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DRAFT GUIDANCE FOR INDUSTRY: DESIGN AND ANALYSIS OF SHEDDING STUDIES FOR VIRUS OR BACTERIA-BASED GENE THERAPY AND ONCOLYTIC PRODUCTS

REFERENCE 2

Viral infections in paediatric patients receiving conventional cancer chemotherapy

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ABSTRACT

In severely immunocompromised patients, the diagnosis of viral infections relies on PCR/RT-PCR based methods. The availability of these modern diagnostic tools facilitates timely diagnosis and contributes to our increasing knowledge of the epidemiology and clinical spectrum of common and emerging viral pathogens in this highly susceptible population. Viral infections may result in life threatening disease in paediatric cancer patients after stem cell transplantation and also during conventional chemotherapy. Often, clinical symptoms are a consequence of endogenous reactivation of latent viral infection. Many of these viruses are easily transmitted between patients, relatives and health care workers. As prolonged symptomatic and asymptomatic viral shedding is a common feature in paediatric cancer patients, it is necessary to implement strategies for the prevention and control of these communicable pathogens in the hospital setting and in the outpatient clinic. Although no randomised controlled studies on paediatric cancer patients are available, physicians should be aware of potential treatment options since early treatment may prevent a complicated or fatal outcome and shorten the period of contagiosity.

Depending on the severity of immunosuppression resulting from underlying disease or intensive chemotherapy, paediatric cancer patients are incapable of mounting adequate cellular and humoral immune responses to viral infection.[1] This results in an increased risk of a complicated clinical course in common viral infections. In addition, atypical manifestations of viral infections may delay recognition of the viral aetiology of clinical symptoms and result in inadequate treatment due to delayed diagnosis. In a recent study performed in four Finnish university hospitals, Koskenvuo *et al*[2] investigated the concomitant presence of 16 viral pathogens in paediatric leukaemia patients with blood stream infection (BSI). Prospective evaluation of 156 febrile episodes in 51 children yielded 19 BSI (11%). In 11 (58%) of these infections, evidence was found for probable concomitant viral infection (five rhinovirus, four respiratory syncytial virus (RSV), two calicivirus, one enterovirus and one human herpesvirus type 6 infection; RSV, enterovirus and rhinovirus were detected in one patient). In a previous study from Turku, Finland, microbiologically confirmed respiratory virus infections were found in 28 of 75 (37%) consecutive febrile episodes in 32 children during anticancer treatment.[3] In this clinical setting, viral infection may per se cause severe clinical symptoms or may pave the way for bacterial infections such as pneumonia or BSI.[4 5] From these studies it can be concluded that there is a diagnostic gap concerning viral aetiologies in paediatric cancer patients with "fever of unknown origin" due to insufficient efforts to diagnose these events in clinical practice.

Many aspects of current approaches for the diagnosis and treatment of viral infections in severely immunocompromised children are based on studies of patients who have received allogeneic stem cell transplants.[6–8] In contrast, this review summarises selected aspects of the management of viral infections in children undergoing conventional chemotherapy. The viral pathogens discussed in this article are listed in table 1.

DIAGNOSTIC APPROACH IN IMMUNOCOMPROMISED CHILDREN

The most useful methods for the diagnosis of viral infections in paediatric cancer patients are listed in table 1. The diagnostic materials commonly used for the diagnosis of viral infections are nasopharyngeal aspirates (NPA), blood, serum, stool, urine and cerebrospinal fluid (CSF). Rarely, a biopsy of infected tissue is required to confirm or exclude a viral aetiology.

NPA specimens should be sampled and tested for respiratory viruses in hospitalised immunocompromised children with respiratory tract infection (RTI).[9] According to a recent comparative study, throat swab and saliva specimens are inferior to NPA for the detection of respiratory viruses in children.[10]

Some viruses can be easily detected in urine samples (measles virus, cytomegalovirus, adenovirus, BK virus), and for some (cytomegalovirus, adenovirus, BK virus) prolonged local shedding has been observed in the absence of systemic infection.

Due to an impaired humoral immune response, paediatric cancer patients often do not mount a specific antibody response to infection. Thus, the direct detection of the virus or its antigens by culture, antigen testing, immune fluorescence or PCR based methods is often the only reliable diagnostic approach.

Today, modern PCR/RT-PCR based diagnostic methods enable us to reach a better understanding of the epidemiology and clinical relevance of "old"[11] and recently discovered "emerging" viral pathogens[9 12 13] in severely immunocompromised children. Real-time quantitative PCR/RT-PCR assays permit the rapid confirmation of a viral infection. In those viral infections for which specific treatment options exist, quantitative PCR assays provide reliable diagnostic tools for early initiation of preemptive or definite therapy and for rapid assessment of the efficacy of antiviral treatment strategies.[14–17]

Table 1 Diagnostic tools and clinical manifestation of viral infections

Virus (family), DNA or RNA virus	Diagnostic tools	Clinical manifestation
Adenovirus (*Adenoviridae*), DNA virus	AT, CC, PCR, qPCR	Pneumonia, hepatitis, gastroenteritis, haemorrhagic cystitis
BK virus (*Papovaviridae*), DNA virus	PCR, qPCR	Haemorrhagic cystitis
Cytomegalovirus (*Herpesviridae*), DNA virus	CC, SVT, pp65 AT, PCR, qPCR, serology (IgG, IgM), TB (lung, oesophagus, colon)	Interstitial pneumonia, hepatitis, oesophagitis, enterocolitis retinitis
Enterovirus (*Enteroviridae*), RNA virus	RT-PCR, qPCR, CC	Gastroenteritis, RTIs, gastroenteritis
Epstein Barr virus (*Herpesviridae*), DNA virus	Serology (IgG, IgM), PCR, TB (lymphatic tissue)	Mononucleosis, hepatitis, secondary haemaphagocytosis
Hepatitis B virus (*Hepadnaviridae*), DNA virus	AT (HBsAg, HBeAg, HBcAg), serology (IgG, IgM), PCR, qPCR, genotyping	Hepatitis, haemolytic anaemia, Gianotti Crosti syndrome
Hepatitis C virus (*Flaviviridae*), RNA virus	Serology (IgG, IgM), RT-PCR, qRT-PCR, genotyping	Hepatitis, liver failure, cold-agglutinin mediated haemolytic anaemia
Herpes simplex virus (*Herpesviridae*), DNA virus	PCR, CC, serology (IgG, IgM)	Vesicular skin lesions, stomatitis, aggravation of chemotherapy induced mucositis, hepatitis, meningoencephalitis
Human bocavirus (*Parvoviridae*), DNA virus	PCR, NASBA	Lower RTI? Disseminated viral infection?
Human herpesvirus type 6 (*Herpesviridae*), DNA virus	PCR, serology (IgG, IgM)	Interstitial pneumonia hepatitis, encephalitis, bone marrow failure
Human metapneumovirus (*Paramyxoviridae*), RNA virus	RT-PCR, CC, AT, SVT, IF	Bronchitis, pneumonia
Influenza virus (*Orthomyxoviridae*), RNA virus	RT-PCR, CC, AT, SVT, IF	Croup syndrome, bronchitis, pneumonia
JK virus (*Papovaviridae*), DNA virus	PCR	Progressive multifocal leukencephalopathy
Measles virus (*Paramyxoviridae*), RNA virus	RT-PCR, CC, SVT	Measles, tracheitis, giant cell pneumonia
	Serology (IgG, IgM)	Measles associated encephalopathy
Norovirus (*Caliciviridae*), RNA virus	RT-PCR*	Gastroenteritis, aggravation of chemotherapy induced mucositis
Parainfluenza virus (*Paramyxoviridae*), RNA virus	AT, IF, SVT, RT-PCR	Croup syndrome, bronchitis, pneumonia
Parvovirus B19 (*Parvoviridae*), DNA virus	PCR, qPCR, (TB; bone marrow)	Erythaema infectiosum, transient aplastic crisis (prolonged anaemia after chemotherapy), thrombocytopaenia, neutropaenia, haemolytic anaemia, arthritis, "gloves and socks" syndrome†
Respiratory syncytial virus (*Paramycoviridae*), RNA virus	AT, IF, CC, SVT, RT-PCR	Croup syndrome, bronchitis, pneumonia
Rotavirus (*Reoviridae*), RNA virus	AT (RT-PCR)	Gastroenteritis, aggravation of chemotherapy induced mucositis
Varicella zoster virus (*Herpesviridae*), DNA virus	PCR, serology (IgG, IgM), (TB)	Chickenpox, disseminated varicella with multiorgan involvement, pneumonitis, hepatitis, encephalitis, cerebellitis, shingles (zoster)

*Commercially available antigen tests for norovirus yield too many false positive results; †for details refer to the text.
AT, antigen testing; CC, cell culture; IF, immune fluorescence; NASBA, nucleic acid sequence-based amplification; PCR, polymerase chain reaction; qPCR, quantitative polymerase chain reaction (defining viral loads); qRT-PCR, quantitative RT-PCR (defining viral loads); RT-PCR, reverse transcriptase-PCR (for RNA viruses); SVT, shell vial technique (viral antigens are detected in the supernatant of cell culture); TB, tissue biopsy with immunologic staining.

MODES OF TRANSMISSION AND PREVENTION OF PATIENT-TO-PATIENT TRANSMISSION

Barrier precautions to prevent patient-to-patient and patient-to-health care worker transmission must be strictly implemented in paediatric haematology and oncology units and in the associated outpatient departments (table 2). Hand hygiene with a hospital grade disinfectant is the most important measure[18] and has to be supplemented with contact, droplet or airborne precautions, depending on the mode of transmission of the suspected or confirmed pathogen.[19 20] Some of these pathogens require the use of specific disinfectants (eg, norovirus)[21] or are not destroyed by common disinfectants (human parvovirus B19).[22]

PROLONGED VIRAL SHEDDING

Prolonged symptomatic[23 24] and asymptomatic[21 25 26] shedding of contagious virus particles is often observed in immunocompromised children. This phenomenon may for last weeks or month and contributes significantly to the risk of nosocomial transmission. Paediatric patients, who continue to shed contagious viruses in respiratory secretions, urine or stool after the cessation of clinical symptoms, have to be separated from other immunocompromised patients by contact or droplet isolation as long as the viral shedding persists (table 2). Thus, in the planning of inpatient care facilities for paediatric oncology patients at least 30% of all rooms for patient care have to be allocated for the isolation of patients infected or colonised with communicable pathogens.[27]

IMMUNISATION OF HEALTH CARE WORKERS, ATTENDING PHYSICIANS AND RELATIVES

Medical personnel (health care workers, physicians, physiotherapists) involved in the clinical care of immunocompromised patients should be immune or immunised against measles[28 29] and varicella[30 31] and should participate in the yearly influenza immunisation campaign.[32–35] This should also be the case for all members of the patient's family to improve herd immunity. In addition, all female health care workers of child bearing age should be informed about their immunity against cytomegalovirus and human parvovirus B19[36] in addition to the routinely tested immunity against rubella virus.

Since vaccine associated rashes after measles and varicella immunisation in healthy family members of immunocompromised children are uncommon and mild, it is likely that the transmission of vaccine virus will also be uncommon.[37] The theoretical possibility of transmission of attenuated vaccine-virus isolates in household contacts is not a contraindication for the immunisation of non-immune healthy household members against measles and varicella. If a vaccine associated rash occurs in a family member, preventive administration of standard immunoglobulin (measles) or acyclovir (varicella) to the patient should be considered during intensive treatment periods.

HERPES SIMPLEX VIRUS

In severely immunocompromised children, any clinical manifestation of herpes simplex virus (HSV) primary infection or reactivation (table 1) should be treated in a timely fashion with acyclovir. Luck *et al*[38] recently presented a concise review of

Table 2 Mode of transmission, prevention (in addition to standard hygiene precautions and isolation) and immunisation options

Virus	Mode of transmission	Prevention[18–20 165]	Immunisation
Measles VZV (chickenpox) (influenza)† (norovirus)‡	Airborne	FFP 3 mask* FFP 3 mask* FFP 3 mask* FFP 3 mask plus contact precautions	Health care workers should be - immune or immunised against measles, VZV - immunised against influenza (yearly) Passive immunisation (patients after contact): - measles: standard immunoglobulin - VZV: VZV hyperimmunoglobulin§
RSV Human metapneumovirus Parainfluenza virus Enterovirus RTI ADV RTI Human parvovirus B19¶ Human bocavirus (?)¶	Droplets	Droplet precautions: surgical masks, gowns, gloves Eye protection in outbreak situations (RSV)	Palivizumab is available but not licensed for prevention of RSV infection in immunocompromised children (no controlled data are available)
VZV (zoster, shingles) Enterovirus GIT	Faecal-oral	Contact precautions	
Hepatitis A, B, C virus Rotavirus, norovirus**	Urinary shedding	Contact precautions	Health care workers should be immunised against hepatitis A and B
ADV GIT ADV/BK virus cystitis Cytomegalovirus Human bocavirus (?)¶	Saliva shedding	Contact precautions	

*Plus droplet precautions; †Still a matter of debate; please refer to Brankston *et al*,[166] Bridges *et al*[167] and Tellier *et al*[168]; ‡still a matter of debate; please refer to Marks *et al*[169]; §some institutions prefer the prophylactic administration of acyclovir (see text); ¶hospital grade hand disinfection or hand washing does not affect the contagiosity of this virus[22]; **use specific hand disinfectant with high ethanol content.[21]
ADV, adenovirus; GIT, gastro-intestinal infection; RSV, respiratory syncytial virus; RTI, respiratory tract infection; VZV, varicella zoster virus.

advances in the antiviral therapy of herpes virus infection in children, which is therefore suggested for further reading. Ramphal *et al*[39] investigated oral swabs and blood specimens for HSV in paediatric cancer patients with treatment related neutropaenia and fever. Oral HSV was not associated with prolonged fever or neutropaenia but was associated with a longer median duration of mucositis (8 days; interquartile range, 0–12 days) compared with HSV-negative episodes (0 days; interquartile range, 0–2.5 days; $p = 0.005$). In addition, the detection of oral HSV diminished the probability of a favourable response to empiric antimicrobial therapy (one of seven patients, 14%) compared with negative episodes (51 of 67 patients, 76%; $p = 0.002$).

CYTOMEGALOVIRUS

In most cases, cytomegalovirus (CMV) infections in patients receiving intensive anticancer chemotherapy are endogenous reactivations. Infections due to blood transfusions or other blood products are of minor significance because the depletion of leukocytes with specific filters and routine donor screening ensure CMV-negative blood products. Enterocolitis or interstitial pneumonia caused by symptomatic CMV reactivation is rare in patients outside the stem cell transplant setting[40] but may have life threatening consequences in case of delayed diagnosis and treatment (table 3).[41] CMV can often be detected in the urine of patients with endogenous reactivation and may be transmitted from patient to patient if standard hygiene precautions have not been thoroughly followed (table 2). Gancyclovir is still the treatment of first choice in immunocompromised children with CMV infection (table 2).[38 42]

EPSTEIN BARR VIRUS

Epstein Barr virus (EBV) may cause acquired haemophagocytic lymphohistiocytosis, a life threatening condition characterised by uncontrolled hyperinflammation with prolonged fever refractory to antibiotic treatment, hepatosplenomegaly, cytopaenias, and elevated serum concentrations of triglycerides, ferritin and soluble interleukin-2 receptor. Treatment relies on the suppression of the increased inflammatory response by immunosuppressive/immunomodulatory agents and cytotoxic drugs. The second potentially life threatening disease related to EBV is described as ''EBV induced lymphoproliferative disease'' (LPD) or ''post-transplant lymphoproliferative disease'' (PTLD).[43 44] In this condition, only rarely detected outside the stem cell transplant setting,[45 46] the uncontrolled proliferation of EBV infected B lymphocytes results in gross infiltration of the lymphatic system (lymphadenopathy, interstitial pneumonia), the gastro-intestinal tract (ileus, intussusception), the liver (hepatomegaly, hepatic failure), and sometimes the central nervous system (seizures, increased intracranial pressure, focal infiltrates). The diagnosis of LPD relies on immunohistochemical staining in biopsies or flow cytometric analysis of B lymphocytes in body fluids (ascites, pleura fluid). The reduction or cessation of immunosuppressive therapy and treatment with rituximab accompanied by repetitive measurement of viral loads (quantitative EBV-PCR) has been suggested for the treatment of LPD, but controlled trials are lacking.

VARICELLA ZOSTER VIRUS

Diagnosing disseminated varicella zoster virus (VZV) infection with visceral involvement is often difficult in immunocompromised patients due to atypical clinical presentation with few or

Table 3 Antiviral treatment options[6 38]

Antiviral drug	Indication	Comments
Acyclovir (iv, oral) Valacyclovir (oral)	HSV, VZV	Avoid peripheral intravenous administration and paravasation. Monitor serum creatinine
Cidofovir (iv)	ADV (BK virus haemorrhagic cystitis)?	Coadministered with probenecid. Monitor serum creatinine
Foscarnet (iv)	Second line CMV, HSV, VZV (HHV-6)*	Evidence from case reports
Gancyclovir (iv, oral) Valgancyclovir (oral)	CMV (HHV-6)*	May cause neutropaenia (consider G-CSF). Neurotoxicity in patients with renal impairment
Lamivudin (oral)	HBV	Prevention of acute liver failure in patients with active HBV replication
Oseltamivir (oral)	Influenza	Administer as early as possible ($\leqslant$48 h) after diagnosis. Not licensed for infants
Palivizumab	RSV (?)	No randomised study, small case series with conflicting results
Pleconaril	Enterovirus meningoencephalitis	Evidence from case reports
Ribavirin (inhalative, iv, oral)	RSV, HCV	Therapeutic benefit in RSV infection unclear outside allogeneic stem cell transplantation. Combined with interferon in HCV treatment
Rituximab	EBV (?)	Data from EBV associated lymphoproliferative disease after transplantation
Standard immunoglobulin	B19	Concise evidence from case series
Vidarabine (iv)	ADV haemorrhagic cystitis (?)	Evidence from case reports
Zanamivir (inhalative)†	Influenza	Administer as early as possible ($\leqslant$48 h) after diagnosis

*For HHV-6: in vitro sensitive; no clinical studies or concise case reports available.
†Feasible in children of school age and adolescents. Oseltamivir is easier to administer.
ADV, adenovirus; B19, human parvovirus B19; EBV, Epstein Barr virus; CMV, cytomegalovirus; HBV, hepatitis B virus; HHV-6, human herpesvirus type 6; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

no skin lesions and severe abdominal or back pain.[47] Prompt initiation of empirical treatment with acyclovir pending the results of PCR for VZV from skin lesions or serum samples is warranted in this clinical setting.[48] The role of varicella zoster immunoglobulin (VZIG) in prophylaxis and treatment is still debated as regards severely immunocompromised children and adolescents.[47] In our unit, children with cancer receiving conventional chemotherapy receive prophylactic acyclovir from day 7 after exposure for 7 days (1200 mg/m^2/day po)[49] Close clinical follow-up investigations are mandatory in these patients. If a breakthrough VZV infection occurs, the child is immediately hospitalised and treated with acyclovir intravenously. Although we have successfully followed this approach for more than 10 years, no randomised controlled study has yet been published confirming the efficacy and safety of this regimen in paediatric cancer patients. The most controversial issue of debate in such a study will be the definition of a relevant exposure event in severely immunocompromised children.[47]

A retrospective case series from the Children's Hospital of Pittsburgh[50] revealed that 49% of 41 children with VZV infection during treatment for acute lymphoblastic leukaemia (ALL) had received prophylaxis with VZIG. Disease was limited to the skin in 29 of the 42 cases (70%). Thirteen cases (30%) had extracutaneous involvement, and five of these episodes (12% of all cases) ended in death. Risk factors for progressive varicella included age greater than 6 years and intensive immunosuppressive therapy at the time of exposure. Six of eight patients with progressive varicella, including two who died, had received VZIG. The clinical presentation in 10 of 13 patients with progressive disease and in four of five patients who died was dominated by severe abdominal and/or back pain. In seven cases, these symptoms preceded the development of skin lesions by several days, and in six patients were associated with extensive involvement of the spleen by varicella, as demonstrated by the presence of Howell-Jolly bodies on peripheral blood smear. No patient with uncomplicated VZV infection was reported to have had premonitory pain.

Hill *et al*[51] examined the relationship between steroid therapy for ALL and the severity of VZV infection in 697 children with ALL. Of these, 110 (15.8%) developed primary VZV infection. Of the patients whose VZV infection was diagnosed within 3 weeks of receipt of prednisone, 70% had severe infection, whereas only 44% of those who had not received prednisone within 3 weeks had severe infection (odds ratio 2.9; 95% CI 1.1 to 7.9). By multivariate analysis, older age at ALL diagnosis, years from ALL diagnosis to VZV diagnosis, and VZV diagnosis during or within 3 weeks of prednisone therapy were all independently associated with an increased risk for severe infection. Mantadakis *et al*[48] recently described a 4-year-old girl with ALL in remission who developed VZV related hepatic failure.

The key clinical objective in immunocompromised patients with herpes zoster is to reduce the incidence of cutaneous and visceral dissemination as it can lead to life threatening complications.[38] Prompt antiviral therapy should be instituted in all immunosuppressed patients with zoster any time before full crusting of lesions.[52] Although most adult cancer patients with localised disease can be treated with oral acyclovir or valacyclovir, initial intravenous acyclovir is preferred in children, particularly in those with high fever, severe immunosuppression, shingles involving more than two dermatomes, ophthalmic involvement, and an inability to take oral medications. Foscarnet is the drug of choice to treat acyclovir resistant herpes zoster.[38 53 54]

Paediatric cancer patients with varicella or zoster may face an increased risk of secondary bacterial infection, for example with invasive isolates of *Streptococcus pyogenes*.[55] The prophylactic use of penicillin has not been investigated in this setting. Early antibacterial treatment after local swabs and blood cultures is mandatory in patients with suspected secondary bacterial infection to prevent septic shock and tissue necrosis.

In any patient with acute loss of vision, it should be borne in mind that reactivation of a retinal herpes virus infection (VZV, HSV and EBV) may lead to acute retinal necrosis in severely immunocompromised patients.[56]

HUMAN HERPESVIRUS TYPE 6

Nearly every child has experienced a primary human herpesvirus type 6 (HHV-6) infection (exanthema subitum) by the age of 3. After the primary infection, latent HHV-6 remains detectable in T lymphocytes (latent infection) and may reactivate in up to

30% of severely immunocompromised children and adolescents.[41 57] In young lymphopaenic children with persisting fever despite antibiotic treatment and recovery of neutrophils, HHV-6 infection should be excluded. No controlled clinical trials or concise case series discussing the antiviral treatment of HHV-6 infection have yet been published.[58] In vitro HHV-6 has been shown to be susceptible to gancyclovir and foscarnet.[59] Thus, compassionate use of these agents may be considered in paediatric cancer patients with HHV-6 related encephalitis or hepatic failure.

RHINOVIRUS AND ENTEROVIRUS

Enteroviruses (EV) are small RNA viruses and include coxsackie viruses A and B, echoviruses, enteroviruses 68–71 and polioviruses. *Enteroviridae* replicate in the gastro-intestinal tract, so their transmission occurs predominantly by the fecal-oral route. EV infection may be accompanied or followed by meningitis, which follows a benign clinical course in most cases, or encephalitis,[60] which has a clinical spectrum ranging from altered mental status to coma and may be associated with long term neurological sequelae.

On the one hand, the clinical significance of a positive rhinovirus or EV PCR from respiratory specimens is uncertain, because after the onset of symptomatic respiratory infection EV RNA may take 2–3 weeks and rhinovirus RNA 5–6 weeks to disappear from nasal mucus.[61] On the other hand, chronic persistence of replicating rhinovirus in the lung with fatal outcome has been reported in lung transplant recipients[62] and severe lower RTIs have been attributed to rhinovirus infections in some prospective case series.[2 3 63] One study from Greece investigated the clinical presentation, severity and outcome of EV infections in paediatric cancer patients.[64] Samples of whole blood, throat swab, CSF, bone marrow and urine underwent EV genome amplification by RT-PCR and nucleotide sequencing. EV infection was confirmed in 55 of 104 evaluated patients. Encephalitis was diagnosed in 10%, myocardial involvement in 5% and haemophagocytosis in 5%. Most children with EV infection had ALL or lymphoma. The fatality rate was 14.5% (n = 8).

Although controlled studies are missing, experience in patients with congenital agammaglobulinaemia and case reports suggest that high dose (2 g/kg) intravenous immunoglobulin (IVIG) treatment may be beneficial in immunocompromised patients with EV infection.[64] Pleconaril, which inhibits the replication of pircornaviruses, has recently become available for clinical use.[65] Pleconaril should be administered in an early stage in severe EV infection to prevent multiorgan failure. Prospective studies in children with cancer are still not available.[66 67]

HEPATITIS B AND HEPATITIS C

Chronic hepatitis B virus (HBV) infection poses a great risk to children who acquire HBV infection while they are on immunosuppressive therapy or are immunocompromised due to underlying disease,[68] since efficient and multi-specific helper and cytotoxic T cell response is essential for the control of HBV. Paediatric cancer patients may face an increased risk of nosocomial HBV infection according to a number of recent reports on outbreaks in paediatric cancer units.[68–71] A nosocomial HBV outbreak affecting 16 paediatric patients was related to fingerstick monitoring procedures.[72] Contamination probably occurred when health care workers failed to disinfect their hands and change gloves between patients. Reactivation of chronic HBV infection may occur during or after chemotherapy in paediatric cancer patients and may result in increased liver injury and fibrosis or even in fulminant hepatic failure in some patients.[73–75] High dose steroids are suspected to activate or promote HBV replication.[76] HBV reactivation should be excluded in patients with recurrent flares of transaminases (AST>10 times the upper limit of normal) and bilirubin elevation during bone marrow recovery after chemotherapy.[77 78] Adjuvant lamivudine treatment (better early than deferred) should be considered before or at the initiation of chemotherapy for all hepatitis B surface antigen-positive/PCR-positive patients undergoing intensive chemotherapy.[79 80] The role of liver biopsy in grading histological changes attributable to chronic HBV infection is not well defined in paediatric cancer patients.[81]

The prognosis is excellent for patients with chronic hepatitis C virus (HCV) infection after chemotherapy for malignant diseases in childhood, with mild, and in most cases asymptomatic, liver disease and a 18-year follow-up rate of cirrhosis of 5%.[82 83] Monitoring of ALT is crucial when prolonged immunosuppressive therapy is decreased or stopped. Fatal necrotising liver disease in patients with acute HCV reactivation is not always accompanied by high HCV RNA titres.[84]

Rieske *et al* described a nosocomial outbreak of HCV infection in 21 children who underwent immunosuppressive therapy mainly for malignant diseases in a German paediatric oncology unit.[85] A common source could not be identified. This is in concordance with the report of Knoll *et al*, who sequenced the hyper-variable genomic region 1 (HVR1) of the E2/NS1 region in nine HCV infected paediatric cancer patients and showed near identity between HCV isolates as evidence of infection with the same virus. Despite a detailed and careful investigation, the source of infection and the mode of virus transmission could not be established.[86] In another outbreak involving 10 paediatric cancer patients, contamination of multidose vials was the most likely mode of HCV transmission.[87]

Treatment of HCV infection should always be directed and supervised by a specialist experienced in the management of HCV infection in children.[88] In recent years, treatment of HCV infection in children has consisted of the administration of interferon (IFN) α-2a or 2b[89] with or without ribavirin. Consistent data on interferon treatment from prospective randomised studies are not available for children during and after anticancer chemotherapy. In most cases, anti-HCV treatment is postponed until chemotherapy is completed.

NOROVIRUS

Norovirus (NV) is the prototype strain of genetically and antigenically diverse single stranded RNA viruses, classified in the genus Norwalk-like viruses, family *Caliciviridae*.[90] NV is the most common cause of outbreaks of non-bacterial gastroenteritis.[91] The low infectious dose (<100 virus particles), prolonged asymptomatic shedding and environmental stability (NV survives drying, freezing and heating to 60°C as well as ⩽10 ppm chlorine in water) often lead to nosocomial infections.[21] Health care workers may serve as a vector of transmission in hospital outbreaks. Index patients are difficult to identify as having NV infection in a paediatric oncology population where chemotherapy induced nausea and emesis is a frequent adverse event. Other NV symptoms such as headaches (tension headaches), fever (bacterial infection or fever of unknown origin presenting as febrile neutropaenia) and myalgia (adverse effects of treatment with vincristine and corticosteroids) are also highly prevalent in this group of patients.

Recently, our group described an NV outbreak[21] which involved 11 paediatric oncology inpatients. Sequencing of the

PCR amplificates confirmed nosocomial transmission from an index patient whose younger sibling had acquired the disease in a kindergarten. Standard contact precautions for gastro-intestinal disease (gowns and gloves, isolation, cohorting and conventional hand disinfection) did not contain the outbreak, which was only controlled after face masks were worn when in close contact with symptomatic patients (vomiting) and staff used a special hand disinfectant for routine hand hygiene which contains 95% (v/v) ethanol (Bode Chemie, Hamburg, Germany). Three patients experienced severe or life threatening symptoms (including one infant with ALL and lower gastro-intestinal haemorrhage) related to NV infection. Follow-up investigation demonstrated prolonged viral shedding (median 23 days; maximum 140 days).[21] Lee *at al*[23] reported the medical course of a 10-month-old boy who developed chronic diarrhoea 2 months after a combined liver, pancreas and small bowel transplant. NV and adenovirus were detected in multiple stool specimens over a 114-day period. Persisting enteric viral infectious should be considered in immunocompromised patients with chronic diarrhoea.

ROTAVIRUS

Rotavirus (RV), a double stranded RNA virus of the family *Reoviridae*, is one of the most important gastro-intestinal pathogens in infants and children and one of the leading pathogens in paediatric nosocomial infections.[92] The incubation period is short (1–3 days) and the infectious dose is low ($\leqslant$100 viral particles, particularly important in patients with pharmacologically blocked acid secretion of the stomach). RV is transmitted primarily by fecal-oral spread; in addition, transmission via water, food, fomites and flies can occur.[93] A nosocomial RV outbreak reported from the Memorial Sloan-Kettering Cancer Center involved eight patients over 3 months.[94] Investigation by the infection control team revealed that communal toys in the playroom were not being cleaned according to the weekly protocol.

Rayani *et al*[25] compared 28 paediatric cancer patients with positive RV antigen tests (January 1995–December 2004) with 28 rota-negative patients matched for age, underlying disease and chemotherapy. The median duration of rota related symptoms (diarrhoea, fever and vomiting) was 7 days (range 4–34 days). The median duration of viral shedding was 17 days (4–73 days). The RV infection was nosocomially acquired in 19 patients (68%). The proportions of patients with fever >39°C, clinically relevant dehydration, metabolic acidosis and mucositis were significantly higher in RV-positive patients. RV-positive patients tended to have a prolonged period of hospitalisation (median 8 vs 4 days; $p = 0.008$). A higher proportion of RV-positive patients needed parenteral nutrition and tube feeding ($p<0.001$).

RV is a clinically relevant but preventable pathogen in paediatric cancer patients since many cases seem to be nosocomial in origin. Despite limited health care budgets, rapid microbiological testing and contact precautions should be strictly applied to any symptomatic patient and to their immediate contacts. Prolonged viral shedding in immunocompromised paediatric patients necessitates repeated testing in order to determine the duration of isolation.

PARVOVIRUS B19

The human parvovirus B19 (B19) (subfamily *Parvovirinae*, genus *Erythrovirus*) is the causative agent of fifth disease, hydrops fetalis[95] and aplastic anaemia in patients with pre-existing haematopoietic disease.[96–101] Paediatric cancer patients may be severely affected by the tropism of B19 to erythropoietic precursor cells.[16 99]

In a recent study by Lindblom *et al*,[102] consecutive bone marrow samples were collected from 117 children with ALL and analysed for B19 DNA by polymerase chain reaction (PCR). Of these, 18 (15%) were found to be positive for B19 DNA. The infection was suspected on clinical grounds in only one of the 18 patients. Patients with active B19 replication during maintenance treatment had significantly longer periods with postponed/interrupted chemotherapy and needed more blood transfusions. Therefore, paediatric patients with ALL and unexplained cytopaenia should be screened for B19 DNA by quantitative PCR.[17 98] B19 may cause a clinical syndrome with symmetric, painful erythaema and oedema of the feet and hands. The condition gradually progresses to petechiae and purpura and may develop into vesicles and bullae with skin sloughing. As a hallmark of the syndrome is a sharp demarcation of the rash at the wrists and ankles, this clinical manifestation is called "gloves and socks" syndrome.[17 103 104]

In a recent report, McMahon *et al*[105] drew attention to the potential association of parvovirus infection with acute left ventricular dysfunction in two paediatric cancer patients previously exposed to anthracyclines. One should be aware that acute viral myocarditis or even a sustained anaemic period after primary B19 infection could trigger the clinical manifestation of a latent chemotherapy induced cardiomyopathy. Paediatric cancer patients with severe symptoms attributable to B19 infection should be treated with standard immunoglobulins[106 107]; with real time quantitative PCR based techniques the response of the B19 viraemia can be quantified dose by dose.[108]

HUMAN BOCAVIRUS

Human bocavirus (HBoV) is a recently identified member of the *Parvoviridae* family[109] and most probably is the second parvovirus responsible for diseases in humans.[110 111] The clinical spectrum is like that of other viral acute RTIs, similar to the situation in RSV[112] and human metapneumovirus (hMPV) infections.[113 114] There are no distinct clinical signs to aid the medical practitioner in differentiating HBoV infection from that associated with other viruses on clinical grounds alone.[115 116] Many case series suggest that HBoV may cause central pneumonia as well as interstitial and lobar pneumonia, especially in newborns and infants.

As in many other viral respiratory tract pathogens, neither clinical symptoms, laboratory parameters or radiological findings are sufficiently specific to clearly distinguish between bacterial and viral causes of pneumonia.[115 117–120] Symptoms seem to persist for 1–2 weeks on average.[121 122] Several clinical research groups have reported HBoV-positive immunosuppressed/immunodeficient patients.[123–125] Arnold and co-workers described two paediatric patients positive for HBoV after organ transplantation.[123] Kupfer *et al* have recently described reported a clinical case of severe infection in a 28-year-old HBoV-positive female patient with malignant B cell lymphoma,[126] while Schenk *et al* recently described a disseminated HBoV infection in a 4.5-year-old child after allogeneic stem cell transplantation.[12]

Gastro-intestinal symptoms have been described in up to 25% of all paediatric patients.[123 127 128] Further studies in these patients should include testing stool samples for HBoV to confirm viral shedding, and broader investigation of a possible role for HBoV as an enteric pathogen. Since other members of the *Parvoviridae* family are known to be highly resistant to

disinfectants,[22 129] such investigations should also be carried out for HBoV.[110]

INFLUENZA VIRUS

Influenza virus infection may cause acute respiratory failure and death in immunocompromised patients.[130] Distinguishing influenza from bacterial infection is extremely difficult in paediatric cancer patients with subtle clinical signs of RTI and with high fever as the leading symptom. Typical complaints in adolescents and adults, such as headache, myalgia, fatigue and dizziness, are difficult to determine in young children. Influenza virus infection may be accompanied or followed by bacterial pneumonia (eg, *Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus*) and sepsis.[4] In order to prevent nosocomial spread, NPA specimens from paediatric cancer patients hospitalised with RTI during the influenza season should be tested in a timely fashion for influenza A and B virus by PCR based methods. In addition to the early implementation of barrier precautions (table 2), this is advisable so that early antiviral treatment can be administered if necessary (table 3). The neuraminidase inhibitors, oseltamivir[131] and zanamivir[132] are effective against both influenza A and B viruses;[133] treatment should start in the first 48 h after the onset of symptoms.[134]

RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV), an RNA virus from the subfamily *Pneumovirus*, family *Paramyxoviridae*, is responsible for up to 70% of all cases of bronchiolitis and 20–50% of all cases of pneumonia in infants and young children.[135] Immunocompromised children face an increased risk of a severe clinical course which may lead to acute respiratory failure and death. El Saleeby *et al*[136] identified profound lymphopaenia, with absolute lymphocyte counts of $<0.1\times10^9$/l, and age of $\leqslant2$ years as significant risk factors for severe disease in 58 RSV infected paediatric cancer patients. In this study, the overall mortality rate was 8.6%.

RSV infected patients should be kept in droplet isolation according to fixed local standards of hygiene.[137] The disinfection of hands[18] and the use of gowns, masks and disposable gloves when in contact with patients and possibly contaminated surfaces are essential. In 25 of 39 (64%) patients with RSV infection from our institution, the next chemotherapy session had to be postponed because of RSV infection. This may result in decreased dose intensity with a negative impact on the efficacy of treatment for the underlying malignancy.

Treatment for RSV infection is symptomatic (adequate fluid intake, treatment of fever, monitoring, oxygen supplementation and, if necessary, mask continuous positive airway pressure (CPAP) or mechanical ventilation). Corticosteroids should be avoided; salbutamol (albuterol) and epinephrine inhalations should only be used in patients who show an objective clinical response. Although secondary bacterial infections in RSV infected healthy children are rare (<5%), standard empirical antibacterial treatment is recommended in cancer patients with febrile neutropaenia and RSV infection.

Mainly because of safety and compliance issues and technical difficulties, it is not feasible to treat non-intubated infants and young children with ribavirin inhalation delivered at a concentration of 20 mg/ml for 18 h via a small particle aerosol generator unit and administered via a face mask inside a scavenging tent to prevent environmental contamination.[138 139] In addition, the objective benefit of this intervention is still under debate.[140] In patients with severe pneumonia due to RSV infection, intravenous administration of ribavirin may be an option.[141] There is still no evidence based treatment algorithm available for patients outside the acute phase of allogeneic stem cell transplantation. Thus, the decision to treat a symptomatic patient with confirmed RSV infection with ribavirin has to be made on an individual basis. In our unit, we use ribavirin (po, iv) only in patients with progressive respiratory failure or in patients with acute myeloid leukaemia (AML) during induction treatment.

Standard immunoglobulin provides no protection because the resulting antibody titres are not sufficient. Passive immunoprophylaxis with humanised monoclonal antibodies against the F-protein of the virus (palivizumab) has not been investigated in paediatric cancer patients.[142 143] Although Chavez-Bueno *et al*[144] reported favourable preliminary data on combination treatment (ribavirin and iv palivizumab), de Fontbrune *et al*[145] could not demonstrate a significant impact of palivizumab on the clinical course and survival of 19 allogeneic stem cell transplant recipients with RSV infection. Considering the very limited options for highly immunocompromised patients,[139 146] a prospective randomised multicentre study with motavizumab, an ultra-potent, affinity matured, humanised monoclonal antibody,[147] should be considered in paediatric cancer patients with severe RSV infection.[148]

HUMAN METAPNEUMOVIRUS

The human metapneumovirus (hMPV), an RNA virus from the subfamily *Pneumovirus*, family *Paramyxoviridae*, was first identified in 2001 in the NPA of young children from the Netherlands with respiratory tract illness.[149] The symptoms of hMPV infection do not differ significantly from those of other viral RTI.[150] Clinical severity has been described to be comparable to RSV infection.[113] hMPV has been detected in immunocompromised patients with severe lower RTI. In 2002, Pelletier *et al*[151] described the clinical course in a girl with ALL who experienced two episodes of hMPV infection at the age of 7 months and 17 months while still receiving cytotoxic chemotherapy. Although the first infection was an episode of febrile neutropaenia without severe complications, the second hMPV infection resulted in acute respiratory failure and death. We cared for a 10-month-old infant with rhabdomyosarcoma who experienced an hMPV infection while receiving intensive induction chemotherapy. This febrile neutropaenic patient received piperacillin-tazobactam and teicoplanin intravenously and hMPV was the only pathogen to be detected in respiratory, blood and urine cultures. The fever subsided and the patient recovered uneventfully when the neutrophil count recovered to above 1×10^9/l. In a recent study, 3% of transplant patients (five out of 163) with pneumonia were found to be hMPV infected. Four of these patients died of respiratory insufficiency within 40 days after transplantation (in three of these only hMPV was detected). All these patients had severe lymphopaenia.[152] Currently no established treatment for hMPV infection exists. Intravenous ribavirin may be considered in mechanically ventilated hMPV infected patients with acute respiratory failure[141] since ribavirin shows antiviral activity in vitro.[153 154]

BK VIRUS

Cheerva *et al*[155] presented three cases of haemorrhagic cystitis (HC) after treatment with high dose cyclophosphamide in non-transplant paediatric oncology patients in whom BK virus (BKV) was detected in urine. These three patients with BKV infection showed more prolonged haematuria (14–16 weeks)

compared with one patient with BKV-negative HC (10 weeks). The HC necessitated chemotherapy delays and also prolonged supportive care. Cidofovir treatment resulted in resolution of haematuria in one patient. Thus, BKV infection may increase the risk of HC in patients receiving high dose oxazophosphorine chemotherapy outside the allogeneic stem cell transplantation setting.

VIRAL INFECTION AFTER TREATMENT WITH RITUXIMAB

Treatment with rituximab, a chimeric anti-CD20 monoclonal antibody directed against human B cells, may cause profound and prolonged peripheral B cell depletion and hypogammaglobulinaemia. Particularly in patients with additional immunosuppression, reactivation of viral infection (CMV, VZV, HCV,[156] HBV,[157–159] B19,[106] EV[160] and JC virus[161 162]) has been observed after rituximab treatment.[163] The paediatric population requiring this treatment is small, and rarely occurring adverse effects must not be considered a contraindication. Nonetheless, the attending physicians should consider specific quantitative monitoring of serum viral loads (in particular HBV and CMV) with PCR based methods during follow-up investigations.[163] However, increased viral loads are not necessarily associated with organ dysfunction. For example, liver damage in patients with HCV infection is the result of an immune reaction against hepatocytes infected with HCV, and in most cases is associated with a substantial decrease in serum HCV RNA levels. Consequently, recently published studies describe the use of rituximab combined with Peg-IFNalpha2b-ribavirin as a safe and effective therapeutic option in severe refractory HCV related mixed-cryoglobulinaemia vasculitis.[164]

CONCLUSION

Physicians attending paediatric cancer patients during intensive conventional anticancer treatment must be aware of potential pathogens and clinical manifestations, as well as the best diagnostic approach to combat viral infections in this high risk population. We conclude that our knowledge concerning this important part of clinical practice will be substantially increased by the advent of more sensitive diagnostic tools, in particular by the routine use of (RT-)PCR based diagnostic methods. In addition, newly detected, emerging viral pathogens with epidemic potential may become a threat to severely immunocompromised paediatric cancer patients. More case series and in particular more controlled studies on therapeutic interventions are needed to complete our understanding of these pathogens.

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