Emerging Viral Infections

22

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Contents

22.1 Introduction

Emerging infectious diseases according to the CDC-hosted journal *Emerging Infectious Diseases* (www.cdc.gov/ncidod/EID/about/background.htm) are defined as diseases "whose incidence in humans has increased in the past two decades or that are expected to have an increased incidence in the near future." These diseases respect no regional, national, or international boarders and include (1) new infections resulting from changes or evolution of existing organisms, (2) known infections spreading to new geographic areas or populations, (3) previously unrecognized infections appearing in areas undergoing ecologic transformation, (4) old infections re-emerging as a result of antimicrobial resistance, and, finally and most importantly for the field of virology, (5) infections caused by newly discovered agents.

After the discovery of the human metapneumovirus (hMPV) in 2001 and the 2002/2003 outbreak of severe acute respiratory syndrome (SARS), the number of known emerging viruses expanded at a fast pace, mainly due to the development of novel virus identification methods and their routine use in patients with suspected infections but negative findings from conventional diagnostic methods. This chapter focuses on these new pathogens and highlights their role in patients with hematological malignancies.

22.2 Human Metapneumovirus

In 2001 the hMPV was described as the third known *Paramyxovirinae* to cause disease in humans, together with the respiratory syncytial virus (RSV) and

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parainfluenza viruses (PIVs), all of which cause respiratory infections [204]. Infections with hMPV and RSV occur worldwide and are associated with a broad clinical spectrum ranging from mild to life-threatening disease. Our group and others have shown that hMPV infections in hospitalized patients or in the elderly are at least as severe as RSV infections [125, 146, 147, 175, 178, 204–206, 218, 220, 221, 229]. Whether hMPV infections cause milder symptoms than RSV infections in otherwise healthy individuals has not yet been systematically investigated. Furthermore, hMPV and RSV often occur as co-pathogens and may then cross-react directly or indirectly [229].

Genetically, hMPV is most closely related to the avian metapneumovirus (APV) [204] and is assumed to have a zoonotic origin, a possibility supported by the fact that it can be transferred to APV-susceptible poultry. Serological and bioinformatic analyses indicate that passage to humans occurred more than 50 years ago [47, 48, 210].

In contrast to RSV, hMPV lacks two genes coding for the nonstructural proteins NS1 and NS2, both of which are assumed to interact with the host's immune response. For this reason, RSV and hMPV may induce different host immune responses [25, 59, 122, 123, 144, 148, 191]. While RSV may be defined as a re-emerging pathogen, at least in some patient cohorts where it was previously underestimated [174], hMPV has been shown to cause a number of severe respiratory events in patients with hematological malignancies. RSV infection and hMPV infection are indistinguishable on clinical grounds alone [229].

In one study including 114 lung transplant recipients, hMPV was detected in bronchoalveolar lavage (BAL) fluid from about 5% of symptomatic patients [45]. Further cases were described after lung and heart–lung transplantation in patients having histological findings of acute pneumonia with diffuse alveolar damage and hyaline membrane formation [112, 192]. In hematopoietic stem-cell transplant recipients, hMPV can cause life-threatening disease. Englund and colleagues described a case series in which the hMPV detection rate by RT-PCR was about 26% among symptomatic patients, and 80% of hMPV-positive patients died from severe infection [63]. Furthermore, in stem-cell transplant recipients, viral shedding and persistence may be prolonged compared to otherwise healthy individuals and may be accompanied by severe infection characterized by rapidly progressive pneumonia with diffuse alveolar hemorrhage [50, 63]. Until now, ribavirin has been the only antiviral agent used to treat severe hMPV infections [28, 85, 93, 165]. Ribavirin was tested in a mouse model and used successfully in two published clinical cases. To date, no other antivirals or vaccines are available.

22.3 Human Bocavirus

Human bocavirus (HBoV) may be an emerging respiratory virus. It was first discovered in 2005 by the Swedish research group led by Tobias Allander at the Karolinska University Hospital in Stockholm [9]. The discovery was made possible by a novel molecular virus screening technique involving DNase treatment, random amplification, cloning, and sequencing. The newly found virus showed up as a possible cause of respiratory disease, particularly acute respiratory tract infections. Clinical symptoms include coughing, fever, and rhinorrhea. It is still unclear whether HBoV is able to trigger disease on its own or occurs only as a co-pathogen [176].

Comparisons of the genomic sequence to other known viruses suggest that HBoV may belong to the *Parvoviridae* family, *Parvovirinae* subfamily, and *Bocavirus* genus. This genus has two other viruses, namely, bovine parvovirus (BPV) and canine minute virus (CnMV). HBoV may be the second *Parvoviridae* known to cause human disease, after parvovirus B19, which belongs to the *Erythrovirus* genus. Several nonpathogenic parvoviruses are also known to infect humans, including the adeno-associated viruses (AAV) of the parvovirus family, *Dependovirus* genus, and, in the same family, parvovirus 4 (PARV4), a possible member of the *Hokovirus* genus [113]. Two new viruses classified as HBoV2 and HBoV3 were discovered recently. HBoV2 has 75% similarity to HBoV, compared to only 18% for HBoV3 and HBoV2 [12, 100]. HBoV2 was detected in children with acute gastroenteritis in England, Pakistan, and Australia, whereas HBoV3 was detected during the course of an HBoV2 surveillance program but could not be associated to any symptoms [12].

HBoV is a non-enveloped single-stranded DNA virus, encapsulated in a simple icosahedral shell with a diameter of 20–26 nm, made up by the arrangement of

two proteins. The main genome body containing the open reading frames (ORFs) encoding viral proteins has been sequenced and shown to be 5,309 nt in length [115]. The entire genome length is predicted to be about 6,000 nt [8, 9]. Experiments to directly sequence the virus genome failed and led to faulty data [9, 27]. HBoV is thought to have palindromic hairpin structures flanking the terminal ends, similar to related *Parvoviridae* (e.g., BPV and CnMV). The function of the terminal folds is not fully understood, but it is thought that they act as primers in viral replication and are important for packaging [101]. Until now, it was not possible to decipher the unknown sequences. Attempts to amplify the regions encoding specific enzymes did not reveal the nucleotide sequence [9]. An undetected protein covalent or other protein modification on the HBoV genome may explain this failure, as other parvoviruses (B19, MVM, and H1) possess protein covalents attached to their genomes [39, 51, 168]. Recent findings reveal that the majority (87.5%) of the ssDNA strands packed in the capsid are of negative polarity, independent from their viral subtypes [27]. The genomic composition is as yet unconfirmed, and so far three ORFs have been identified, similar to BPV and CnMV. One of these ORFs encodes for the viral capsid proteins VP1 and VP2, whereas the other two encode for non-structural proteins. The VP2 gene sequence is nested within the VP1 gene sequence. The VP1 sequence, compared to VP2, contains a unique terminal sequence, VP1u [163], which may be required for HBoV genome transfer to the nucleus for replication [236]. The HBoV capsid is composed of 60 proteins, derived from the structural molecule VP1 and its derivative VP2 [9]. The functions of the non-structural proteins NS1 and NP-1 are still equivocal. NS1 may play a role in replication. It generally acts as an initiator protein (for parvoviruses), specifically controlling the process by which several concatemeric intermediates are processed by rolling-hairpin replication [15]. The role for NP-1, located in the middle ORF, is still unclear, but probably also involves parvovirus replication. The transmission route of HBoV is still unknown, but suggested tissue sites for replication are the respiratory and intestinal epithelia, as well as the lymphatic organs. Parvoviruses replicate only in proliferating cells, and the viral proteins are transcribed only during the S-phase. Recently, an in vitro replication system for HBoV using stratified human airway epithelium to imitate the human trachea was successfully established. The cells were inoculated with HBoV-positive material from respiratory tract secretions of hospitalized children. Apical HBoV release from the cells was confirmed using PCR. This study further showed that the transcription model resembled that of both of the other known bocaviruses (BPV and MVC) [52].

Symptoms associated with possible HBoV infection are wheezing, fever, bronchiolitis, and pneumonia [8, 12, 19, 31, 33, 41, 43, 44, 49, 97, 114, 118–121, 124, 126, 141, 176, 177, 179, 183, 195, 198, 203, 213, 219, 226, 235, 237, 239]. However, the presence of HBoV in the respiratory tract does not prove that the virus is the cause of infection. HBoV is often detected concomitantly with other respiratory viruses [41, 216, 226], a fact that adds to the uncertainty regarding the pathogenic potential for HBoV [41, 66, 91, 97, 118, 124, 128, 136, 176, 200, 203, 213, 217, 226, 239]. The symptoms are identical in patients positive for HBoV alone or combined with another virus, but the viral load is higher in mono-infections than in coinfections. Asymptomatic patients can carry the virus. In one study, 43% of tested asymptomatic children were HBoV-positive. These patients were admitted for elective surgery, and the group undergoing mainly ear, nose, and throat surgery had the highest prevalence of asymptomatic HBoV infection [124]. These data suggested that HBoV may persist in the host in the tonsillar lymphoid tissue, contributing to tonsillar hyperplasia [126]. HBoV has been detected in patients with symptoms of gastrointestinal infection, but it is unclear whether the virus is only excreted in stool or is a cause of gastroenteritis. In these studies, HBoV was found concomitantly with a norovirus or other enteric viruses, and HBoV was not directly proven to be a cause of gastrointestinal infection. The virus in suspension in respiratory secretions may be simply swallowed and excreted in stool. The newly discovered HBoV2 and HBoV3 have both been detected in stool samples. HBoV2 was identified in a study involving stool sample screening in children with non-polio acute flaccid paralysis [12, 100, 179], and HBoV2 and HBoV3 were detected in hospitalized children with acute gastroenteritis. More studies on the two new HBoV types are needed to gain a better understanding of their role in gastrointestinal infections. No evidence that HBoV2 and HBoV3 can infect gastrointestinal tissue exists to date. Furthermore, whether detection of these viruses in serum indicates viremia or infection of blood cells is unknown, because there are no currently established methods for detecting HBoV particles. The related parvovirus B19

can infect erythroid progenitor cells in the bone marrow, but no HBoV DNA was detected in bone marrow samples from human immunodeficiency virus (HIV)-positive and -negative individuals, whereas B19 was present in both groups [76, 146]. So far, there is one published report of HBoV associated with severe pneumonia in a pediatric hematopoietic stem cell transplant recipient [172, 173] and one of HBoV infection in an adult with leukemia [109]. However, none of these patients had clinical symptoms different from those caused by other "common cold" pathogens, and no specific antiviral therapy was available.

Since the discovery of HBoV, infections with this virus have been found worldwide. The prevalence of infections in which HBoV may be a causative factor ranges from 1.5% to 19.3%. No seasonal variations have been described. HoBV occurs mainly in pediatric patients aged 6–24 months [4, 5, 9, 10, 12, 16, 17, 37, 40, 42, 44, 61, 74, 77, 86, 91, 95, 99, 103, 116, 127, 132, 143, 149, 158, 160, 162, 166, 167, 179, 187, 189, 194, 214, 219, 226, 235, 238]. Younger children may be protected by maternal antibodies [38]. HBoV-IgG can cross the placental barrier, but it is unclear whether HBoV can be transmitted from the mother to her fetus. Antibodies against HBoV have been found in about 94% of individuals older than 19 years of age [44]. At the moment, only two different genotypes of the single HBoV lineage are known. A simple verification test is available for rapidly differentiating between these two genotypes. Digestion of a 309-bp fragment of the VP1/VP2 gene with BstAPI endonuclease yields two fragments with genotype 1, but induces no cleavage with genotype 2 [54]. Three HBoV2 genotypes have been identified [5], but no information is available for HBoV3.

Despite a large number of clinical studies, the biological background of HBoV is still unknown. The virus can be replicated in a cell line. However, complete genome sequencing is needed to fully understand the virus. As this virus may cause acute respiratory disease, it is crucial to understand the disease process and its causative agent.

22.4 Human Coronaviruses

As of August 2009, five human coronaviruses (CoVs) were known, of which three meet the definition of emerging pathogens. The five human CoVs are OC43 and 229E, two long-known viruses that cause respiratory and/or gastrointestinal disease, and the emerging viruses SARS-CoV [56], NL63 [207], and HKU-1 [233]. SARS-CoV appears to be an archetypical zoonosis responsible for a single outbreak, which was unfortunately accompanied with high mortality and had the potential for a pandemic event. The two other newly detected CoVs, NL63 and HKU-1, occur periodically and infect all age groups worldwide.

After the identification in the 1960s of the first CoVs known to cause human disease, HCoV-229E and HCoV-OC43, and their association with mild respiratory disease [30, 34, 67, 84, 137, 142], little new information emerged in this field until the beginning of the twenty-first century. In 2002/2003, a CoV appeared in the Guangdong province of China, causing severe acute respiratory syndrome (SARS) [56, 108, 156]. SARS was fatal in some patients, although at the time CoVs were believed to cause only mild disease. Strenuous efforts were made to identify and to characterize this new virus and to curb its potential for causing a pandemic.

Among the heterogeneous *Coronaviridae* family, CoV NL63 (HCoV-NL63) was identified in 2004 [207] and CoV HKU1 (HCoV-HKU1) in 2005 [232]. In contrast to SARS-CoV, these newly detected CoV led to clinical symptoms similar to those caused by HCoV-229E and HCoV-OC43. Considerable research has been undertaken to learn more about these viruses, their differences, similarities, and characteristics. This review focuses mainly on SARS-CoV and HCoV-NL63.

Several techniques were employed to characterize and to identify the agent causing SARS. Tests for known respiratory viruses were negative. Patient samples were inoculated onto Rhesus monkey kidney cells (fRhk4) to look for cytopathic effects. Electron microscopy revealed the morphology of the virus and led to characterization of the virus family. Histopathological studies showed mild interstitial inflammation with scattered alveolar pneumocytes. In an immunofluorescence antibody assay, sera from patients had high titers of antibodies against the infected cells. A random RT-PCR assay generated DNA fragments of unknown origin, but with homology to viruses of the *Coronaviridae* family, and confirmed the results of electron microscopy. A few days later, these results were confirmed by two other groups [56, 108, 156].

SARS and its causative agent appeared unexpectedly and spread explosively. The infection was transmitted from palm civets to humans, although it has since been confirmed that bats are the natural reservoir of SARS-CoV. Due to the fast mutation rate of RNA viruses and their resulting genotypic markers, the course of the infection could be reconstituted in great detail. In the early phase of the SARS near pandemic, the very first index patient fulfilling the subsequent WHO definition of SARS resided in Foshan near Guangzhou and was identified on November 16, 2002. One month later, the second case occurred, in Shenzhen, where a man who had regular contact with wild animals was infected and transmitted the disease to his family and to several staff members at the hospital where he was admitted. Similar cases were reported nearby. In January 2003, the second phase of the SARS outbreak started in Guangzhou. Several patients died, and patients were transferred to major hospitals, leading to nosocomial spread of the virus to other patients and health-care workers.

The next and final phase started in mid-February 2003 and heralded the pandemic. A doctor was infected in Guangdong province and took the disease to Hong Kong, where he stayed in a hotel ("hotel M"). He infected 17 other people, who were admitted to different hospitals, where further nosocomial infections occurred. Some of the infected patients transferred the virus via air travel to Vietnam, Singapore, and Toronto, where new cases emerged. A novel CoV was identified on March 21, 2003, and confirmed a few days later. The first strain (Tor2) was fully sequenced on April 12, 2003, and SARS-CoV was proven to be the cause of SARS [134]. In July 2003, the epidemic ended, with no further human-to-human transmissions being reported. In September 2003, a new case was reported at a laboratory in Singapore, and over the next 2 years other accidents occurred in laboratories.

HCoV-NL63 was discovered in a 7-month-old child with bronchiolitis. Diagnostic tests for all known respiratory viruses were negative. Inoculation of a sample on tMK and, later on, LLC-MK2 cell cultures produced a cytopathic effect. In the LLC-MK2 cell culture supernatant, a new virus was identified using the VIDISCA method [161, 207]. Sequence comparisons established that the virus was most closely related to HCoV-229E and, together with PEDV and Bat-CoV, belonged to the coronavirus subgroup 1b. Two further research groups obtained identical results soon afterward [65, 72].

There is some indication in the literature that HCoV-NL63 was detected much earlier. Viruses were described that did not exhibit all the characteristics of HCoV-229E or HCoV-OC43. Unfortunately, these isolates were lost, so that studies could not be done to determine whether one or more of them were identical to HCoV-NL63. SARS-CoV and HCoV-NL63 are both members of the *Coronavirus* genus, *Coronaviridae* family, within the *Nidovirales* order. Both organisms are positive single-stranded RNA viruses with a large genome of about 30 kb. The virus particles are enveloped and possess peculiar spike-shaped proteins on their surface that produce a crown-like appearance. Electron microscopy revealed particles of 80–140 nm located either within the infected cells at the rough endoplasmic reticulum in double-membraned vesicles or outside the cells attached to the plasma membrane.

The genomes of both SARS-CoV and HCoV-NL63 can be roughly divided into two parts. The 5′ two-thirds consists of one large polyprotein (ORF1ab) including several domains with autocatalytic activities, producing nonstructural proteins (NSPs) involved in replication and immune evasion. ORF1ab encodes 16 NSPs in toto in both SARS-CoV and HCoV-NL63.

The last third at the 3′ end of the genome contains the ORFs coding for the functional proteins – spike (S), envelope (E), membrane (M), and nucleocapsid (N) – and for accessory protein genes that vary in number and position across species.

Traditionally, CoVs were classified – due to their antigenic cross-reactivity – into three groups, which were largely confirmed later on by sequence analysis results. Group I and II viruses infect mammals, whereas group III viruses infect only birds. While HCoV-NL63 belongs to group 1b, SARS-CoV and the bat CoVs are considered group 2b viruses, although bat CoVs constitute a newly identified CoV group.

HCoV-NL63 is most closely related to HCoV-229E, and phylogenetic analysis findings suggest that HCoV-NL63 may have diverged from HCoV229E in the twenty-first century. Furthermore, there seem to be two main genetic clusters of HCoV-NL63, and there is evidence that the HCoV-NL63 genome is arranged in a mosaic-like manner.

Patients infected with HCoV-NL63 usually experience only mild symptoms, including cough, rhinitis, rhinorrhea, and pharyngitis, often with a fever. In rare cases, pneumonia can occur, chiefly in children aged 0–3 years, older people, and immunocompromised

individuals. Among children with severe lower respiratory tract infection, a substantial number have croup compared to a control group. Croup or laryngotracheobronchitis is characterized by a loud barking cough, inspiratory stridor, and hoarseness. An association with Kawasaki disease has been postulated but not confirmed despite studies by a number of research groups [11, 14, 15, 53, 58, 87, 106, 111, 140, 188, 190, 193, 202, 208].

After the detection of HCoV-NL63 in The Netherlands and, later on, in New Haven, CT, USA, this virus was found in a number of countries, suggesting a worldwide distribution. Except in subtropical regions, HCoV-NL63 was mainly detected in the winter months and often turned up with other co-pathogens, such as influenza, RSV, parainfluenza, and hMPV. The HCoV-NL63 load is attenuated when there is another pathogen. However, and not surprisingly, the infection itself seems more severe in co-infections. As with SARS-CoV, HCoV-NL63 is detectable up to 2 months after recovery from the disease. Seroprevalence studies showed that virtually every adult encounters HCoV-NL63 at least once in a lifetime. Antibodies specific for the S protein are produced and display a neutralizing effect.

People infected with SARS-CoV had a fever, chills, myalgia, rigor, and a nonproductive cough. Clinical symptoms such as rhinorrhea and sore throat were less common. In contrast to HCoV-NL63, SARS-CoV did not infect children, and the disease occurred instead in normal and healthy adults and in the elderly. Of 8,096 infected people, 774 died, demonstrating a nearly 10% mortality rate. SARS-CoV spread to more than 30 countries [26, 29, 35, 94, 186, 227]. The first outbreak occurred in late 2002/early 2003. Seasonality of HCoV-NL63 infection is not known, as the pandemic occurred only once, with the peak in winter. It has been confirmed that SARS-CoV is a zoonosis that originates primarily from bats. Although SARS-CoV was initially spread from civets to humans, the actual transmission route was from humans to humans, most likely by droplets, and probably occurred in health-care facilities, at workplaces, and when using public transportation. The virus was detected not only in the respiratory tract, but also in the gastrointestinal tract, liver, kidney, brain, and other tissues.

Seroprevalence was quite low among the general population, ranging across studies from 0% to 1.81% and being slightly higher in asymptomatic health-care workers. In contrast, a much higher rate (up to 40%) was found in asymptomatic animal handlers, which was not surprising, as these individuals probably acquired immunity via less pathogenic SARS-CoV-like strains that also emerged by zoonotic recombinations. SARS-CoV infection can be accompanied by co-pathogens such as other respiratory viruses (e.g., hMPV) or other CoVs.

The association of SARS-CoV with severe pneumonia in patients with hematological malignancies occurred only during the single outbreak, and studies on the role for NL63 in these high-risk patients are still limited. However, 229E has been detected in hematopoietic stem cell transplant recipients with high fever, cough, and interstitial and alveolar lung disease [157].

22.5 Polyomaviruses

Recently, two novel polyomaviruses were detected in respiratory aspirates. Allander et al. in Sweden discovered a previously unrecognized third human polyomavirus in 6 (1%) of 637 nasopharyngeal aspirates and 1 (0.5%) of 192 fecal samples, and suggested the name KI polyomavirus (KIPyV) [7]. The second newly identified polyomavirus was found by Gaynor et al. in respiratory samples from Bribane, Australia, and St. Louis, MO, USA. This "Washington University" (WU) genome polyomavirus (WUPyV) was amplified and cloned from the nasopharyngeal aspirate of a 3-year-old patient with pneumonia and negative tests for other respiratory viruses. Screening of 2,135 patients with respiratory tract infections identified 43 additional cases [79]. Of note, KIPyV was not named for the Karolinska Institute in Stockholm where it was detected. Since the first description of KIPyV and WUPyV, a number of prevalence studies from various areas have been published, but the association of these viruses with acute respiratory tract infections remains unclear [2, 13, 117].

Prevalence studies of KIPyV and WUPyV showed a worldwide distribution. The prevalence of KIPyV was 1% in Sweden, 1.4% in the United Kingdom, 1.99% in Thailand, and 2.6% in Australia [7, 23, 152, 155]. The prevalence of WUPyV was higher, 7% in South Korea, and 6.29% in Thailand [88, 155]. Australia, the USA, and the UK had WUPyV prevalences of 4.5%, 1.2%,

and 1.0%, respectively [23, 79, 152]. The age distribution of KIPyV- and WUPyV-infected patients showed two peaks, in patients younger than 15 years (with the highest rates occurring before 5 years of age) and older than 45 years [3, 150]. Seasonal variations in KIPyV and WUPyV did not appear consistently. KIPyV infections predominated during the winter months in Thailand but not in Australia. In contrast, WUPyV infections were predominantly detected during late winter, peaking in December to early summer in Australia but not in Thailand [23, 24, 155].

KIPyV and WUPyV are frequently associated with other respiratory viruses. High co-detection rates were found in Australia, 74.7% for KIPyV and 79.7% for WUPyV, and the most commonly co-detected viruses were human rhinovirus and HBoV. Co-detection of KIPyV and WUPyV was found in 14 patients, of whom only 1 had no other respiratory virus [23]. Norja et al. detected KIPyV or WUPyV in 19 patients and found a viral coinfection rate of nearly 50% with predominant detection of adenoviruses. The overall frequencies of KIPyV and WUPyV detection were similar in patients with upper respiratory tract infection, lower respiratory tract infection, or no respiratory symptoms, and eight patients were immunosuppressed, although overall the patient groups were not very well described [152].

Data are not available to determine whether KIPyV and WUPyV detection represents a similar phenomenon to JCV and BKV reactivation in immunocompromised patients, or whether KIPyV and WUPyV share the oncogenic potential of other human and animal polyomaviruses, and further studies are needed [242]. However, Koch's modified postulates have not been verified so far, and whether KIPyV and WUPyV are respiratory pathogens or innocent bystanders is still debated. Further studies are required to evaluate the clinical relevance of KIPyV and WUPyV detection in respiratory specimens.

Another newly recognized polyoma virus of interest may be the Merkel cell polyoma virus, MCPyV, recently identified in Merkel cell carcinoma. MCPyV may have oncogenic potential, as it is found mainly in lesional and non-lesional skin from patients with Merkel cell carcinoma and other skin diseases [73]. This oncogenic potential, as well as experience with other oncogenic viruses such as EBV, suggests a high likelihood of MCPyV generating clinical events in patients with hematological malignancies. However, until now, there are more questions than answers regarding this new virus. The role for MCPyV in disease is unclear, and cell-culture and animal models are not yet available [169].

22.6 Picornaviruses

Within the group of picornaviruses, two emerging virus lines were identified recently, namely, rhinovirus X associated with severe respiratory disease and the parechoviruses. The newly identified rhinovirus [105, 129, 171] causes common colds that can progress to fatal infections in high-risk patients. The role for this virus in patients with hematological malignancies is unclear. The number of known parechoviruses is growing rapidly, as novel identification methods have led to the discovery of new variants. Parechoviruses were classified in the *Enterovirus* genus initially, then found to exhibit different biological features, leading to their reclassification in their own genus. Clinically, they cause the same spectrum of disease as enteroviruses. The rodent parechovirus known as Ljungan virus is believed to be associated with greater disease severity [1, 6, 20–22, 55, 68, 90, 96, 107, 151, 170, 199, 209, 212, 223, 230, 231, 234, 240, 241]. As with enteroviruses, parechoviruses deserve careful attention in high-risk patients.

22.7 Reemerging Viruses

22.7.1 Respiratory Syncytial Virus

The RSV has been known for decades and is not believed to be an emerging pathogen. However, recent investigations have demonstrated clearly that RSV infection is underestimated in the elderly and in patients with other malignancies, where it may cause severe to fatal pneumonia [174, 182, 184, 185, 196, 197, 215, 222]. This increasing incidence in some patient groups may define the RSV as a reemerging pathogen, although it is ascribable to the use, for the first time, of molecular RSV diagnostic methods in vulnerable patient groups. In all likelihood, the RSV was present in these groups previously but went unrecognized.

RSV accounts for a large number of infections throughout the treatment of patients with acute lymphoblastic leukemia. In one study, about 57% of patients were positive for RSV at some point in time [102]. RSV is also of clinical significance following allogeneic bone marrow transplantation and has been found in a substantial proportion of patients with lung infections [64, 133]. Furthermore, RSV was responsible for 55% of fatal pneumonia cases in adult immunocompromised patients treated for lymphoma and leukemia in a retrospective study and was a major cause of viral pneumonia in several cohorts of patients with these hematological malignancies [57, 78, 81, 82, 164, 201, 228].

In patients with hematological malignancies, and most notably in hematopoietic stem cell recipients, RSV infection is fatal in up to 80% of cases [89]. In these patients, ribavirin, immunoglobulins, and the RSV-specific humanized monoclonal antibody palivizumab may be used as specific therapy and/or prophylaxis [18, 32, 36, 38, 60, 69, 70, 75, 80, 83, 104, 110, 138, 139, 145, 159, 181, 211, 224, 225]. However, evidence supporting the use of these treatments remains weak at this time.

22.7.2 Parainfluenza Viruses

Clinically, parainfluenza viruses 1–4 cannot be differentiated from RSV or hMPV infection. As they infect the same groups of patients and cause identical symptoms, they require the same attention as other pathogens. They can also be classified among reemerging viruses, as screening was recently introduced. Parainfluenza viruses should be considered in the differential diagnosis of respiratory infection and distinguished from emerging pathogens [98, 154].

22.7.3 Influenza Viruses

Influenza viruses are not emerging viruses, as in theory all potential variants and reassortants are identified based on well-known data on the mode of replication and influenza-associated biological phenomena such as antigen shift. Nevertheless, perhaps due to concern that a lethal variant similar to the Spanish flu may return, or due to the awarding of research grants based on this fear, any "novel" influenza virus variant is estimated to have pandemic potential and is therefore classified as an emerging pathogen (and as an opportunity for the media to generate widespread fear of general social disorganization and massive mortality). The most recent virus classified as an emerging influenza virus was the Mexican H1N1 strain identified in 2009.

Recent developments in the swine-originated H1N1 pandemic indicate that the main target is not the elderly population but, instead, younger adults (www.who.org [153, 180]). The immunosenescence concept suggested that older people would be at greatest risk. The predominant involvement of younger individuals suggests a role for unknown factors that contribute to clinical disease. Alternatively, aging might exert a protective effect. However, it must be hoped that the current wave of H1N1 influenza is not a relatively harmless prelude to a second severe outbreak later in the flu season.

As with any influenza variant, the H1N1 strain warrants close attention in high-risk patients. All influenza variants can cause severe pneumonia in patients with hematological malignancies.

22.7.4 Adenoviruses

Adenoviruses are small naked DNA viruses that occur worldwide and mainly infect children between 0.5 and 5 years of age. The clinical spectrum ranges from mild to severe respiratory diseases to epidemic keratoconjunctivitis ("pink eye"), tonsillopharyngitis, and gastroenteric disorders (vomiting, diarrhea). Adenoviruses occur in over 50 serotypes, affecting all age groups and causing diseases that are usually self-limiting within 14 days or asymptomatic [46, 62, 71, 92, 130, 131, 135]. Importantly, adenoviruses may persist in the infected host [46, 62, 71, 92, 130, 131, 135] and may undergo reactivation in immunosuppressed patients, including those with hematological malignancies. Adenoviruses play a major role in solid-organ transplant recipients but occur less often in stem cell recipients [46, 62, 71, 92, 130, 131, 135], However, novel and more aggressive adenovirus strains may meet the definition for emerging pathogens and may play a future role in patients with hematological

malignancies. Consequently, adenoviruses deserve attention. More specifically, shedding may be prolonged in high-risk patients, patient isolation may be required, and no antiviral therapy for adenoviruses is available so far [46, 62, 71, 92, 130, 131, 135].

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