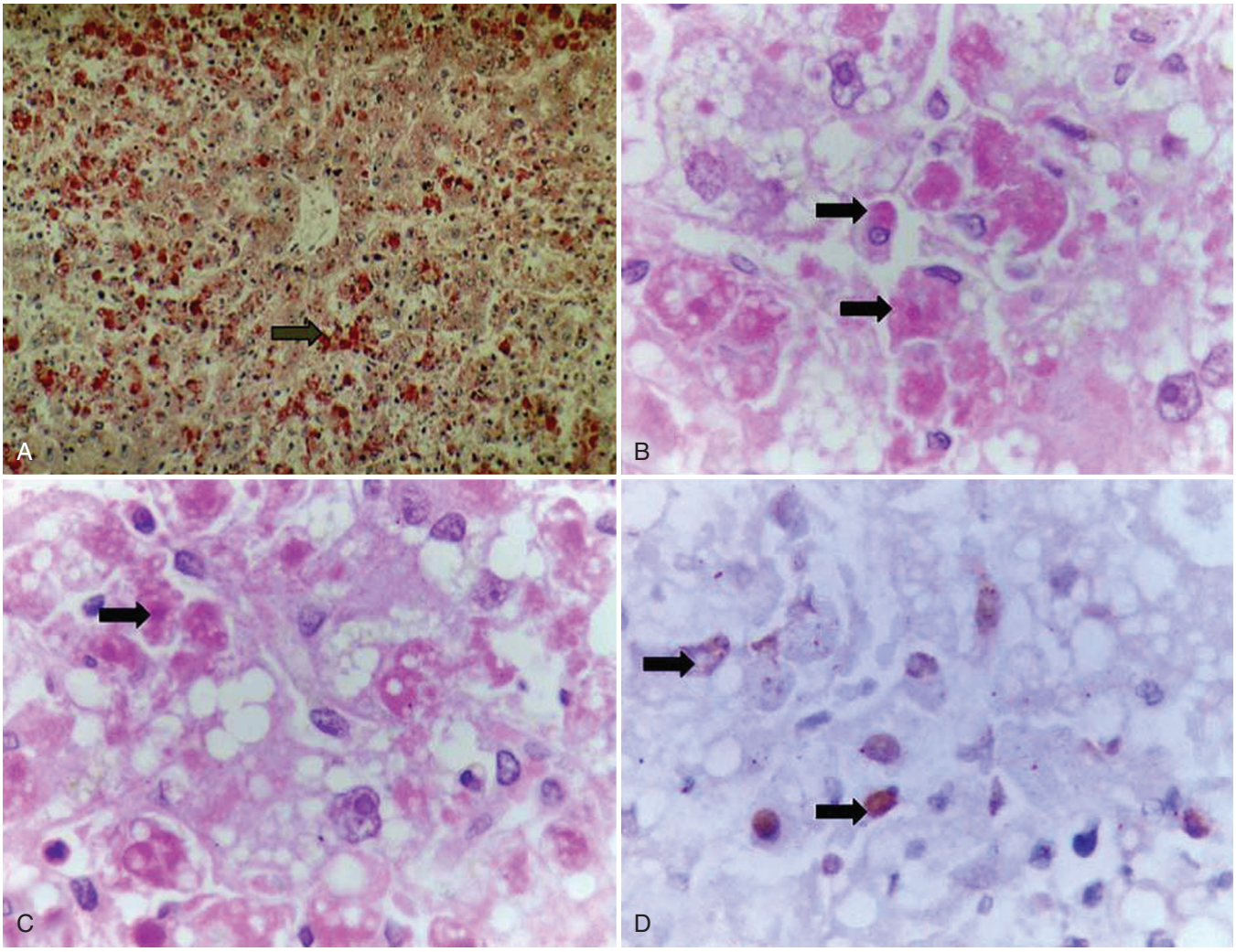
Yellow fever is the prototype member of the family *Flaviviridae*. The primary transmission cycle involves monkeys and daytime biting mosquitoes (*Aedes* species in Africa, *Haemagogus* species in South America). The classic illness is characterized by three stages: infection (3 to 4 days), remission (2 days), and intoxication. Hepatic involvement is apparent at all stages, in varying degrees of severity. The infection phase manifests as fever and nonspecific flulike symptoms. Tender hepatomegaly may be present. Serum transaminase levels start to rise 48 hours and 72 hours after the onset of illness, before the appearance of jaundice. The degree of liver enzyme abnormalities at this stage may predict the severity of subsequent hepatic dysfunction.[106] Most patients enter the remission phase and recover within 2 days. However 15% of patients enter the intoxication phase, characterized by recurrent fever, hemorrhagic diathesis, and multiorgan dysfunction. This stage has a mortality rate of 20% to 50%. Hepatic injury is reflected by the level of aminotransferase elevation, as high as 2000 U/L to 3000 U/L.[106] The levels are proportional to disease severity. Alkaline phosphatase levels are normal or only slightly elevated, whereas direct bilirubin levels are typically between 5 mg/dL and 10 mg/dL, with higher levels in fatal cases.[107] Hepatocyte apoptosis is a result of direct viral damage to the midzone of the liver lobule, with sparing of cells bordering the central vein and portal tracts[108] (Fig. 38-7). Autopsy reveals midzonal hepatocyte necrosis with mild nonspecific lymphocytic infiltration and eosinophilic degeneration (Councilman bodies).[109] In the nonfatal cases healing is complete, without residual hepatic abnormalities, although jaundice and liver enzyme elevations can take weeks or months to resolve. The diagnosis is confirmed by the presence of IgM (determined using enzyme-linked immunosorbent assay, or ELISA) or virus (determined using PCR or culture) in the blood. Organ biopsy is not recommended because of the high hemorrhagic risk.

Treatment is supportive. Ribavirin has *in vitro* activity against yellow fever virus but at concentrations that exceed clinical safety.[110] A highly effective live attenuated vaccine with nearly 100% seroconversion rates has been available since 1936 and should be offered to travelers to and natives of endemic areas.[111] As with all live vaccines, it is contraindicated in pregnant women and immunocompromised individuals. Serious adverse reactions to the vaccine include two syndromes, yellow fever vaccine–associated neurotropic disease (incidence 0.8 per 100,000) and yellow fever vaccine–associated viscerotropic disease (incidence 0.4 per 100,000).[112]

Lassa Fever

Lassa virus (family *Arenaviridae*) is responsible for up to 300,000 annual infections in West Africa.[113] The infection occurs through contact with body fluids of infected multimammate mice (*Mastomys natalensis*), via the oral route, or via aerosols.[114] Most infections are mild or asymptomatic. Clinically overt disease manifests in 5% to 10% of cases, and is associated with a 1% mortality rate.[115] After an incubation period of 7 to 21 days, flulike symptoms associated with nausea, vomiting, and diarrhea develop. Further symptoms associated with increased vascular permeability are central to Lassa fever: pleural and pericardial effusions, facial edema, bleeding from mucosal surfaces.[116] Recovery begins after 8 to 10 days, but in 20% of cases the infection can progress to pulmonary edema, encephalopathy, and shock.

The liver damage can differ significantly in Lassa fever, and it is generally a key feature in the cases with a fatal outcome.[117] Lassa hepatitis is a result of direct viral damage of hepatocytes and manifests as elevated levels of serum aminotransferases, and not commonly as jaundice or coagulopathy. The histologic findings are characteristic of three phases: focal hepatocyte necrosis (<20%) with cytoplasmic degeneration, followed by a peak of necrosis of 20% to 50% of hepatocytes with phagocytic infiltration, then



• **Fig. 38-7** Histopathology of hepatic injury in yellow fever. **A,** Immunohistochemistry showing the standard of marking for the viral antigen in hepatocytes of the lobules (×200). **B** and **C**, Hematoxylin and eosin staining showing the diverse morphologic standards of the Councilman bodies in the hepatic lobules (×400). **D,** Immunohistochemistry for apoptosis (ApopTag) showing the standard of marking of the hepatocytes (×400). (From Quaresma J, et al. Reconsideration of histopathology and ultrastructural aspects of the human liver in yellow fever. *Acta Trop* 2005;94:116-127.)

a recovery phase with less than 10% necrotic hepatocytes and hepatocellular mitoses, suggestive of liver regeneration.[116]

Laboratory diagnosis of Lassa fever relies on detection of viral antigen or genetic material, or virus-specific antibodies by methods including indirect fluorescent antibody tests, enzyme-linked immunosorbent assays, and conventional and real-time RT-PCR. The challenges of accurate and timely diagnosis revolve around the nonspecific presentation, genetic diversity of virus strains, and lack of a commercially available diagnostic test.[118,119]

Treatment of mild infection is supportive. Intravenously or orally administered ribavirin is effective in patients with high mortality risk (AST level >150 IU/L and high-level viremia), with greater efficacy if it is administered early in the course of the disease.[120] There is no effective vaccine for Lassa virus.

Ebola Virus Disease

Ebola virus is a single-stranded RNA virus that is a member of the family *Filoviridae*, along with Marburg virus. The two genera are among the most virulent human pathogens. Previous outbreaks have been described in Central Africa, until the 2014-2015 Ebola epidemic (caused by the Zaire species of the virus), which was the first to occur in West Africa, and were larger than all previous outbreaks combined.[121,122] As of June 2015, 27,479 cases were attributed to Ebola virus, including 11,222 deaths.[123]

The natural reservoir of the virus is not clearly defined but bats seem to be at least one of the hosts. The virus is transmitted by direct contact with body fluid from an infected animal or blood, body fluids, or skin of patients with Ebola virus disease. Ebola virus may be transmitted though contact with contaminated surfaces and objects. Healthcare workers may be at risk of Ebola virus disease if they are exposed to aerosols generated during medical procedures, although no human cases of aerosol transmission have been reported.[124]

Symptoms occur after an incubation period of 6 to 12 days and include fever, vomiting, and diarrhea, followed by a diffuse maculopapular rash in selected cases. Although the infection was previously categorized as a hemorrhagic fever, in the recent West

Africa epidemic unexplained hemorrhage was noted in only 20% of cases. Hypotension, shock, and death were mostly the results of major fluid losses from gastrointestinal sources. Liver disease is a result of multifocal hepatic necrosis caused by the virus. Aminotransferase elevations (AST higher than ALT, suggestive of concomitant rhabdomyolysis) and mild elevation in alkaline phosphatase level but not in bilirubin level are a characteristic pattern for Ebola virus disease.[125]

Most acute infections are diagnosed by viral RNA detection through the use of RT-PCR. The virus can be detected within 3 days after the onset of symptoms.[126] A heightened level of suspicion and risk stratification is crucial for timely diagnosis and management of Ebola virus disease. The treatment is supportive, as there are no approved medications for the treatment of Ebola virus disease and there is no approved postexposure prophylaxis or vaccination.[127]

Conclusion

Liver disease can be associated with opportunistic viral infections, ubiquitous systemic viral infections, or viral hemorrhagic fevers. In most viral infections, liver inflammation is generally a consequence of the immune response to viral antigens rather than a direct hepatic infection. In healthy individuals, systemic viral infections typically manifest as mild derangement of liver biochemistry. When infection occurs in individuals with compromised immunity, such as liver transplant recipients, and individuals with HIV infection or malignancy, it can be associated with substantial mortality and morbidity, including acute liver failure. Treatment of severe hepatitis includes use of direct antiviral agents in select infections, reduction in immunosuppression if applicable, or liver transplantation. Viral hemorrhagic fevers affect individuals irrespective of their immune status and cause liver damage via a direct viral hepatotropic effect.

SUMMARY

Recent Progress

Since 2014, when the largest outbreak of Ebola virus disease in history developed in West Africa, multiple organizations, including the Centers for Disease Control and Prevention, the World Health Organization, and government agencies, have coordinated extensive efforts to control widespread transmission of the virus. The outbreak has been halted because of significant progress toward screening, development of rapid diagnostic tools, and guidance regarding travel, isolation, and effective decontamination to prevent human-to-human transmission. A candidate Ebola vaccine was launched in April 2015 in Sierra Leone, and is currently in phase III trials.[124]

Future Directions

Continued efforts toward robust surveillance systems, diagnostic strategies, and international infrastructures prepared to respond to existing or future health threats similar to Ebola virus disease should be undertaken. As the indirect consequences of the recent epidemic are still to manifest themselves, epidemiologic, genomic, and clinical data should continue to be collected and analyzed. Likewise, research into the development of vaccines and effective treatment agents against other viruses associated with high motality and morbidity (dengue fever virus, Lassa fever virus, yellow fever virus) should continue to be prioritized.

References

The complete reference list is available at www.expertconsult.com.

References

1. Babcock GJ, et al: EBV persistence in memory B cells in vivo. *Immunity* 9:395–404, 1998.
2. Kofteridis DP, et al: Epstein Barr virus hepatitis. *Eur J Intern Med* 22:73–76, 2011.
3. Crum NF: Epstein Barr virus hepatitis: case series and review. *South Med J* 99:544–547, 2006.
4. Kikuchi K, et al: Vanishing bile duct syndrome associated with chronic EBV infection. *Dig Dis Sci* 45:160–165, 2000.
5. Mellinger JL, et al: Epstein-Barr virus (EBV) related acute liver failure: a case series from the US Acute Liver Failure Study Group. *Dig Dis Sci* 59:1630–1637, 2014.
6. Ader F, et al: Fulminant Epstein-Barr virus (EBV) hepatitis in a young immunocompetent subject. *Med Mal Infect* 36:396–398, 2006.
7. Pagidipati N, et al: Acute hepatitis due to Epstein-Barr virus in an immunocompetent patient. *Dig Dis Sci* 55:1182–1185, 2010.
8. Posthuma EF, et al: Fatal infectious mononucleosis: a severe complication in the treatment of Crohn's disease with azathioprine. *Gut* 36:311–313, 1995.
9. N'Guyen Y, et al: Fatal Epstein-Barr virus primo infection in a 25-year-old man treated with azathioprine for Crohn's disease. *J Clin Microbiol* 47:1252–1254, 2009.
10. Yuge A, et al: Persistent hepatitis associated with chronic active Epstein-Barr virus infection. *Pediatr Infect Dis J* 23:74–76, 2004.
11. Vento S, Cainelli F: Is there a role for viruses in triggering autoimmune hepatitis? *Autoimmun Rev* 3:61–69, 2004.
12. Biest S, Schubert TT: Chronic Epstein-Barr virus infection: a cause of granulomatous hepatitis? *J Clin Gastroenterol* 11:343–346, 1989.
13. Si MW, et al: Hepatocellular lymphoepithelioma-like carcinoma associated with Epstein Barr virus: a hitherto unrecognized entity. *Diagn Mol Pathol* 13:183–189, 2004.
14. Jeng YM, Chen CL, Hsu HC: Lymphoepithelioma-like cholangiocarcinoma: an Epstein-Barr virus-associated tumor. *Am J Surg Pathol* 25:516–520, 2001.
15. Pedersen M, Seetharam A: Infections after orthotopic liver transplantation. *J Clin Exp Hepatol* 4:347–360, 2014.
16. Kremers WK, et al: Post-transplant lymphoproliferative disorders following liver transplantation: incidence, risk factors and survival. *Am J Transplant* 6:1017–1024, 2006.
17. Suh N, et al: Epstein-Barr virus hepatitis: diagnostic value of in situ hybridization, polymerase chain reaction, and immunohistochemistry on liver biopsy from immunocompetent patients. *Am J Surg Pathol* 31:1403–1409, 2007.
18. Torre D, Tambini R: Acyclovir for treatment of infectious mononucleosis: a meta-analysis. *Scand J Infect Dis* 31:543–547, 1999.
19. Koch DG, et al: Posttransplantation lymphoproliferative disorder—the great mimic in liver transplantation: appraisal of the clinicopathologic spectrum and the role of Epstein-Barr virus. *Liver Transpl* 13:904–912, 2007.
20. Ho M: Epidemiology of cytomegalovirus infections. *Rev Infect Dis* 12(Suppl 7):S701–S710, 1990.
21. Cohen JI, Corey GR: Cytomegalovirus infection in the normal host. *Medicine (Baltimore)* 64:100–114, 1985.
22. Squizzato A, et al: A case report and literature review of portal vein thrombosis associated with cytomegalovirus infection in immunocompetent patients. *Clin Infect Dis* 44:e13–e16, 2007.
23. Snover DC, Horwitz CA: Liver disease in cytomegalovirus mononucleosis: a light microscopical and immunoperoxidase study of six cases. *Hepatology* 4:408–412, 1984.
24. Bonkowsky HL, Lee RV, Klatskin G: Acute granulomatous hepatitis. Occurrence in cytomegalovirus mononucleosis. *JAMA* 233:1284–1288, 1975.
25. Clarke J, et al: Cytomegalovirus granulomatous hepatitis. *Am J Med* 66:264–269, 1979.
26. Bosch W, et al: Association of cytomegalovirus infection and disease with death and graft loss after liver transplant in high-risk recipients. *Am J Transplant* 11:2181–2189, 2011.
27. Limaye AP, et al: Impact of cytomegalovirus in organ transplant recipients in the era of antiviral prophylaxis. *Transplantation* 81:1645–1652, 2006.
28. Razonable RR, et al: Allograft rejection predicts the occurrence of late-onset cytomegalovirus (CMV) disease among CMV-mismatched solid organ transplant patients receiving prophylaxis with oral ganciclovir. *J Infect Dis* 184:1461–1464, 2001.
29. Benhamou Y, et al: AIDS-related cholangiopathy. Critical analysis of a prospective series of 26 patients. *Dig Dis Sci* 38:1113–1118, 1993.
30. Tonolini M, Bianco R: HIV-related/AIDS cholangiopathy: pictorial review with emphasis on MRCP findings and differential diagnosis. *Clin Imaging* 37:219–226, 2013.
31. Bruminhent J, Razonable RR: Management of cytomegalovirus infection and disease in liver transplant recipients. *World J Hepatol* 6:370–383, 2014.
32. Norvell JP, et al: Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. *Liver Transpl* 13:1428–1434, 2007.
33. Kaufman B, et al: Herpes simplex virus hepatitis: case report and review. *Clin Infect Dis* 24:334–338, 1997.
34. Pinna AD, et al: Five cases of fulminant hepatitis due to herpes simplex virus in adults. *Dig Dis Sci* 47:750–754, 2002.
35. Kusne S, et al: Herpes simplex virus hepatitis after solid organ transplantation in adults. *J Infect Dis* 163:1001–1007, 1991.
36. Pietrucha-Dilanchian P, et al: Fatal herpes simplex virus type 2 hepatitis in a heart transplant recipient: a case report and review of the literature. *Transpl Infect Dis* 15:E87–E96, 2013.
37. Levitsky J, et al: Detection and diagnosis of herpes simplex virus infection in adults with acute liver failure. *Liver Transpl* 14:1498–1504, 2008.
38. Longerich T, et al: Recurrent herpes simplex virus hepatitis after liver retransplantation despite acyclovir therapy. *Liver Transpl* 11:1289–1294, 2005.
39. Harpaz R, Ortega-Sanchez IR, Seward JF: Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 57:1–30, quiz CE2-CE4, 2008.
40. Lauzurica R, et al: Disseminated varicella infection in adult renal allograft recipients: role of mycophenolate mofetil. *Transplant Proc* 35:1758–1759, 2003.
41. Rogers SY, et al: Visceral varicella zoster infection after bone marrow transplantation without skin involvement and the use of PCR for diagnosis. *Bone Marrow Transplant* 15:805–807, 1995.
42. Fehr T, et al: Disseminated varicella infection in adult renal allograft recipients: four cases and a review of the literature. *Transplantation* 73:608–611, 2002.
43. Kimberlin DW, et al: Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics* 108:230–238, 2001.
44. Fagiuoli S, et al: Management of infections pre- and post-liver transplantation: report of an AISF consensus conference. *J Hepatol* 60:1075–1089, 2014.
45. Wyatt LS, et al: Human herpesvirus 7: antigenic properties and prevalence in children and adults. *J Virol* 65:6260–6265, 1991.
46. Razonable RR, et al: Selective reactivation of human herpesvirus 6 variant a occurs in critically ill immunocompetent hosts. *J Infect Dis* 185:110–113, 2002.
47. Dockrell DH, Paya CV: Human herpesvirus-6 and -7 in transplantation. *Rev Med Virol* 11:23–36, 2001.
48. Mendel I, et al: Fulminant hepatitis in neonates with human herpesvirus 6 infection. *Pediatr Infect Dis J* 14:993–997, 1995.
49. Asano Y, et al: Fatal fulminant hepatitis in an infant with human herpesvirus-6 infection. *Lancet* 335:862–863, 1990.

50. Harma M, Hockerstedt K, Lautenschlager I: Human herpesvirus-6 and acute liver failure. *Transplantation* 76:536–539, 2003.
51. Cacheux W, et al: HHV-6-related acute liver failure in two immunocompetent adults: favourable outcome after liver transplantation and/or ganciclovir therapy. *J Intern Med* 258:573–578, 2005.
52. Harma M, Hockerstedt K, Lautenschlager I: The long-term outcomes of patients transplanted due to acute liver failure with hepatic human herpesvirus-6 infection. *Transplant Proc* 45:1910–1912, 2013.
53. Griffiths PD, et al: Human herpesviruses 6 and 7 as potential pathogens after liver transplant: prospective comparison with the effect of cytomegalovirus. *J Med Virol* 59:496–501, 1999.
54. Humar A, et al: Clinical impact of human herpesvirus 6 infection after liver transplantation. *Transplantation* 73:599–604, 2002.
55. Ohashi M, et al: Human herpesvirus 6 infection in adult living related liver transplant recipients. *Liver Transpl* 14:100–109, 2008.
56. Humar A, et al: Human herpesvirus-6 is associated with cytomegalovirus reactivation in liver transplant recipients. *J Infect Dis* 181:1450–1453, 2000.
57. Rogers J, et al: Human herpesvirus-6 in liver transplant recipients: role in pathogenesis of fungal infections, neurologic complications, and outcome. *Transplantation* 69:2566–2673, 2000.
58. Lautenschlager I, Razonable RR: Human herpesvirus-6 infections in kidney, liver, lung, and heart transplantation: review. *Transpl Int* 25:493–502, 2012.
59. Rabkin CS, et al: Interassay correlation of human herpesvirus 8 serologic tests. *J Infect Dis* 178:304–309, 1998.
60. Verbeek W, et al: Seroprevalence of HHV-8 antibodies in HIV-positive homosexual men without Kaposi's sarcoma and their clinical follow-up. *Am J Clin Pathol* 109:778–783, 1998.
61. Penn I: Kaposi's sarcoma in transplant recipients. *Transplantation* 64:669–673, 1997.
62. Farge D: Kaposi's sarcoma in organ transplant recipients. The Collaborative Transplantation Research Group of Ile de France. *Eur J Med* 2:339–343, 1993.
63. Penn I: Sarcomas in organ allograft recipients. *Transplantation* 60:1485–1491, 1995.
64. Hasan FA, et al: Hepatic involvement as the primary manifestation of Kaposi's sarcoma in the acquired immune deficiency syndrome. *Am J Gastroenterol* 84:1449–1451, 1989.
65. Glasgow BJ, et al: Clinical and pathologic findings of the liver in the acquired immune deficiency syndrome (AIDS). *Am J Clin Pathol* 83:582–588, 1985.
66. Stallone G, et al: Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 352:1317–1323, 2005.
67. Casper C, et al: Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. *J Infect Dis* 198:23–30, 2008.
68. Northfelt DW, et al: Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. *J Clin Oncol* 16:2445–2451, 1998.
69. Stewart S, et al: Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. International Pegylated Liposomal Doxorubicin Study Group. *J Clin Oncol* 16:683–6891, 1998.
70. Lim ST, et al: Weekly docetaxel is safe and effective in the treatment of advanced-stage acquired immunodeficiency syndrome-related Kaposi sarcoma. *Cancer* 103:417–421, 2005.
71. Uldrick TS, et al: Rituximab plus liposomal doxorubicin in HIV-infected patients with KSHV-associated multicentric Castleman disease. *Blood* 124:3544–3552, 2014.
72. Koneru B, et al: Serological studies of adenoviral hepatitis following pediatric liver transplantation. *Transplant Proc* 22:1547–1548, 1990.
73. Neofytos D, et al: Treatment of adenovirus disease in stem cell transplant recipients with cidofovir. *Biol Blood Marrow Transplant* 13:74–81, 2007.
74. Molina JM, et al: Hepatitis associated with primary HIV infection. *Gastroenterology* 102:739, 1992.
75. Boag FC, et al: Abnormalities of liver function during HIV seroconversion illness. *Int J STD AIDS* 3:46–48, 1992.
76. Wertheim DL, Valderamma E, Bonagura VR: Use of zidovudine in human immunodeficiency virus-induced hepatitis. *Clin Diagn Lab Immunol* 1:361–363, 1994.
77. Housset C, et al: Presence of HIV-1 in human parenchymal and non-parenchymal liver cells in vivo. *J Hepatol* 19:252–258, 1993.
78. Esposito A, et al: Management of HIV-1 associated hepatitis in patients with acquired immunodeficiency syndrome: role of a successful control of viral replication. *AIDS Res Ther* 8:9, 2011.
79. Devarbhavi H, et al: HIV/AIDS cholangiopathy: clinical spectrum, cholangiographic features and outcome in 30 patients. *J Gastroenterol Hepatol* 25:1656–1660, 2010.
80. Yuen KY, Wong SS: Human infection by avian influenza A H5N1. *Hong Kong Med J* 11:189–199, 2005.
81. Polakos NK, et al: Kupffer cell-dependent hepatitis occurs during influenza infection. *Am J Pathol* 168:1169–1178, quiz 1404-1405, 2006.
82. To KF, et al: Pathology of fatal human infection associated with avian influenza A H5N1 virus. *J Med Virol* 63:242–246, 2001.
83. Wong WM, et al: Temporal patterns of hepatic dysfunction and disease severity in patients with SARS. *JAMA* 290:2663–2665, 2003.
84. Chau TN, et al: SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. *Hepatology* 39:302–310, 2004.
85. Tsuda H: Liver dysfunction caused by parvovirus B19. *Am J Gastroenterol* 88:1463, 1993.
86. Pardi DS, et al: Hepatitis-associated aplastic anemia and acute parvovirus B19 infection: a report of two cases and a review of the literature. *Am J Gastroenterol* 93:468–470, 1998.
87. Bathla L, et al: Parvovirus associated fulminant hepatic failure and aplastic anemia treated successfully with liver and bone marrow transplantation. A report of two cases. *Am J Transplant* 14:2645–2650, 2014.
88. Anand A, et al: Human parvovirus infection in pregnancy and hydrops fetalis. *N Engl J Med* 316:183–186, 1987.
89. Eid AJ, et al: Parvovirus B19 infection after transplantation: a review of 98 cases. *Clin Infect Dis* 43:40–48, 2006.
90. Gavish D, et al: Hepatitis and jaundice associated with measles in young adults. An analysis of 65 cases. *Arch Intern Med* 143:674–677, 1983.
91. Khatib R, Siddique M, Abbass M: Measles associated hepatobiliary disease: an overview. *Infection* 21:112–114, 1993.
92. Satoh A, et al: Clinicopathological study on liver dysfunction in measles. *Intern Med* 38:454–457, 1999.
93. Robertson DA, et al: Persistent measles virus genome in autoimmune chronic active hepatitis. *Lancet* 2:9–11, 1987.
94. Hussey GD, Klein M: A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med* 323:160–164, 1990.
95. Stern H, Williams BM: Isolation of rubella virus in a case of neonatal giant-cell hepatitis. *Lancet* 1:293–295, 1966.
96. Morgan C, et al: A case of fulminant hepatitis due to echovirus 9 in a patient on maintenance rituximab therapy for follicular lymphoma. *Case Rep Hematol* 2015:454890, 2015.
97. Lefterova MI, et al: Severe hepatitis associated with an echovirus 18 infection in an immune-compromised adult. *J Clin Microbiol* 51:684–687, 2013.
98. Sun NC, Smith VM: Hepatitis associated with myocarditis. Unusual manifestation of infection with Coxsackie virus group B, type 3. *N Engl J Med* 274:190–193, 1966.
99. Bhatt S, et al: The global distribution and burden of dengue. *Nature* 496:504–507, 2013.
100. Stienlauf S, et al: Epidemiology of travel-related hospitalization. *J Travel Med* 12:136–141, 2005.
101. Schwartz E, et al: Changing epidemiology of dengue fever in travelers to Thailand. *Eur J Clin Microbiol Infect Dis* 19:784–786, 2000.

102. Simmons CP, et al: Dengue. *N Engl J Med* 366:1423–1432, 2012.
103. Schwartz E, Mendelson E, Sidi Y: Dengue fever among travelers. *Am J Med* 101:516–520, 1996.
104. Monath TP, Cetron MS: Prevention of yellow fever in persons traveling to the tropics. *Clin Infect Dis* 34:1369–1378, 2002.
105. Garske T, et al: Yellow Fever in Africa: estimating the burden of disease and impact of mass vaccination from outbreak and serological data. *PLoS Med* 11:e1001638, 2014.
106. Oudart JL, Rey M: Proteinuria, proteinaemia, and serum transaminase activity in 23 confirmed cases of yellow fever. *Bull World Health Organ* 42:95–102, 1970.
107. Elton NW, Romero A, Trejos A: Clinical pathology of yellow fever. *Am J Clin Pathol* 25:135–146, 1955.
108. Quaresma JA, et al: Reconsideration of histopathology and ultrastructural aspects of the human liver in yellow fever. *Acta Trop* 94:116–127, 2005.
109. Quaresma JA, et al: Revisiting the liver in human yellow fever: virus-induced apoptosis in hepatocytes associated with TGF-β, TNF-α and NK cells activity. *Virology* 345:22–30, 2006.
110. Sbrana E, et al: Efficacy of post-exposure treatment of yellow fever with ribavirin in a hamster model of the disease. *Am J Trop Med Hyg* 71:306–312, 2004.
111. Monath TP, et al: Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. *Am J Trop Med Hyg* 66: 533–541, 2002.
112. Levy S, et al: Adverse events associated with 17D-derived yellow fever vaccination—United States, 2001-2002. *MMWR Recomm Rep* 51:989–993, 2002.
113. Centers for Disease Control and Prevention: Lassa fever. Available at: <https://www.cdc.gov/vhf/lassa/>. Accessed November 3, 2016.
114. Monath TP: Lassa fever: review of epidemiology and epizootiology. *Bull World Health Organ* 52:577–592, 1975.
115. Centers for Disease Control and Prevention: Lassa fever: signs and symptoms. Available at: <http://www.cdc.gov/vhf/lassa/symptoms/index.html>. Accessed November 3, 2016.
116. Yun NE, Walker DH: Pathogenesis of Lassa fever. *Viruses* 4:2031–2048, 2012.
117. McCormick JB, et al: Lassa virus hepatitis: a study of fatal Lassa fever in humans. *Am J Trop Med Hyg* 35:401–407, 1986.
118. Bowen MD, et al: Genetic diversity among Lassa virus strains. *J Virol* 74:6992–7004, 2000.
119. Vieth S, et al: RT-PCR assay for detection of Lassa virus and related Old World arenaviruses targeting the L gene. *Trans R Soc Trop Med Hyg* 101:1253–1264, 2007.
120. McCormick JB, et al: Lassa fever. Effective therapy with ribavirin. *N Engl J Med* 314:20–26, 1986.
121. Feldmann H: Ebola—a growing threat? *N Engl J Med* 371:1375–1378, 2014.
122. Ansumana R, et al: Ebola in Sierra Leone: a call for action. *Lancet* 384:303, 2014.
123. World Health Organization: Ebola situation report—24 June 2015. Available at: <http://apps.who.int/ebola/current-situation/ebola-situation-report-24-june-2015>.
124. Centers for Disease Control and Prevention: Interim guidance for environmental infection control in hospitals for Ebola virus. Available at: <http://www.cdc.gov/vhf/ebola/hcp/environmental-infection-control-in-hospitals.html>.
125. Schieffelin JS, et al: Clinical illness and outcomes in patients with Ebola in Sierra Leone. *The N Engl J Med* 371:2092–2100, 2014.
126. Chertow DS, et al: Ebola virus disease in West Africa—clinical manifestations and management. *N Engl J Med* 371:2054–2057, 2014.
127. Galvani AP, et al: Ebola vaccination: if not now, when? *Ann Intern Med* 161:749–750, 2014.