Viral infections in the pediatric oncology patient.

Maria Moschovi, Maria Adamaki, and Ioannis Kopsidas
Haematology/Oncology Unit, 1st Department of Pediatrics, Aghia Sofia Children’s Hospital, Thivon & Levadeias Str., 11527 Goudi, Athens, Greece.

The incidence of children diagnosed with all forms of invasive cancer has significantly increased over the past 30 years. At the same time, high cure rates have also been achieved, with 5-year survival rates reaching 70-80% for most childhood malignancies. This improvement has been accomplished through significant advances in treatment, also resulting in the better management of infections during the immunosuppression period. Treatment failure is usually associated with a negative response to chemotherapy (no remission status or relapse) and immunocompromise. The latter is usually caused from the disease itself, especially in the case of lymphoid immune system malignancies, but chemotherapy and radiotherapy can also enhance immunocompromise in the pediatric oncology patient. The direct consequence of the above therapeutic modalities results in prolonged immunosuppression, which constitutes the particular patient group highly susceptible to emerging viral pathogens, sometimes with serious complications that could lead to infectious morbidity. The current chapter aims to present an updated review of the viral infections encountered in the field of pediatric oncology. First, we give a brief overview of the nature of immunosuppression in the particular type of pediatric host, the factors contributing to it, and the current principles in managing immunocompromise. Secondly, we review the types of viral infection, both from the international literature and from the experience of our Oncology Unit, which resides in a tertiary referral hospital serving 5 million people, and the available treatment strategies. Finally, we discuss possible ways for prevention of infection in childhood cancer patients, including medicinal prophylactic treatments, special dietary regimes, as well as active and passive immunisation strategies. At the same time we highlight the need for raising awareness in medical providers and patient relatives about the essential prophylactic measures involved in the evaluation and management of immunocompromised pediatric oncology patients. It is only through achieving a deeper understanding of the factors contributing to viral infections and of the procedures that we can follow to treat or prevent them that we can improve the quality of life of the children with cancer.

Keywords: immunosuppression, pediatric, oncology, infection, chemotherapy.

Introduction

The outcome of children with cancer has improved significantly over the last 30 years. This has been achieved through the combined use of chemotherapy, radiotherapy, surgery and bone marrow transplantation (BMT). However, viral infections are a common cause of severe complications in children with hematologic malignancies, solid tumors, or following allogeneic BMT. Childhood cancer patients are often neutropenic during treatment, and immunodeficiency is defined by both humoral and cellular immunity impairment, resulting in an increased risk for viral infections. The reasons are both the disease itself and the antineoplastic therapy that leads to neutropenia, lymphopenia and to damages of the natural anatomical barriers of the skin and mucosal membranes. Certain types of cancer, such as leukemias and lymphomas, are often directly involved in the malfunctioning of the immune system, predisposing to infection with particular pathogens (eg. herpes simplex virus, varicella-zoster virus). Additional deficiencies to host defense are conferred by therapeutic modalities, resulting in prolonged immunosuppression, which in turn constitutes the particular patient group highly susceptible to emerging viral pathogens, sometimes with serious, life-threatening complications.

Infection in the immunocompromised host

Childhood cancers and their respective therapeutic modalities compromise the immune system in a variety of ways. Both qualitative and quantitative changes have been recorded as defects of immune response. Examples of quantiative changes include: a reduction in lymphocyte numbers, delayed hypersensitivity, decreased mitogen responses, reduced immunoglobulin (Ig) synthesis, reduced monocyte oxidative responses, a decrease in cytokine responses, and increased monocyte suppressor activity; qualitative changes include deficiencies in chemotaxis and phagocytosis [1]. Antineoplastic treatment on the other hand may cause serious defects in humoral immunity, such as granulocytopenia (chemotherapy), lymphopenia (irradiation), damage of the skin and mucosal membranes (surgery) and suppressed anti-inflammatory responses (glucocorticoids and steroids). The severity of immunosuppression is usually directly correlated to the intensity and the type of treatment.

The first line of defence against external pathogens is the mucocutaneous barrier, a specialised network of cells of the skin and of the respiratory, gastrointestinal (GI) and genitourinary tracts. Infections can be transmitted through any bodily fluid but the blood is an excellent means for transporting microorganisms. Indwelling surgical devices placed during therapy (eg. central venus catheter, ventricular drain, chest tube, nasogastric tube and urinary catheter) and frequent blood draws not only compromise the epidermal barrier, but also provide additional opportunity for
introducing pathogens directly into the bloodstream. Although the most frequent complication of transfusion is regarded to be the transmission of microbial infections, viral pathogens can also be transferred in this way. Viral infections can be either primary or due to a reactivation of the virus that has remained dormant in the body of the patient. Unlike bacterial and fungal infections which usually follow long periods of neutropenia, the reactivation of a virus appears to be the result of increased immunosuppression.

The spleen is another organ that can contribute to immunosuppression. Since it is the principal organ involved in the production of antibodies and in the filtering of the blood from damaged cells and opsonin-coated organisms, it can logically be assumed that splenectomised patients have impaired antibody production and are at increased risk of infections. In addition, obstruction of hollow organs such as the biliary tree and organs of the gastrointestinal, genitourinary and respiratory tracts by growing tumor masses, make it easier for the pathogens colonizing the site of infections. In addition, obstruction of hollow organs such as the biliary tree and organs of the gastrointestinal, genitourinary and respiratory tracts by growing tumor masses, make it easier for the pathogens colonizing the site of infection. Similarly, an impaired function of the central nervous system, which may be caused by tumor obstruction or damage from radiation therapy, could lead to decreased levels of awareness and cognition and an increased risk of aspiration pneumonia [2].

Patients undergoing BMT seem to be the most susceptible group of immunocompromised host and are at an extremely high risk of developing infections with serious consequences for morbidity and mortality. The immunological status of the patient and the susceptibility to infection greatly varies with the stage of BMT, with different infections occurring at various phases following BMT. These greatly depend on: a) the underlying disease, b) the type of preceding chemotherapy, c) the history of infections for the particular patient, d) the immune status of both donor and recipient, e) the intensity of the preparatory treatment (such as myeloablative regimens and total body irradiation), f) the specific treatment of the transplant (such as the removal of T-cells), g) the development of immunological complications (such as graft versus host disease, GVHD), and h) the compatibility of the transplant.

Finally, the nutritional status of the children with cancer is believed to influence their prognostic outcome, and malnutrition is thought to make a compromising impact on immune function in a multitude of ways. Even though the nutritional aspects of pediatric oncology have not been extensively studied, some reports have documented a link between vitamin A deficiency and immunocompromise [3, 4]. Others have reported that children with low vitamin A levels are more susceptible to cancer treatment-related complications (such as infections) and have a higher prevalence of morbidity and mortality than children who were not vitamin A deficient during similar treatment [5].

In pediatric oncology, immunosuppression is usually deliberately induced in order to decrease the strength of the abnormally proliferating cells of the immune system (as in the case of leukemia), or to prevent the rejection of an organ transplant, or to treat GVHD after BMT. Since these therapeutic modalities seem to be very effective in the overall outcome of the children with cancer, if immunosuppression was to be reversed it could have a negative influence in disease progression and the overall survival. Therefore, the current principles in managing immunocompromise in pediatric oncology patients are limited to the effective monitoring of the immunological state of these children and to the control of severe complications by early diagnosis. The detection of certain antibodies in blood samples can greatly assist in the diagnosis of viral infections, but there may be no antibody response in immunocompromised children. The PCR techniques that detect the DNA or RNA of the viruses appear to have high sensitivity and specificity, and hence are currently widely used in the rapid and timely diagnosis of viral infections.

Overview of the viruses most commonly encountered in the field of pediatric oncology

CYTOMEGALOVIRUS

Human cytomegalovirus (CMV), or otherwise human herpes virus 5 (HHV-5), belongs to the taxonomic family of Herpesviridae (subfamily Betaherpesvirinae) and is regarded the most common cause of prenatal viral infection [6]. Children can be infected with CMV in utero, during birth, through breast feeding, through blood transfusions, and from close contact with other children, mainly through salivary glands. Seroprevalence seems to be age-specific, with around 60% of children aged 6 or older being CMV positive. While the infection is usually asymptomatic in healthy children, the virus can remain latent in the body for a long time and reactivate in periods of immunosuppression, thus establishing persistent infections. Symptomatic CMV reactivation is mostly known to cause enterocolitis or interstitial pneumonia in patients receiving BMT or organ transplantation, but it can also become life threatening to childhood patients outside the transplant setting, especially in the context of delayed diagnosis and treatment [7, 8]. Ganciclovir and valganciclovir are the first-choice antiviral therapies for the treatment of immunocompromised patients, while foscarnet and cidofovir are reserved mainly for treatment of ganciclovir-resistant cytomegalovirus infections [9].

EBSTEIN BARR VIRUS

The Epstein Barr Virus (EBV), or otherwise called Human Herpes Virus 4 (HHV-4), is essentially one of the most common viruses in humans, with around 90% of the world’s population being EBV positive [10]. Since its discovery in 1964 EBV has been linked to a variety of conditions, all associated with the latent cycle of the virus. Primary EBV
infection is mostly asymptomatic or causes a self-limiting disease called infectious mononucleosis (IM), usually characterized by fever, sore throat and fatigue. Infection usually occurs through close contacts between parents and children within the first 3 years of life, hence why IM is also referred to as kissing disease, but in developed countries it is estimated that up to 50% of the population encounter primary infection after the first decade of life [11, 12]. Infected B cells express many highly immunogenic viral antigens so most people that become infected with EBV develop adaptive immunity and clear the infection. In the case of immunosuppressed individuals, the risk clearly correlates with impaired specific immunity to the virus and EBV infection may cause overt disease that is potentially lethal. One such life-threatening complication is acquired hemophagocytic lymphohistiocytosis (HLH), a condition characterized by excessive activation of the immune system, via over-stimulation of macrophages and lymphocytes. Symptoms include hyperinflammation, fever, hepatosplenomegaly, hypertriglyceridemia, hypofibrinogenemia, and possible central nervous system involvement such as seizures and encephalopathy [13]. The increased inflammatory response does not result in increased immunity, but rather in an impairment of the cytolytic activity, leading to phagocytosis, cytopenia and eventually multiple organ failure [14]. Treatment strategies aim at suppressing the increased inflammatory response through chemotherapy/immunotherapy drugs such as etoposide, a macrophage cytotoxic drug, in conjunction with dexamethasone or prednisolone [15, 16]. The second life-threatening condition that can be caused by EBV is “EBV-induced lymphoproliferative disease” (LPD), which is mostly related to post-transplant lymphoproliferative disorder (PTLD) in organ and bone marrow recipients [17, 18]. LPD, as the name implies, is characterized by an uncontrolled proliferation of EBV-infected lymphocytes, resulting in gross infiltration of the lymphatic system, the gastrointestinal tract, the liver, and sometimes the central nervous system [19]. Symptoms include lymphadenopathy, interstitial pneumonia, ileus, hepatomegaly and/or hepatic failure, increased intracranial pressure and seizures. Recent data suggest that the risk of a transplant recipient developing EBV-LPD also largely depends on the pre-transplant EBV status of the patient [20], so effective monitoring using real-time quantitative EBV-PCR prior to transplantation is highly recommended [21]. Most patients respond well to a reduction or cessation of immunosuppression and additional therapies and monoclonal antibodies [22, 23].

VARICELLA ZOSTER VIRUS

The varicella-zoster virus (VZV) is a highly contagious virus, transmitted either via direct contact or through inhalation of respiratory secretions from an affected individual. Primary infection results in chickenpox, but VZV can remain dormant in the nervous system of affected individuals and reactivate later in life causing a disease known as shingles [24]. Immunocompromised patients are at an increased risk of developing serious complications, such as disseminated disease, pneumonia, and encephalitis. Others have reported an increased risk of secondary bacterial infection with invasive Streptococcus pyogenes [25]. VZV infection in immunosuppressed patients is usually asymptomatic, though some reports have documented a generalized maculopapulovesicular rash, skin lesions, severe abdominal or back pain and, in cases of progressive disease, extensive spleen involvement [26, 27]. Antiviral therapy is highly recommended in immunosuppressed patients within 1 week from the appearance of a rash or before the formation of full crusting of lesions [28]. Acyclovir administered intravenously is the first-choice treatment for VZV infection in childhood cancer patients, while foscarnet can also be administered in cases of acyclovir-resistant VZV [29, 30]. A live attenuated vaccine is also available under the name Varivax.

HUMAN HERPES VIRUS 6

Primary infection with the Human Herpes Virus 6 (HHV-6) usually occurs before the age of 2, with infection rates being highest in infants between 6 and 12 months old. HHV-6 has two variants: HHV-6A and HHV-6B. HHV-6A has not been associated with any type of human disease but HHV-6B has been identified as the causal agent for the childhood disease roseola infantum (or exanthema subitum). HHV-6 is transmitted through the saliva, with seroprevalence in the world population considered to be as high as 90%. Immunocompromised patients are at a relatively high-risk of HHV-6 infection, and it has been documented that latent HHV-6 may reactivate in up to 30% of immunosuppressed children [8, 31]. Symptoms include fever, malaise, rash, leukopenia, lymphadenopathy, convulsions, myocarditis, hepatitis, severe pneumonitis, encephalitis, and in BMT recipients delayed engraftment, graft failure, or GVHD [32-35]. Treating HHV-6 infection following BMT is often a difficult task, since reversing the immunosuppression could lead to the body rejecting the transplant. There are currently no available treatments specific to HHV-6 infection and classic anti-herpes drugs produce secondary effects that are often problematic for transplant patients [36]. However, it was recently reported that administration of cidofovir and foscarnet effectively clears HHV-6 infection in vitro, suggesting that a combination of these antivirals could hold promise for the treatment of pediatric cancer patients with HHV-6 infection [37].
HEPATITIS B AND HEPATITIS C

HBV and HCV infections are major causes of morbidity and mortality in oncologic pediatric patients [38]. HBV-DNA may persist in intra-hepatic or extra-hepatic sites and therefore reactivate when the patient is immunosuppressed. This makes a complete screening of HBV markers of the outmost importance in patients about to undergo hematopoietic stem cell transplantation (HSCT) [39]. The infection is a two step process. At first, when the patient is treated with cytotoxic or immunosuppressive agents, there is an abrupt rise of viral replication which is confirmed by higher HBV DNA and HBeAg serum titres. Then, when the treatment is stopped the immune-mediated destruction of hepatocytes occurs [40]. Nucleoside analogues and in particular Lamuvudine are used quite successfully to prevent the Hepatitis B reactivation and consequently decrease clinical hepatitis and mortality associated with hepatitis B viral injury [41, 42]. It is recommended not to wait for signs of hepatic injury such as increased ALTs to start treatment. On the contrary, it has been shown that it is better to start lamuvudine on hepatitis B surface antigen-positive lymphoma patients before the initiation of chemotherapy or at least concurrently [43]. Of importance is also the increase of awareness of the risks of hepatitis B reactivation amongst physicians. A recent study revealed that from a total of 134 physicians who specialize in treatment of oncology patients, only 27 % screened all patients before chemotherapy [44]. On the other hand, chronic HCV infection after chemotherapy for malignant diseases in childhood has a good prognosis with a 21-year follow-up rate of cirrhosis of only 5% [45]. Treatment consists of interferon with or without ribavirin and in most cases it is postponed until after the completion of chemotherapy [46]. However, there have been reports of successful concurrent treatment [47]. A small report on combined HBV-HCV infection of oncologic patients showed that combined treatment seems to be effective. However, there is a need of a research with larger groups to validate the effectiveness of combined treatment of co-infected patients [48].

NOROVIRUS

Norovirus (NV) is the prototype strain of a genetically diverse group of RNA viruses (taxonomic family *Caliciviridae*) and is responsible for approximately 90% of non-bacterial gastroenteritis worldwide [49, 50]. NV can be transmitted directly from person to person, or indirectly via contaminated food or water, or via aerosolization through subsequent contamination of surfaces [51]. The virus is highly infectious, with only a few particles being capable of conferring infection, whereas transmission from one person to another is still possible even when symptoms have subsided [52]. This property, along with the fact that NV is resilient to extreme environmental conditions (it may survive drying, freezing, heating to 60°C, and even chlorine-based disinfectants), make it a serious cause of severe epidemic gastroenteritis in closed communities such as schools, nursing homes, prisons, dormitories and hospitals. Diagnosis in pediatric oncology patients is however difficult, since the main symptoms of nausea and emesis can also be induced by chemotherapy. Other symptoms include: fever, sometimes presenting as febrile neutropenia, dehydration, anorexia, headache, abdominal cramps, and myalgia, mostly presenting as an adverse reaction to treatment with vincristine and corticosteroids [19]. More severe, life threatening complications, have recently been reported in the pediatric oncology population, such as chronic diarrhoea, gastrointestinal bleeding, and peritonitis, [53, 54]. Currently, there is no antiviral medication specific to NV, but the pharmaceutical company Ligocyte is testing an NV vaccine in human clinical trials.

ROTA VIRUS

Rotavirus (RV) is a double-stranded DNA virus (taxonomic family *Reoviridae*) and is considered one of the leading viral pathogens of pediatric nosocomial gastroenteritis [55]. The virus has 5 strains, referred to as A, B, C, D, and E, but it is RV-A that is responsible for over 90% of infections in humans [56]. RV rarely affects adults and it is estimated that every child has been infected with RV at least once by the age of 5. Immunity develops with each infection, so subsequent infections are usually less severe, unless reinfection by a different RV serotype takes place. The virus is primarily transmitted via the faecal-oral route, but transmission via food, water, fomites and flies is also possible [57]. Gastroenteritis caused by RV is characterized by vomiting, diarrhoea and low-grade fever; in immunocompromised children RV infection is a self-limiting disease with a duration of 3 to 6 days, but symptoms may become more severe in infants, with dehydration being the most common and, if left untreated, the most serious life-threatening complication. Many cases of RV infection in pediatric oncology units seem to be of nosocomial origin [58, 59] so RV is regarded as a preventable pathogen. The few trials that have examined the potential preventive role of oral probiotics in the spread of infection in hospitalized children have yielded conflicting results [60, 61], so the primary means of prevention remain the early diagnosis and the implementation of the necessary sanitization and contact precautions. With no antiviral treatment currently available, public health campaigns focus on providing dehydration therapy, and two generation RV vaccines have been undergoing clinical trials [62].

HUMAN BOCAVIRUS

The Human Bocavirus (HBoV) is a single-stranded DNA virus and a relatively newly discovered member of the taxonomic family *Paroviridae* [63]. While it has been linked to both gastroenteritis and lower respiratory tract
infections, HBoV is considered the fourth most common pathogen of respiratory disease, especially in young children, following Adenovirus, Respiratory Syncytial Virus (RSV), and Rhinovirus [64, 65]. Clinical symptoms resemble those of other viral acute infections (such as those inflicted by RSV and Human Metapneumovirus or hMPV) and include fever, coughing, and wheezing, with peribronchial infiltrates and bronchopneumonia being the most common clinical observations [66-68]. Diarrhoea and other gastrointestinal symptoms may also manifest independently of respiratory symptoms [69]. A few groups have reported EBoV infection in immunocompromised pediatric patients, including two organ-transplant and an allogeneic stem cell transplant recipient [66, 70, 71]. Overall, there are no clinical presentations specific to HBoV and diagnosis relies on specific PCR protocols [68, 72]. Further investigations are needed in order to determine the exact pathogenic nature of HBoV and possible routes for its prevention and treatment.

INFLUENZA VIRUS

Influenza viruses are RNA viruses that spread mostly by droplets of respiratory secretions or with direct contact of contaminated surfaces. Influenza virus infection can cause serious illness to immunocompromised patients. It poses one extra challenge as the differentiation with a bacterial infection is difficult since the main symptom is high fever in conjunction with other milder clinical signs. Older and newer studies, relate influenza infection with prolonged duration of symptoms, high rate of concurrent bacteremia and delays in chemotherapy [73, 74]. Regarding recent H1N1 outbreaks, different reports agree that it caused mild symptoms in children with cancer and/or hematological conditions and the main consequence was on the intensity of the anticancer treatment [75-77]. There is not enough data on the efficacy of the influenza vaccines. A recent study concluded that seroconversion rates for the pediatric oncology population are well below those for the general population. In addition, patients with ALL had better response when it was given early in the course of treatment. Due to the seasonal nature of the of the influenza vaccine this causes an additional problem to the possibility of arranging the timing of the vaccine to have the optimal result [78]. Overall, however, it is not yet clear whether the seroconversion that occurs in these patients is efficient to protect them from an influenza infection or its complications [79]. Treatment must be started within 48 hours of the onset of symptoms and consists of neuraminidase inhibitors, oseltamivir and zanamivir, which are effective for both influenza A and B [80]. Lately there have been reports of oseltamivir resistant strands and more rarely of strains resistant to zanamivir [77, 81, 82].

RESPIRATORY SYNCYTIAL VIRUS

The human Respiratory Syncytial Virus (RSV) is a single-stranded RNA virus of the taxonomic family Paramyxoviridae, subfamily Pneumoviridae, and is considered the leading cause of serious upper and lower respiratory tract infection in infants and children worldwide, with additional predisposition to asthma development later in life [83, 84]. The virus is transmitted via direct contact from person-to-person but can not remain viable on hands or surfaces for more than a few hours. Disinfection of hands, medical accessories (such as masks, gloves and gowns), and contaminated surfaces is usually sufficient to prevent its spreading. The symptoms are often very mild, resembling those of the common cold, with bronchiolitis and pneumonia being the most common RSV characteristic in young children. However, in immunocompromised children, and especially in transplant recipients, bronchiolitis may lead to acute respiratory failure and occasionally death, so PCR testing for RSV is highly recommended in this group of patients. Treatment of RSV infections is usually symptomatic and supportive care includes adequate fluid intake and oxygen supplementation until the illness runs its course. Salbutamol and epinephrine inhalations should only be used in immunocompromised patients with a profound clinical response, otherwise the corticosteroids will enhance the immunosuppression status and produce adverse effects [19]. Palivizumab, a monoclonal antibody specific for the RSV surface protein, is the only available prophylactic drug but its effectiveness has not been thoroughly investigated in pediatric oncology patients, while preliminary studies show conflicting results [85, 86]. Similarly, the use and efficacy of the licensed antiviral drug ribavirin in pediatric oncology patients is still under debate [85, 87]. Recently, the development of motavizumab, a second-generation monoclonal antibody that has evolved from palivizumab, has proved superior to palivizumab in phase III clinical trials in reducing the incidence of lower respiratory tract infections in high-risk infants [88, 89]. Until a specific and safe vaccine against RSV is produced, motavizumab is the only promising agent for the efficient prevention of RSV infection in pediatric oncology patients.

HUMAN METAPNEUMOVIRUS

Human metapneumovirus (hMPV) is a single-stranded RNA virus of the taxonomic family Paramyxoviridae (subfamily Pneumovirinae) and is regarded the second most common cause of respiratory tract infection in young children, following RSV. Whereas infection is usually milder compared to RSV, co-infection with both viruses is also possible, and is associated with a worse clinical presentation. It is estimated that all children have been exposed to the virus by the age of 5 and re-infections are very common throughout the life of an individual. Symptoms resemble those of other respiratory tract infections and include fever (usually presenting as febrile neutropenia), coughing, wheezing,
BKV VIRUS

The BK virus (BKV) is a member of the taxonomic family Polyomaviridae, known to affect the kidneys and the genitourinary tract. Even though the exact mode of transmission of BKV has not yet been established, the virus is believed to transfer from one person to the next by either respiratory fluids or urine [96, 97]. BKV infection is very common and widespread in childhood, with seropositivity reaching 90% in children between the age of 5 and 9 [98]. Primary BKV infections are either asymptomatic or produce very mild symptoms, such as respiratory infection or fever. However, the latent form of the virus is contained in up to 80% of the population [99], where it remains dormant until the body undergoes some form of immunosuppression. For this reason, in immunocompromised patients the clinical presentation is more severe and symptoms include renal dysfunction (accompanied by elevated levels of serum creatinine), ureteral stenosis, interstitial nephritis, hemorrhagic cystitis (HC) in BMT recipients, graft loss in renal transplant recipients, and BK-related nephropathy, a condition in which the immunosuppression allows the virus to replicate within the graft [100]. Most studies regarding BKV infections in immunocompromised patients have been conducted in adults but not in children with cancer, so there is limited information in this field. A recent study presented three cases of pediatric oncology patients who developed HC after having been treated with high dose cyclophosphamide, where the HC caused delays in the chemotherapy and prolonged supportive care [101]. The main treatment against BKV infection is a reduction in immunosuppression but this could cause transplant failure in BMT recipients. Other therapeutic options tested on adult patients include Leflunomide (combined immunosuppressive and antiviral properties), Cidofovir (albeit associated with dose-related nephrotoxicity in some patients), intravenous immunoglobulin (IVIG) (efficacy of treatment not yet established) and quinolone antibiotics such as Ciprofloxacin, which are known to reduce the viral load in non-graft-recipients [102, 103].

General guidelines for the prevention of infectious complications in pediatric oncology patients

Viral infections can cause the most serious complications in pediatric oncology, since not only may they limit the effects of antineoplastic therapy, but they are also associated with significant morbidity and mortality in the particular patient group. The pediatric oncologist should be aware of the potential pathogens, the clinical symptoms, as well as the means for their prevention and treatment. The availability of sensitive quantitative RT-PCR-based diagnostic methods that allow the rapid detection of most viruses can lead to an early diagnosis. Similarly, seroprevalence tests should be performed before the induction of therapy for the timely detection of viruses in the latent phase. Sites of indwelling surgical devices, as well as biopsy and resection sites, should be regularly examined for signs of infection. The ultimate goal is the prompt diagnosis of infection and the precise identification of the pathogenic organism in order to allow for a timely initiation of the appropriate treatment with the least side effects.

Nosocomial infections remain the main cause of infectious morbidity, with pathogens primarily transmitted from patient to patient either via the hands of hospital workers or via contaminated surfaces in communal areas. Therefore, the most important anti-infective measure identified so far is hand hygiene, including the use of alcohol-based hand sanitizers, followed by effective sterilization of medical equipment and sanitization of communal hospital areas, such as bathrooms, kitchens and playgrounds. Special attention should also be given to the personal oral hygiene of patients, visitors, and health professionals. Educational campaigns of health care workers, patients, relatives and visitors using educational material such as videos and information booklets should build the basis for the prevention of hospital infections.

Another means that can aid significantly in the prevention of infection is a dietary regime that consists mainly of cooked food; raw fruit and vegetables could carry dangerous pathogens regardless of washing, especially if imported from foreign tropical countries.

In the case of severely immunocompromised patients such as BMT recipients, patient isolation in a total protective environment (TPE) could also prove an effective means of protection. Reverse isolation in a high-efficiency air-filtered room, accompanied by surface decontamination and sterilization of all objects in the room, has been shown to reduce infection rates and improve survival for patients with profound neutropenia [104].

The use of certain antivirals as prophylactic treatment could prove useful in the prevention of infectious complications, provided that these are carefully considered after close consultation between an oncologist and an infectious disease specialist.

Finally, immunization by vaccination is regarded as the most effective means in preventing infectious complications in children receiving treatment for cancer. The obvious advantage is in preventing primary infection in infancy and
early childhood so as to diminish the possibility of viral re-activation later in life. However, one has to take into account that certain children with cancer are too young to have completed their primary immunizations. Even though there are some general guidelines in suspending vaccinations during induction and consolidation chemotherapy, there has been an ongoing debate on whether these should be performed during maintenance therapy or after the elective end of neotoplastic treatment [105-108]. Inactivated vaccines pose no risk to immunocompromised children, but they have limited or no efficacy in eliciting an immune response during therapy due to inadequate antibody responses. On the other hand, live virus immunizations can cause fatal complications in children with impaired immune function and so are administered 3 to 6 months after the cessation of cancer therapy, when the immune system has fully reconstituted itself. Nonetheless, taking into account the high morbidity rate and the serious complications of VZV infection in pediatric oncology patients, varicella vaccination of children in continuous complete remission for 1 year while still receiving chemotherapy (where the risk of VZV infection is high) is still considered a reasonable option, despite controversial issues surrounding the risks and benefits [109, 110]. For the same reasons, hepatitis vaccination is also approved in children with cancer receiving chemotherapy, whereas the combined hepatitis A/B vaccine seems to be much more effective than the monovalent vaccine in cancer patients, characterized by high seroconversion of hepatitis A [111-113]. Similarly, given the high risk of interruption and delaying of chemotherapy, as well as the high risk of serious morbidity and mortality caused by influenza infection in pediatric oncology patients, annual influenza vaccination is currently recommended for all children receiving chemotherapy, including those still within 6 months from completion of therapy, despite the limited immunity response compared to healthy children [114-118]. Antiviral prophylaxis instead of vaccination should be considered for those patients receiving intense chemotherapy or those undergoing BMT, as the vaccine is unlikely to be immunogenic due to the extent of immunosuppression in these patients. Family members and health care providers should also be vaccinated, and annual updating of the vaccine should ensure that the antigens included match those of the circulating strains.

Recent advances in T-cell based immunotherapy have shown enough promise in preventing infectious complications in pediatric oncology patients. Adoptive T-cell transfer has proved particularly effective in the prevention and treatment of viral infections following allogeneic transplantation and in EBV-induced PTLD, whereas immunogenic epitopes have also been identified for other viral pathogens such as CMV, HBV, and HPV [119-122].

**Bibliography**


