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Chapter 6

Viral Diseases in Transplant and Immunocompromised Patients

Liliya Ivanova, Denitza Tsaneva, Zhivka Stoykova and Tcvetelina Kostadinova

Additional information is available at the end of the chapter

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Abstract

For the last few years, the number of immunocompromised individuals is growing fast, due to more intensive antitumor therapy, transplantations and the concomitant immunosuppressive therapy, and the HIV epidemic, as well. Immunosuppressed patients very often are affected with nosocomial infections in hospitals, and with infections in the society. The defense from viral diseases depends mainly on the immune system. When there is immune deficiency, the illness is taking severely longer and has complicated outcome. Usually immunocompromised individuals have one or more defects in the defensive mechanisms and leading cause of death is infection.The viruses taking part in this process are Epstein Barr virus (EBV), Cytomegalovius (CMV), Herpes simplex viruses (HSV1, HSV2), Varicella zoster virus (VZV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Human Polyomaviruses (BKV, JC). Many viruses (HIV, CMV, EBV) are depressing the immune resistance and are leading to co-infections with other microbial agents. Some viruses (HSV1/2, HPV, CMV, EBV, BKV, JC) are at latent condition in the infected persons for life. They become activated when decline in the immunity occurs, leading to serious illnesses. For this reason, accurate screening and prompt and precise diagnosis can be performed to prevent exacerbation of diseases and provide appropriate treatment.

Keywords: immunosupression, immunocompromised individuals, transplantation, viral infections

1. Introduction

According to several studies during the last few years, a tendency toward decreasing immune protection in human population has been under review. In the second half of the 20th century,

the number of immunocompromised individuals is growing fast, due to more intensive antitumor therapy, transplantations, and the concomitant application of immunosuppressors and the HIV epidemic, as well. New syndromes and diseases appear, such as post-transplant lymphoproliferative disease (PTLD), caused in most cases by Epstein-Barr virus (EBV), and pneumonia by Cytomegalovirus (CMV). Other viruses taking part in this process are Herpes simplex viruses (HSV1, HSV2), Varicella zoster virus (VZV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Human Polyomaviruses (BKV, JC). Usually immunocompromised individuals have one or more defects in the defensive mechanisms and leading cause of death is infection. The problem with viral causers of infections and diseases has become complicated for a few reasons:

1. The defense from viral diseases depends mainly on the immune system. When there is immune deficiency, the illness is taking severely longer from its normal course and has complicated outcome. In such patients, the disease often becomes chronic or lead to neoplasms.

2. Many viruses (HIV, CMV, EBV) are depressing the immune resistance and are leading to co-infections with other microbial agents.

3. Some viruses (HSV1/2, HPV, CMV, EBV, BKV, JC) are at latent condition in the infected persons for life. They become activated when decline in the immunity occurs, leading to serious illnesses.

4. In seronegative pregnant women and those with immune deficiency, the risk for congenital infections rises substantially.

The immune deficiency can be primary (congenital) and secondary (acquired).

Primary immunodeficiency is developed because of genetic block in differentiation of immunocompetent cells and impairment of immune mechanisms in antibody and/or T-lymphocytes production. There are three groups of primary immune deficiency:

1. Combined immune deficiency affecting T and B cell population with insufficient cellular and humoral immunity (hypogammaglobulinaemia of Glanzmann-Riniker).

2. Immunodeficiency due to a defect in the function of B cells with hypo- and agammaglobulinaemia and especially IgA deficiency (agammaglobulinaemia of Bruton, common variable hypogammaglobulinaemia).

3. Immunodeficiency based on T cell insufficiency with thymus aplasia (DiGeorge Syndrome), defect in α- and γ-interferon synthesis.

Other than the primary immune deficits mentioned above, there are others, such as defect in the enzyme assuring purine nucleotides' phosphorylation and structural defects in the 14th chromosome.

The congenital B cell insufficiency leads to serious diseases after live vaccine application (poliomyelitis, measles, mumps, rubella). There is affecting of central nervous system and development of paresis and frequent recurrent viral infections of respiratory track. After

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infections caused by enteroviruses, encephalitis and myositis can occur. Chronic diarrhea is typical in rotavirus infection.

The congenital T-cell insufficiency brings about systematic infections caused by different viruses such as CMV, EBV, VZV, and by viruses of families ortho- and paramyxoviridae also.

Patients with interferon failure suffer from frequent respiratory diseases.

Secondary immune deficiency can be seen in:

1. Viral diseases as measles, mumps, and mononucleosis syndrome (EBV, CMV).
2. Autoimmune and malignant diseases, especially to the blood and reticuloendothelial system (myeloid leukemia, lymphoid leukemia, multiple myelomas, Morbus of Hodgkin), affecting T cell precursors and macrophages and causing deficiency in cell-mediated immunity.
3. Renal failure and uremia in patients on hemodialysis.
4. Viral infections of the immune system (HIV) affecting the function of CD4+ T-helper cells, humoral and cell-mediated immune response afterwords are suppressed.
5. Medical treatment with immunosuppressive therapy, treatment with glycocorticoids, radiotherapy are affected barrier function of the epithelium of upper respiratory track and intestinal mucosa. This results in severe respiratory and intestinal infections. Cell proliferation is suppressed, leading to neutropenia, lymphopenia, monocytopenia. The advance of PMN cells into the space of inflammation is also suppressed. There is also difference in the sensitivity of macrophages to macrophage-activating cytokine (α-interferons). Precursors of T cell and macrophages are affected, which leads to the deficiency of cell-mediated immunity.
6. Organ transplantation and immunosuppressive therapy during post-transplant period.

Etiology and pathogenesis of viral infections in immunocompromised patients depends on the type of the immune deficiency. Clinical disease usually includes nonspecific symptoms. In most cases, it cannot be differentiated from organ rejection in patients with transplantation. The specific laboratory virological and serological tests are important for diagnosis.

More significant viral infections and diseases in immunocompromised patients are described below.

2. Epstein-Barr Virus (EBV)

EBV is a herpesvirus that is thought to infect up to 95% of the adult population. Primary infection in childhood usually results in mild, self-limiting illness [1, 2]. Asymptomatic carriers in childhood are often seen. Immunocompetent older children and adult patients get sick from infectious mononucleosis with benign lymphoproliferation of B cells under the control of the cytotoxic T cells and cellular immune response consisting of CD4+ and CD8+ T cells, which

control both primary infection ant periodic reactivation that occur in all EBV-seropositive persons [1, 3, 4]. The EBV causes nasopharyngeal carcinoma, Burkitt lymphoma, and other lymphoepithelic tumors (non-Hodgkin's lymphoma, B- and T-cellular lymphomas) [5]. Development of these diseases is based on some cellular factors, as well as 14th chromosome translocation. Once infected with EBV, the virus persists latently in a person for life, in B cell lymphocytes, and chronically replicating in the cells of the oropharynx [5, 6]. In patients with HIV and transplanted ones, EBV becomes a main problem because of the inability of the immune system to control B cell proliferation and immortalization. EBV infection is registered in nearly 75% of transplanted recipients as the source usually is the donor. Contagion can also occur after blood transfusion. In the course of the immunosuppression, the latent EBV infection can be reactivated. Clinical disease represent mononuclear syndrome with temperature, lymphadenopathy, hepatosplenomegaly and monocytosis. The central nervous system is rarely involved with symptoms of serous meningitis, encephalitis, Guillen Barre syndrome.

The immunosuppression required to prevent graft rejection post-transplantation impairs T cell immunity, potentially allowing for uncontrolled proliferation of EBV-infected B cells, which may result in a spectrum of B cell proliferations that range from hyperplasia to true lymphoma [7, 8]. In the initial stages of PTLD, prolypheration is polyclonal. With mutation and selective growth, the lesion becomes oligoclonal and later, monoclonal. Lymphocytes from patients treated with cyclosporine do not exhibit an appropriate T cell response to EBV-infected B cells in vitro. The activity of natural killer cells is reduced for several months following transplantation [9, 10].

PTLD is a well-recognized complication of both solid organ transplantation and allogeneic hematopoietic stem cell transplantation (HSCT). It is one of the most common post-transplant malignancies. In most cases, it is associated with EBV infection of B cells, either as a consequence of post-transplant reactivation of the virus or from primary EBV infection. The median onset of disease in solid organ transplant population is 6 months and in hematopoietic stem cell recipients 70–90 days [11, 12] after transplantation. The frequency of PTLD depends largely on the type of transplant received and the immunosuppression that the particular transplant requires [6, 11, 12]. Primary EBV infection may develop, such as in an EBV seronegative recipient who received an allograft from an EBV-seropositive donor. This is recognized as probably the most significant risk factor for developing PTLD and be higher in pediatric transplant recipients [12]. The incidence ranged from 0.6%–2.1% in adult kidney recipients to 4.4%–6.9% in pediatric kidney recipients [12, 13] at different time after transplantation. Lung and heart transplantation in adult population is associated with a relatively high rate of PTLD with an incidence of approximately 5% or more [14]. After liver transplantation, reported rate of incidence is approximately 1% in adult recipients and pediatric recipients [15]. In the setting of allogeneic hematopoietic stem cell transplantation, PTLD rates vary greatly depending on the conditioning regimen and the amount of T cell depletion. In pediatric recipients, PTLD occurs in less than 1% of non-T-cell-depleted grafts from matched siblings, compared with as high as 30% of patients with unrelated or HLA-mismatched donors when extensive T cell depletion of the donor bone marrow is performed. Treatment of graft versus host disease with antitimocyte globulin or anti-T-cell monoclonal antibodies is another risk factor for PTLD [16].

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According to the laboratory data, PTLD is characterized by leukopenia, thrombocytopenia, atypical lymphocytosis, generalized lymphadenopathy. Also B-cell lymphoma, non-Hodgkin's lymphoma (90%), lung lymphoid hyperplasia and lymphoid interstitial pneumonia (after lung transplantation), oral "hairy" leukoplakia (in association with HPV), and malignant transformation are developed. Of note, PTLD may be very difficult to distinguish from episodes of organ rejection and infection. Cell factors take part in the progress of PTLD, as well as co-infection with CMV. Different clinical symptoms can go along with the functional disorder. Mortality rate after solid-organ transplantation is more than 50% and after hematopoietic stem cell transplantation early mortality rate approached 90% [17, 18].

PTLD is an often-fatal complication of transplanted patients. Early diagnosis is important. Good medical practice requires elucidating the serological status of the patients for EBV before transplantation or immunosuppression. ELISA and immunofluorescence are used. Those who have latent infection have positive results for IgG against capsid antigen of the virus (VCA), and in most cases, against nuclear Ag (EBNA). Patients with primary or activated latent infection may have IgM and IgG anti EBV VCA, and high titer against early Ag (EA), usually EBNA are not formed. Other special studies to confirm the diagnosis of PTLD include immunophenotyping by flow cytometry or immunohistochemistry and molecular studies such as fluorescent in situ hybridization for EBV early RNA (EBER). EBV PCR of peripheral blood may be useful at the time of diagnosis and during follow-up as a method of monitoring the patient's response to treatment [18]. Surveillance by monthly PCR for circulating EBV DNA may be appropriate in such high-risk settings as EBV-seromismatched (donor-positive, recipient-negative) solid organ transplants and T cell depleted, HLA-mismatched stem cell transplants [18, 19].

Reduction in immunosuppression remains the primary therapy and often results in permanent disease eradication (19). Antiviral drugs are used (acyclovir, valacyclovir, famcyclovir, gancyclovir) combined with immunotherapy with anti-B-cell antibodies or conventional chemotherapy. Adoptive immunotherapy with EBV-specific donor T cells is highly effective. There is some data for the prophylactic administration of gancyclovir before transplantation and immunosuppression (20).

3. Cytomegalovirus (CMV)

CMV is a ubiquitous herpesvirus that infects majority of humans and is transmitted via saliva, body fluids, cell, and tissue. Primary infection in immunocompetent individuals manifests as an asymptomatic or self-limited febrile illness or as mononucleosa-like syndrome in childhood and older age. The seroprevalence depends on the socioeconomic status and ranges from 30%–97% in Europe and North America [2, 21]. Following primary viral replication in seronegative individuals, CMV establishes non-replicative infection for life, named latency, in CD34+ myeloid progenitor cells as a major site [22] and in lymphoid organs and tissues as well (23). Various latently infected cells serve as reservoirs for reactivation and as carriers of infection to susceptible individuals [24]. After reactivation, CMV multiplies inside. In immunocompro-

mised patients and especially after transplantation, CMV is one of the main clinical problems in almost all types of allograft recipients. Basic risk factor in the development CMV replication and disease is transmission via transplanted organs or tissues including the heart, kidney, lung, liver, and hematopoietic stem cells [25, 26]. CMV disease risk is highest when primary infection occurs in seronegative transplant recipients by the transplanted organ from the seropositive donor (27). On the other hand, secondary infection presumably occurs following the reactivation of the recipient's endogenous latent infection and is more common than primary infection. The frequency depends on the specific immunosuppression utilized. The third type of infection can be correlated with a presumed superinfection that is reinfection of the previously seropositive recipients by donor virus present in allograft [28].

The initial infection is dangerous for all immunosuppressed patients, because of numerous CMV indirect effects, due to the ability to modulate the immune system, and is an important contributor to active and chronic allograft injury [26, 29]. CMV can cause dysfunction of the transplanted organ or can participate in its rejection from the organism, which is often seen in recipients of liver, heart, and lungs. Infections and diseases with CMV are also typical for recipients of kidneys and bone marrow, as mortality is in the rate of 32–70%. Other risk factors are the overall state of immunosuppression as determined by the immunosuppressive protocol (e.g. type of drug, dose, timing, and duration), host factors (e.g. age, comorbidity, leucopenia and lymphopenia, genetic factors), and others [30]. The degree of immunosuppression correlates with the severity of the clinical symptoms of CMV infection. According to the data, conventional immunosuppressive therapy is increasing the gravity of the disease.

Source of primary infection and reinfection are also blood and blood products, which have not been checked for the presence of latent CMV virus in lymphocytes. A CMV seronegative recipient who received donor organ of a seronegative individual has the lowest risk of CMV disease when receiving CMV-negative blood or leuco-depleted blood products. The use of mTOR inhibitors (everolimus, sirolimus) is associated with a lower risk of CMV disease [31]. Transplant recipients who receive treatment with lymphocyte-depleted drugs, especially if given for the treatment of rejection, should be considered at high risk for CMV disease [32].

It is considered that in almost 100% of immunocompromised patients, the latent CMV infection will become reactivated. This reactivation refers, especially, to recipients from seropositive donors, although clinical manifestation is developed in 20–25 % of them [28, 33].

To assess the risk for CMV-related disease, serology testing of all donors and transplant candidates prior to transplantation can be performed. The clinical symptoms of active CMV infection are often nonspecific, also known as CMV syndrome (prolonged fever, weakness, hematological abnormalities such as thrombocytopenia, atypical lymphocytosis and leukopenia, and abnormalities of hepatic function). The symptoms occur 1–4 months after transplantation, in some cases, even later and sometimes it is difficult to differentiate them from those of organ rejection. The greatest risk for this condition is at the first 30 days after the immunosuppression. Tissue-invasive CMV disease is when it implicates the gastrointestinal tract, pneumonitis, hepatitis, nephritis, myocarditis, pancreatitis, retinitis, etc. [34]. In patients with transplanted liver, CMV hepatitis occurs in 17% of the cases. The "vanishing bile duct syndrome" (VBS) is related with CMV infection and organ rejection. Heart and lung recipients

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usually develop interstitial pneumonia, as those with bone marrow transplantation. Mortality is from 33–100% in a half of the patients. Atherosclerosis of coronary vessels develops three times faster in patients with active CMV infection in heart recipients [35–42].

Laboratory diagnosis of CMV infection and CMV disease can be accomplished with various methods. Preliminarily, before starting with the immunosuppression or transplantation, the serological status of the donor and recipient is defined. Generally, the method used for this purpose is ELISA, which detects specific IgG Ab in the serum of the patient. CMV infection after transplantation represents the presence of the virus and viral replication in body fluids or tissue samples regardless of clinical symptoms. CMV disease after transplantation represents the presence of any clinical symptoms in patients with CMV infection [43]. The laboratory methods to confirm CMV infections are histology, culture, serology, antigenemia (pp65 antigenemia), and molecular assay that detect and quantify CMV nucleic acid (NAT) [35]. Serology to detect CMV-IgM and IgG has limited use for diagnosis of CMV disease after transplantation (44). Molecular tests that detect CMV DNA or RNA are the preferred methods. Detection of CMV RNA is indicative of CMV replication. Detection of CMV DNA may or may not reflect CMV replication since a highly sensitive NAT may amplify latent viral DNA. Quantitative NAT (QNAT) assay have been developed to potentially differentiate active viral replication typically associated with high viral load from latent virus with low level CMV DNAemia [35, 45]. QNAT is useful for guiding preemptive therapy, for rapid and sensitive diagnosis of CMV infection, and to guide treatment responses [45]. Patients suspected to have tissue-invasive CMV disease but with negative QNAT or pp65 antgenemia should undergo tissue biopsy and histopathology to confirm the clinical suspicion of CMV disease [35].

The approaches to CMV prevention in recipients vary among different transplant population and risk profile. The two major strategies for CMV prevention are: antiviral prophylaxis and preemptive therapy. Antiviral prophylaxis is the administration of antiviral drug to "at-risk" patients for a defined period after transplantation. Preemptive therapy is the administration of antiviral drug only to asymptomatic patients with evidence of early CMV replication in order to prevent disease. Recipients are monitored at regular intervals (usually once weekly) using a laboratory assay such as CMV QNAT or pp65 antgenemia.

Antiviral prophylaxis has the advantage of preventing reactivation of other herpesviruses, and has been associated with lower incidence of indirect CMV effects [46]. Antiviral prophylaxis can be administered to any at-risk recipients. The duration varies depending on the CMV donor and recipient serostatus and the transplant types, extended between 100 days and 12 months in different group [35]. Valgancyclovir is the preferred drug. Alternative options are intravenous gancyclovir, oral gancyclovir, and for kidney recipients only valacyclovir. Unselected intravenous immunoglobulin (IVIG) may also be used but only as an adjunct to antiviral therapy in lung, heart, and intestinal transplant recipients. In general, antiviral prophylaxis should be started as early as possible and within the first 10 days after transplantation [35]. However, antiviral prophylaxis is associated with late-onset CMV disease particularly among CMV D+/R- patients, probably due to development of drug resistance [47]. The potential options for prevention and management of late-onset CMV disease are careful clinical follow up with early treatment of CMV disease when symptoms occur, CMV QNAT or pp65

antgenemia monitoring after completion of antiviral prophylaxis, and prolonged antiviral prophylaxis.

Preemptive therapy requires weekly patient monitoring for evidence of early CMV replication, which is then treated with valgancyclovir or intravenous gancyclovir. The recommended doses are valgancyclovir (900 mg twice daily) or intravenous ganciclovir (5 mg/kg every 12 h). Many authors prefer antiviral prophylaxis for D+/R- and lung transplant recipients while recognizing the clinical utility of preemptive therapy in CMV R+ kidney, liver, pancreas, and heart recipients [21, 35]. The same laboratory test for monitoring is recommended, with frequency of once weekly for 12 weeks after transplantation.

Indications of use of ganciclovir also include severe local (often eye damages) and life threatening conditions in patients with HIV, organ transplantations, and neoplasms. The use of lymphocyte-depleting therapy is a major risk factor for CMV disease when used for rejection treatment. The optimal duration of antiviral prophylaxis is given for 1–3 months with valgancyclovir (900 mg once daily, oral gancyclovir 1 g p.o. thrice daily) or intravenous gancyclovir (5 mg/kg every 24 h) [35].

Patients who develop CMV disease after prolonged courses of gancyclovir or vagancyclovir administration, and those failing to respond to standard gancyclovir treatment, should be suspected of having gancyclovir resistant virus. In these conditions, genotype testing should be performed. Immunosupression should be cautiously reduced. Therapeutic options for gancyclovir resistant CMV are limited. Foscarnet is often the first line for the treatment of UL97-mutant gancyclovir-resistent CMV (48). Switching to sirolimus-containing regimen may be an option for patients receiving mTOR inhibitors. Other therapeutic options are administration of cidofovir or its new oral formulation that may be available for compassionate release brinsidofovir (CMX001), compassionate release letermovir (AIC246), compassionate release maribavir, off-label leflunomid and off-label artesunate [49, 50]. Due to the virus, ability to evade host defenses of primary infection with CMV has not been shown to confer immunity from subsequent infections. Notwithstanding this, there are efforts to develop a CMV vaccine for prevention and therapy [51]. Due to some toxic effects of ganciclovir, patients need preliminary tests for renal function and blood count. Renal function is defined with the means of creatinine clearance, which has to be more than 70 ml/min. In blood, the number of neutrophiles has to be more than 1000 cells/mm^3, platelets –above 25000 cells/mm^3. During the treatment process these indicators are monitored every week and if they begin to decrease drastically, therapy is ceased. CMV therapy is not recommended in pregnant women, children under 12 years old and people more than 65 years old.

4. Varicella Zoster Virus (VZV)

VZV is a human herpesvirus that spreads through direct contact with skin lesions or through air from respiratory droplets. Primary exposure, usually in childhood, leads to varicella, typically presents with fever, constitutional symptoms, and widely disseminated vesicular rush that primary involves the trunk and face [52]. Symptoms usually resolve within 7–10 days

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in immunocompetent children and young adults. More than 90% of adults acquire the infection in childhood and will be seropositive for VZV [2]. After initial infection, VZV establishes lifelong latency in the cranial nerve and dorsal root ganglia, and can reactivate years to decades later as herpes zoster in some individuals [53]. In children with primary and secondary immunodeficiency because of immunosuppressive therapy (leukemia, lymphoma, solid tumors), after transplantation VZV causes progressive varicella characterized by the continuous development of vesicular rash because of high viral replication and inadequate immune response [54, 55]. The high mortality among these children and adult organ recipients is because of systematic infection with multiple organ involvement, especially in the lungs, liver, pancreas, and central nervous system and, in some cases, disseminated intravascular coagulopathy. Relapses are often seen. More recent reports have shown that pediatric renal and liver transplant recipients are at lower risk (4%–6.2%) for complication when given immediate antiviral therapy [56–60].

Herpes zoster is characterized by vesicular rash units all over the corresponding nerve and estimated to occur in up to 20% of the immunocompetent individuals during their lifetime. In immunosuppressed and transplanted patients, herpes zoster is a frequent infectious complication during the first four years after the transplantation [61, 62]. About half of the cases in the first year after the transplantation, a disseminated infection with mortality about 9% is observed, especially in the cases of organ rejection. Allogeneic stem cell transplantation is another procedure that greatly heightens the risk of herpes zoster. The incidence of VZV reactivation is 20.7%. VZV-related complications occur in 29% of patients with reactivation, most common of which is disseminated disease and postherpetic neuralgia. Radiotherapy can also become a reason for herpes zoster in about 15%–34 %. There is dissemination of the rash units outside the affected dermatome. In about 1% of all cases, encephalitis develops. This is typical, a second relapse that manifests, involving other body parts. In children with leukemia, herpes zoster or varicella develops more than one episode of clinical manifestation. Older transplant recipients are at greater risk for the development of herpes zoster and postherpetic neuralgia as secondary complication [62–65].

To determine the risks of VZV primary infection or reactivation after immunosupression and transplantation, all patients being considered for these procedures should undergo serologic testing (ELISA anti VZV IgG) to document prior exposure to VZV. Patients who are seronegative are at high risk for the development of primary VZV, and seropositive patients are at high risk for developing herpes zoster. In general, both primary varicella and herpes zoster have typical clinical presentations. Definitive laboratory testing can be used for atypical cases and should be used for suspected disseminated, visceral disease, or central nervous system disease. Rapid diagnostic methods, including polymerase chain reaction (PCR) and direct immunofluorescent assay, are the methods of choice. PCR can be used for detecting VZV in vesicle fluid, serum, spinal fluid, and other tissues. Viral culture is specific and can help distinguish VZV from other herpesvirus pathogens (herpes simplex virus - HSV) [66].

Post-transplant and immunosuppressive patients who develop primary varicella should be treated with intravenous (IV) acyclovir early in the course of the illness, especially within 24 hours of rash onset. Reduction of immunosuppressive therapy should be considered. How-

ever, IVIG or VZV immunoglobulin (VZIG) have been used in those with severe infection. Patients with disseminated or organ invasive herpes zoster should be treated with IV acyclovir. Localized nonsevere dermatomal herpes zoster can be treated with oral acyclovir, valacyclovir or famcyclovir [65].

Oral acyclovir and its pro-drugs have been shown to prevent VZV reactivation in immunosuppressed population. During the early post-transplant period, many current regimens used for CMV prevention will likely prevent VZV reactivation. In patients who do not receive CMV prophylaxis, short-term antivirals given for HSV prophylaxis may also be effective against VZV during the period immediately post-transplant [65]. Other authors recommended one year prophylactic with acyclovir, which has been shown to effectively prevent VZV-reactivation after allogeneic hematopoietic stem cell transplantation [61].

In the U.S., potential transplant recipients who are susceptible to VZV should be given varicella vaccination (one or two doses) with live attenuated Oka vaccine (Varivax, Merck & Co., Inc., Whitehouse Station, NJ, USA). There is currently a herpes zoster vaccine (Zostavax, Merck & Co., Inc.) that has not been studied in patients with end-organ disease awaiting transplantation. The Oka varicella vaccines have been shown to be safe in select children undergoing chemotherapy, and studies have shown that they can be given safely to posttransplant recipients receiving immunosupression. Inactivated VZV vaccines, which are in development, may eventually provide another option for this high-risk population [65–68].

5. Herpes simplex virus

Herpes simplex virus type 1 (HSV1) and herpes simplex virus type 2 (HSV2) are members of the Herpesvirus family and is transmitted via close personal contact. Seroprevalence studies indicated that infections are common worldwide and increases with age [2, 69]. More than 90% of adult have acquired HSV infection by their fifth decade of live, though only a minority develop clinically apparent disease at the time of acquisition [70]. After the first contagion, HSV stays in latent condition for a lifetime. HSV1 is acquired predominantly during childhood age, while HSV2 is acquired by sexual contact. A recent study indicated that HSV1 can also cause genital herpes (71). In immunocompetent individuals, symptomatic disease is presented as orolabial or genital herpes [72, 73]. Symptomatic disease may occur as a first episode that heals in 10–21 days, followed by the establishment of latency and the risk of subsequent episodes of reactivation. Cell-mediated immunity plays an important role in host defense and the containment of infection [74]. Individuals with impaired cell-mediated immunity, such as immunosupressed and transplanted patients, are subject to more frequent episodes of reactivation, prolonged duration of symptoms and shedding, increased severity of infection, and a greater potential for dissemination [75]. Solid organ transplant patients have had pretransplant HSV seropositivity rates and age distributions similar to the general population. In the absence of antiviral prophylaxis, seropositive recipients often experience reactivation of latent infection within one or two months after transplantation [76]. Mucocutaneous lesions are the majority of HSV disease in transplant population, mainly with orolabial and anogenital

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localizations. HSV esophagitis, pneumonia, meningitis, and viremia dissemination either from reactivation or primary infection, may involve the spread to multiple organs such as the liver, adrenal glands, gastrointestinal tract, lungs, skin, and bone marrow [77].

To determine the risk of HSV primary infection or reactivation after immunosupression and transplantation, all patients being considered for these procedures should undergo serologic testing (ELISA anti HSV1 IgG and anti HSV2 IgG) to document prior exposure to the viruses. Patients who are seronegative are at high risk for the development of primary HSV, and seropositive patients are at high risk for developing reactivation. In the presence of characteristic mucocutaneous lesions, clinical diagnosis may be considered reliable. Laboratory testing can be used for atypical cases and should be used for suspected disseminated, visceral disease, or central nervous system disease. Viral culture is the definitive method of diagnosis for isolation of the virus from vesicles, urine, stool, nasopharynx, throat, conjunctive, and cerebrospinal fluid. Nucleic acid amplification method of DNA detection (PCR) is increasing utility, and has been shown to be 3 to 4 times more sensitive than viral culture [79]. Direct fluorescent antibody test is another mode of diagnosis of HSV; it offers rapid diagnosis and can also give type-specific diagnoses [75–79].

Acyclovir is the drug of choice for treatment of HSV infections in both immunocompetent and immunocompromized patients. Transplant patients with mucocutaneous lesions may be treated with IV acyclovir (5 mg/kg/dose given every 8 hours) for 7–14 days, oral acyclovir, or one of the alternative oral antiviral agents with better bioavailability (valacyclovir or famcyclovir). Disseminated infections and herpes simplex encephalitis, due to the potentially life-threatening nature of these infections, should be treated with a high dose IV acyclovir (10 mg/kg/dose given every 8 hours) for 7–14 days. Recently, in the last few years, some mutated acyclovir resistant strains of HSV have been isolated. These mutants are founded in patients with HIV and those with bone marrow transplantation and preventive treatment with acyclovir. These patients are treated according to a scheme with pencyclovir [76]. Gancyclovi, valgancyclovir, foscarnet or cidofovir are other antiviral agents with activity against herpesviruses, including HSV and CMV co-infections. Acyclovir can also be used for prophylaxis of the infection before immunosuppression and transplantation to prevent reactivation of the latent infection and considerably reduced incidence of disease in the early posttransplant period.

Numerous efforts have been made to develop an HSV vaccine using several different methods including inactivated virus, live attenuated virus, viral subunits and more recently, recombinant viruses. Many of these attempts shower promising results in their early phase of development [79–80].

6. Polyomaviruses (BKV, JCV)

Polyomaviruses are ubiquitous, infecting many different mammalian species including humans. Most human polyoma-diseases are caused by JCV and BKV. The prevalence of infections differs in geographical and age distribution, suggesting they circulate independ-

ently. BKV infection is acquired in early childhood, whereas JC presents later. Transmission of BKV occurs typically via oral and respiratory routes, but data suggests transmission via cells and tissues, in particular by kidney transplantation [81]. Approximately 50%–80% of humans have seropositivity to JCV and BKV viruses due to multiple routes of transmission [82, 83]. Clinically apparent diseases in immunocompetent hosts are extremely rare and are not associated with any well-defined clinical syndrome. After primary infection, viruses remain latent possibly in the lymphoid organs, neuronal tissue, kidney, and tubular epithelial cells. About 5% of healthy individuals intermittently reactivate BKV replication with detectible viruria [84]. Under the circumstances of severe immunosuppression both viruses reactivate. BKV can cause pneumonitis, hepatitis, retinitis, and meningoencephalitis [85]. Hemorrhagic cystitis is seen in 25–60% of bone marrow transplant patients, usually 2 weeks after transplantation [86]. Up to 80% of renal transplant patients have BK viruria, and 5%–10% progress to BKV nephropathy (BKVN) [87]. Given that polyomavirus is widely latent in the kidney, renal transplantation is believed to be an important mode of infection in patients with end stage kidney disease. Graft loss rate have been reported to be as high as 30%–50% following a diagnosis of BKVN [88]. More recent data indicate that with early diagnosis of BK viremia or viruria using regular screening, the majority of patients respond favorably [89, 90].

Serologic testing may be used in risk-assessment of virus transmission via organ transplantation. The greatest risk of post-transplant viral reactivation is associated with positive serostatus of both the donor and recipient. The presence of IgG antibody to BKV-VP-1 in serum is associated with increased risk of virus transmission and disease in renal allograft recipient [91]. To detect viral replication in urine and blood, real time PCR is the method of choice for diagnosis of BKVN [92] and screening every 3 months for the first two years after transplant or when allograft dysfunction occurs is recommended [93].

The first line of treatment of BKV nephropathy is reduction of immunosupression [92, 93]. A variety of drugs with possible anti-BKV activity that are being utilized as adjuvant therapy but fraught with side-effects are cidofovir, leflunomide, and intravenous immunoglobulin [94]. Fluoroguinolons have been reported to display anti-BK activity because of its large T-antigen helicase activity [95]. Further studies are needed to firmly establish the role of polyoma viruses in human cancer [96].

Other polyomavirus with importance of human pathology is JCV. Progressive multifocal leukoencephalopathy (PML) is a progressive demyelinating central nervous system disorder involving cerebral white matter caused by the JCV. It most often presents as an opportunistic infection in HIV patients with lymphopenia but has recently been seen with new immunosuppressives. After reactivation in severely immunosuppressed states, the virus travels to the central nervous system through infected B-lymphocytes, where it produces lytic destruction of myelin producing glial cells (i.e., oligodendrocytes) and non-lytic infection of astrocytes, causing progressive disease in central nervous system. Typical PML patients have very low CD4+T cell counts even less than 200/mm^2 [97, 98]. The estimated incidence of PML in HIV patients is 5%, but is decreasing with the introduction of highly active anti-retroviral therapy (HAART) [99]. The differential diagnosis of PML is HIV-associated encephalopathy and primary CNS lymphoma. Brain biopsy is the gold standard for diagnosis. Staining with

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immunohistochemistry using antibodies directed to SV40-T antigen is confirmatory. Analysis of cerebrospinal fluid for JCV by PCR has a sensitivity of to 92% and specificity up to 100% (100). For patients with PML and HIV, introduction or optimization of HAART needs to be implemented to decrease viral replication. In non-HIV patients, such as organ transplant patients, immunosupression needs to be decreased or stopped [101]. At this stage, there is no specific antiviral agent for JC virus [97].

7. Respiratory viruses

Every year, the number of patients undergoing stem cell and solid organ transplantation to treat malignancy and end-organ failure increases. Despite advances in screening and prophylaxis strategies, infections remain a significant cause of morbidity and mortality among transplant recipients. From the available data, respiratory viruses remain common pathogens. The respiratory viruses, including Adenovirus, Influenza virus, Human Metapneumovirus (hMPV), Parainfluenza virus (PIV), Respiratory Syncytial virus (RSV), and Rhinovirus (HRV) are increasingly recognized as contributing to significant morbidity and mortality among hematpoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients [102]. Iimmunocompromized patients often have atypical presentation of respiratory infections and viral shedding can be prolonged [103]. Not one virus is exclusively associated with one clinical syndrome and there is a high risk of infectious complications as viral pneumonia or bronchiolitis obliterans following acute respiratory infection. Lymphopenia is consistently a risk factor for more serious infections. Respiratory viral infections appear to be risk factors for acute and chronic rejection, especially in lung transplant patients [104]. There is increased risk of severe respiratory viral infections and its sequels among pediatric recipients, as compared to adult recipients (103).

All respiratory viruses are extremely dangerous for lung and HSCT cell recipients with high mortality rate [105, 106]. Adenoviruses induce respiratory and gastrointestinal diseases. Disseminated infections are characterized by fever, pneumonia, diarrhea, hemorrhagic cystitis, hepatitis, and CNS involvement in up to 10% of the cases. In some patients Adenoviruses can become a reason for organ rejection. Cases of death can occur if there is co-infection with CMV and different bacteria. Adenoviruses are usually in latent condition in the human body and the infection becomes clinically manifested after reactivation of the virus (107). HRV is probably the most common respiratory viral pathogen in the upper and lower respiratory tract in transplant recipients [108].

In general, all patients with presumed respiratory viral infections have a nasopharyngeal swab, wash, or brohoalbeolar aspirate performed. Diagnosis of the respiratory viruses can be achieved by the combination of serology, virus culture, antigen detection, nucleic acid testing, and histopathology. Serology is not useful for initial diagnosis and has reduced sensitivity in transplant recipients. Viral culture can be achieved for most viruses except hMPV and Coronaviruses because special cell lines are needed. Shell vial assays allow earlier detection of viruses with application of monoclonal and polyclonal antibodies. Recently, several fixed

mixture of cells (R-Mix) has become commercially available [109]. Rapid antigen detection using several different techniques is available for Influenza, RSV, and Adenovirus. Direct fluorescent antibody (DFA) testing of primary patient specimens has documented sensitivity that approached PCR [110]. Nucleic acid amplification assay appears to be the most sensitive diagnostic tool available, and most allow for simultaneous detection of a broad range of respiratory pathogens from a simple sample [111].

Treatment depends on the etiological agent. Reduction of immune suppression, if possible, is recommended for all the transplanted recipients. For infections caused by RSV, combination therapy with aerosolized ribavirin and intravenous immunoglobulins appears to have the greatest benefit in reducing mortality [103, 112]. PIV and hMPV infections are treated with oral, aerosolized, or intravenous ribavirin in a combination with intravenous immunoglobulins [113]. Adenovirus infections are treated with cidofovir, vidarabin, and gancyclovir. Lymphocyte reconstitution plays a crucial role in the clearance of Adenovirus [114]. Treatment of Rhinovirus infections is done with pleconaril and 3C-protease inhibitors, but there is insufficient experience with them and this limits their application. Topical interferon might be efficacious in moderating viral shedding and symptoms [115, 116]. Prevention of Influenza depends on aider vaccination with Influenza vaccine [117] or antiviral therapy. Vaccination is not suitable for bone marrow transplant patients 6–12 months after the transplantation. Patients with severe Influenza should be treated with both M2 inhibitors (rimantadin and amantadin) and neuraminidase inhibitors (relenza and tamiflu [118].

8. Hepatitis B Virus (HBV)

Acute infection with HBV can result in fulminant hepatic failure, whereas chronic HBV infection can lead to end-stage liver disease, including cirrhosis and hepatocellular carcinoma. Understanding of the natural history and basic biology of HBV has increased greatly in recent years. HBV infection is by far the most common chronic viral infection affecting the liver [119]. Reactivation of HBV replication in patients undergoing immunosuppressive therapy is well recognized and is a frequently reported complication of considerable clinical importance [120, 121]. HBV reactivation following immunosuppression is defined by an abrupt rise in HBV replication followed by laboratory signs of hepatocellular injury in “silent” HBV-infected individuals (HBsAg carriers). Reactivation can also occur at a lower rate in patients with “occult” HBV infections. The clinical presentation of reactivation is variable, ranging from an asymptomatic course to severe hepatitis, liver failure, and death. It is most frequently observed in patients with lymphoma treated with rituximab and corticosteroids, as well as in patients undergoing stem cell and bone marrow transplantation. Others risk groups include patients with solid tumors, subjects infected with HIV, organ transplant recipients, and those with autoimmune diseases [122, 123]. It is believed that about 12% of patients with malignancy have chronic HBV infection. In transplanted patients, infection can also reactivate after immunosuppressive therapy. For these reasons, high-risk individuals should be identified and screened. Recommendation for screening for all three serologies, including HBcAb, HBsAg, and HBsAb in those planned for immunosuppression is available [124]. Despite advances in

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treatment of chronic HBV infection, liver transplantation remains the only hope for many HBV-related end-stage liver disease patients. The high rate of HBV reinfection or recurrence after liver transplantation is probably due to enhanced virus replication resulting from immunosuppression and other mechanisms. In the recent years, liver transplantation has shown encouraging results. The introduction of effective measures to prevent and treat reinfection or recurrence using strategies involving hepatitis B immune globulin (HBIG) and subsequently nucleos(t)ide analogues have significantly improved the outcome of liver transplantation [125, 126]. Overall HBsAg positive patients who are candidates for chemotherapy or treatment with biological agents, preemptive treatment with an antiviral agents such as lamivudine, and lately with the more potent tenofovir, entecavir, or adefovir, has become a standard of care, effectively preventing HBV reactivation. Patients with occult HBV should be monitored for alanine aminotransferase and HBV DNA (by real-time PCR) during the course of immunosuppression. Prompt administration of a potent antiviral agent upon diagnosis of reactivation may be lifesaving in such patients [122].

9. Hepatitis C Virus (HCV)

Infections with HCV can result in both acute and chronic hepatitis. Acute HCV typically leads to chronic infection in about 80% of cases. This condition leads to both extrahepatic and hepatic disorders, mainly chronic liver inflammation, cirrhosis and liver cancer [127, 128]. Chronic HCV infection is usually slowly progressive. Approximately 20% to 30% of chronic-infected individuals develop cirrhosis over a 20–30-year period of time. HCV-associated cirrhosis is the most common indication for orthotopic liver transplantation among adults. It is well documented, that recurrence of HCV and reinfection of the graft following liver transplantation more frequently occurs. The observations indicate that up to 40% of the patients experience recurrent hepatitis and cirrhosis 5 years later [129]. This progression depends on the age of the donor (below 40 years old), the gravity of the immunosuppression, viral status of the patient before transplantation and a month after it. Prevention and treatment of HCV reinfection and reactivation after liver transplantation remains an unsolved major clinical challenge. HCV-positive patients have poorer long-term outcomes after liver transplantation in comparison with patients with other underlying liver diseases. While treatment with pegilated interferon alpha and ribavirin can cure up to one-third of HCV-positive transplanted patients, there are many promising drugs in clinical and preclinical development targeting either the virion or essential host factors. New strategies to prevent HCV reinfection include neutralizing antibodies or drugs targeting cellular HCV entry factors. Unfortunately, it will take at least several years until most of these drugs will reach routine clinical practice.

The relationship between HCV infection and immunosuppression is complex. The complexity is further complicated by the intrinsic tendency of HCV infection in itself to lead to disorders of the immune system. After HCV discovery, it was shown that HCV is also a lymphotropic virus, and as a consequence of lymphatic infection, several lymphoproliferative disorders have been associated. Although HCV-related hepatocytolysis is classically interpreted as secondary to attack by cytotoxic T-lymphocytes against infected cells, the liver disease is usually exacerbated and more rapidly evolutive in immunosuppressed patients [130, 131]. Liver disease

secondary to chronic HCV infection is an important cause of morbidity and mortality in dialysis patients and kidney transplant recipients. Eradication of infection before transplantation seems to reduce the risk for HCV-associated renal dysfunction after transplantation, and may reduce risk of HCV disease progression. For dialysis patients, ribavirtin is generally contraindicated and alternatives are needed to enhance antiviral effects of interferon. New therapies with taribavirin may offer specific advantage in this patient group [132, 133]. In individuals with defects in cell-mediated immunity, predominantly CD4Th1, occurring in HIV infection and in patients requiring multi-drug immunosuppression following solid organ transplantation, chronic liver disease caused by HCV progresses more rapidly than in immunocompetent individuals. The rate of progress seems to correlate with the degree of immunosuppression. The prolonged suppressive therapy aggravates liver function [134]. Liver-related mortality is higher in those patients who are co-infected with HCV and HIV. All immunosuppressed and HIV infected patients should be screened for HCV infection using sensitive immunoassay licensed for detection of antibodies to HCV. For laboratory tests, ELISA is most widely used from the serological methods. HCV seropositive patients should be tested for HCV RNA using a sensitive quantitative assay to confirm the presence of active infection by RT PCR. Patients with positive HCV-RNA test should be genotyped and should be evaluated for HCV therapy [134, 135]. Liver disease in an immunosuppressed patient is typically severe with unusual progression to cirrhosis. However, accurate screening and specialized advice is recommended as soon as possible in HCV-positive patients.

For the last few years, there has been great progress in the production and application of drugs for prophylaxis and treatment of latent and chronic viral infections in immunosuppressed and transplanted patients. Various schemes for drug usage have been developed and have been permanently completed. Immunosuppressed patients very often are affected with nosocomial infections in hospitals, and with infections in the society. For this reason, accurate screening and prompt and precise diagnosis can be performed to prevent exacerbation of diseases and provide appropriate treatment.

Author details

Liliya Ivanova*, Denitza Tsaneva, Zhivka Stoykova and Tcvetelina Kostadinova

*Address all correspondence to: liivanova@abv.bg

Medical University "Prof. d-r Paraskev Stoyanov" – Varna, Department of Microbiology and Virology, St. Marina University Hospital – Varna, Bulgaria

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