Chapter 32
Respiratory Viruses

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Abstract  The respiratory viruses as a group are the most common cause of an acute infectious illness in developed societies. The immunocompromised state of many cancer patients constitutes the basis for the frequent failure of the host to promote a normal and rapid recovery from an acute respiratory viral infection and results in a more severe and prolonged infection that causes significant morbidity and mortality in these patients. Those respiratory viruses that are most prevalent and most prone to produce lower respiratory illnesses and pneumonia in healthy hosts, RSV, influenza viruses, and parainfluenza viruses, are those most likely to cause severe illness and pneumonia leading to hospitalization in immunocompromised persons. However, viruses less prone to produce a lower respiratory illness but that are highly prevalent, such as rhinoviruses, may frequently be associated with severe illness. The limited availability of antivirals and vaccines for the acute respiratory viruses means that these infections will continue to be important for many years and dictate a need for utilizing infection control procedures as much as possible, particularly in hospitals and institutions, so as to minimize spread. Efforts to develop specific vaccines are important as their use could prevent as well as reduce exposure of cancer patients to these viruses. Development of specific antivirals is important for use in immunocompromised patients as normal recovery mechanisms may be seriously impaired.

Keywords  Influenza • Cancer • Transplant • RSV • Adenovirus • Metapneumovirus

Introduction

Community respiratory virus infections were once primarily considered to be infections of children and generally nonserious. However, over the past two decades, it has become clear that these viruses can cause serious infections that require medical attention, particularly in infant, elderly, and immunocompromised patients. Historically, the most common causes of respiratory infections in cancer patients were thought to be opportunistic bacteria and fungi, but newer diagnostic methods have revealed that respiratory viruses can cause serious morbidity and mortality in such patients, including leukemia patients and hematopoietic stem cell transplant (HSCT) recipients.

Many viruses are known to cause respiratory tract infections, but the most common in hospitalized cancer patients are influenza viruses, respiratory syncytial virus (RSV), and parainfluenza viruses (PIV) [1, 2]. However, all respiratory viruses can cause respiratory infections in cancer patients including rhinoviruses, enteroviruses, coronaviruses, human metapneumoviruses (hMPVs), adenoviruses, as well as cytomegaloviruses, herpes simplex, and varicella zoster viruses. In this chapter, we discuss the common clinical presentations, diagnostic methods, treatments, and prevention measures for respiratory virus infections in general and in cancer patients in particular (Table 32.1).

Data from September 2008 to February 2010 (18-month period) at our institution (Fig. 32.1) demonstrate the cyclical pattern of the three major respiratory viruses: RSV, influenza, and PIV. During the 2009–2010 season, influenza infections in our cancer patients were reported starting July 2009 with a peak in October 2009 due to the pandemic A (H1N1) influenza virus. More recently, a total of 181 cases of influenza, parainfluenza, and RSV were identified at our institution between 1 September 2009 and 28 February 2010 (Fig. 32.2). Of these cases, most were in HSCT recipients (45%).

Respiratory Syncytial Virus

Most RSV infections occur in infants and young children throughout the world [2, 3]. In the United States, these infections usually occur from late fall to the end of spring, with a peak from January to February; few cases are reported during
RSV infections can present with a wide array of upper or lower respiratory symptoms. The incubation period is 4–6 days in adults. In infants and young children, the primary infection starts in the upper respiratory tract, with rhinorrhea, low-grade fever, and cough; it may progress to lower respiratory infection (LRI) (bronchiolitis or pneumonia), at which stage most patients seek medical attention [3, 6]. It is also likely to involve the sinuses and the middle ear. RSV is known to cause apnea in infants, although the mechanism of this action remains unknown. Older children and adults typically present with upper respiratory tract symptoms, but may also have constitutional symptoms such as fever and malaise [3, 7]. RSV upper respiratory infections (URIs) can also progress to the lower respiratory tract, particularly in institutionalized adults and those with severe combined immunodeficiency, leukemia, HSCT, and in lung transplant recipients [2, 8, 9]. These patients may present with wheezing and shortness of breath, with or without underlying comorbidities or known hyperactive airways. Almost 35% of elderly patients with RSV infections report wheezing [8–11].

Infections in Immunocompromised Patients

Patients with weakened immune systems because of malignancy, chemotherapy, steroid use, HSCT, or solid organ transplantation are at high risk for developing severe illnesses. They also tend to have a longer duration of infection, with a varied presentation [12, 13]. Leukemia patients and solid organ and stem cell transplant recipients are particularly at risk, with the latter being at high risk for pneumonia and death prior to engraftment [11].

Leukemia Patients and HSCT Recipients

RSV infections begin as URI, but progress to LRI in 30–60% of HSCT recipients, leading to respiratory failure with significant morbidity and mortality; some early studies described a mortality rate of 70–100% [14, 15]. In HSCT recipients, the risk factors for progression to LRI
include lymphopenia, older age, stage of malignancy, graft-versus-host disease, and no ribavirin treatment [16–19]. Torres et al. [20] found that a high APACHE II score and not giving aerosolized ribavirin treatment were independent predictors of progression to pneumonia in leukemia patients; those with URI who were treated with aerosolized ribavirin were less likely than untreated patients to develop pneumonia (68 vs. 96%, \( p < 0.01 \)) and die with RSV infection (6 vs. 36%, \( p = 0.1 \)). The overall mortality rate in the study was 10% [20].

**Solid Organ Transplant Recipients**

Solid organ transplantation patients with RSV infection may present with dyspnea, cough, fever, and wheezing which progress to pneumonia in more than 70% of patients [21]. In lung transplant recipients, a higher frequency of RSV pneumonia has been reported, but the mortality rate is low; the mortality rate is also low in kidney transplant recipients [21]. In pediatric liver transplant patients, Pohl et al. reported a mortality rate of 17% for RSV pneumonia with early infection onset and preexisting lung disease as predictors of severe disease [22].

**Other Immunocompromised Patients**

In children, genetic polymorphisms in cytokine and chemokine-related genes (interleukin [IL]-4, IL-8, IL-10, IL-13, and CCR5) and genes related to potential virus-cell surface interactions or cell signaling (TLR-4, CX3CR1, SP-A, and SP-D) have been associated with severe RSV infections [23].

Data on HIV patients with RSV infections are scarce; however, a cohort study by Miller et al. [24] performed in the winter of 1994–1995 found no evidence of influenza, RSV, parainfluenza, adenovirus, or enterovirus infections in the bronchoscopic alveolar lavage fluids of 44 HIV-1-positive patients.

**Diagnosis**

RSV can be diagnosed on the basis of the clinical presentation in infants with LRI during an outbreak period [3]. RSV infections in adults cannot be clinically differentiated from other viral infections that cause upper respiratory symptoms. For a specific diagnosis, RSV must be detected in respiratory secretions. Nasal aspirates or washes are most likely to give a positive RSV test in young children. If a nasal aspirate or wash cannot be obtained, a nasopharyngeal swab or throat swab may be used. Because immunocompromised or intubated patients are more likely to develop an LRI due to RSV, tracheal aspiration or bronchoalveolar lavage should be performed [8, 25]. The gold standard for diagnosing RSV remains the identification of virus causing typical syncytia in cultures of HEp-2 cells [25]. Viral cultures may take 2 days (shell vial cultures) and up to 2 weeks (routine cultures) to become positive, making isolation less relevant in most clinical settings. Other available methods include antigen detection by enzyme-linked immunosorbent assay (ELISA), immunofluorescence assay, and polymerase chain reaction (PCR) tests. Fan et al. [26] reported a sensitivity of 65–95% for RSV detection using rapid antigen testing with ELISA. PCR tests have been shown to be more sensitive than direct antigen detection [27, 28].

**Treatment**

For most immunocompromised patients, RSV treatment is focused on reducing symptom severity and preventing progression to LRIs. Nonsteroidal anti-inflammatory drugs and antihistamines have been used in patients with a URI. Ribavirin, a nucleoside analog, has in vitro activity against RSV and has been approved by the United States Food and Drug Administration for the treatment of RSV infections in children. Two schedules of aerosolized ribavirin have been used in immunocompromised patients: continuous and intermittent. On the continuous schedule, a daily dose of 6 g (concentration, 20 mg/mL) is delivered over 18 h via a small particle aerosol generator unit, administered via a face mask in a tent. On the intermittent schedule, a concentration of 60 mg/mL is delivered over 3 h every 8 h.

Aerosolized ribavirin may be beneficial in certain adults and children with LRIs. Its early use has been shown in some retrospective studies to reduce morbidity and mortality in HSCT recipients [3, 29] and patients with hematologic malignancies, particularly when the infection is treated early on [30]. However, its effectiveness in solid organ transplantation patients remains unknown [31]. An RSV-specific monoclonal antibody (Palivizumab) did not demonstrate a therapeutic benefit in a major study conducted in children [32]. Although the combination of ribavirin and intravenous immunoglobulin (IVIG) or palivizumab has not been evaluated in a randomized trial, it is sometimes used in severely ill patients with RSV pneumonia, especially HSCT recipients, given that they have high mortality rates from this infection [3, 11, 14]. In patients at risk for progression to LRI, aerosolized ribavirin should be considered at an early stage. A recent trial demonstrated that both the intermittent and continuous schedules of aerosolized ribavirin were effective at preventing progression to LRIs in 91% and 80% of patients with RSV URIs and hematologic malignancies (including HSCT recipients), respectively [33].
**Prevention/Vaccination**

RSV infection may be acquired nosocomially, thus specific infection control measures should be implemented when dealing with patients with known or suspected infections. Briefly, patients should be isolated in private rooms when possible, and appropriate personnel protective equipment should be used (i.e., disposable gloves, masks, and gowns) [34]. No licensed vaccine is available for RSV; however, two agents, RSV-IVIG and palivizumab, have been used to prevent RSV infection. RSV-IVIG has been studied in children younger than 24 months with severe lung disease and those who were born prematurely [35], but it was removed from the market in 2003. A randomized double-blind placebo-controlled study in children found that palivizumab recipients had a 45% relative reduction in RSV hospitalizations ($p = 0.003$). Twenty-one children (3.3%) died in the palivizumab group vs. 27 (4.2%) in the placebo group with no deaths attributable to palivizumab [36]. Palivizumab is easier to administer than regular IVIG, which must be given over 4–6 h, and does not interfere with other vaccinations. However, RSV-IVIG and IVIG may provide additional protection against other respiratory viruses as well [35, 37, 38].

**Clinical Presentation**

Influenza typically has a short incubation period and an abrupt onset of symptoms, such as headache, fever, chills, myalgia, and malaise, along with respiratory symptoms of runny nose, cough, and sore throat. It can also present as a febrile URI or with constitutional manifestations only or with few-to-no respiratory symptoms.

Influenza can progress to pneumonia in otherwise healthy persons, but particularly in patients with comorbidities such as lung diseases, heart disease, diabetes mellitus, renal diseases, and hemoglobinopathies, in immunocompromised individuals, residents of nursing homes or chronic care facilities, and in individuals over 65 years of age [41].

Primary pneumonia occurs when the influenza virus directly involves the lung and should be suspected when clinical symptoms progress to high fever, dyspnea, and hypoxemia [42]. Influenza virus infections also affect the epithelium of the tracheobronchial tree, leading to impaired defense and a secondary bacterial pneumonia.

**Influenza Viruses**

Influenza viruses infect both the upper and lower respiratory tracts. Outbreaks are common every winter, although the severity of the disease varies considerably. Influenza viruses belong to the *Orthomyxoviridae* family, with influenza types A, B, and C constituting one genus. These RNA viruses are enveloped and measure about 80–120 nm in diameter. The designation of the viruses into types is based on the stable antigenic characteristics of the nucleoprotein and the matrix protein antigens. Influenza A and B viruses have surface glycoproteins known as hemagglutinins (HA) and neuraminidase (NA). Three hemagglutinin subtypes (H1, H2, and H3) and two neuraminidase subtypes (N1 and N2) have been described for the influenza A viruses that infect humans. Major antigenic changes in the glycoprotein (basis for new subtypes) are called antigenic shift and can cause pandemics; minor antigenic changes occur frequently, are called antigenic drift, and cause the annual epidemics. Influenza B has only exhibited minor antigenic drift [3, 39]. The 2009 pandemic influenza A (H1N1) contains segments present in North American swine for years, but is a new reassortant virus that acquired M and NA gene segments from a Eurasian adamantane-resistant swine influenza virus [40].

**Infections in Immunocompromised Patients**

Influenza infections can increase morbidity and mortality rates in cancer patients [2].

**Leukemia Patients and HSCT Recipients**

In a study of leukemia patients with influenza infections, 39% of patients developed pneumonia [43], with cough and dyspnea being the most common manifestations. Half of the patients had lymphopenia [43]. The incidence of influenza infection in HSCT recipients is reported as 0.4% [44], with a mortality rate up to 38% [43], mainly due to respiratory failure. In one study [44], 17% of patients who developed influenza after HSCT presented with pneumonia; of those who presented with URIs, 14% experienced progression to LRI. Risk factors associated with progression to LRI were lymphopenia and days from transplantation (i.e., pneumonia developed more commonly among those infected earlier after transplantation); whereas use of systemic steroids and autologous stem cell transplantation appeared to be protective. X-ray findings include a diffuse interstitial pattern or focal pulmonary infiltrates [45].
Solid Organ Transplant Patients

Among patients with solid organ transplantation, lung transplant recipients are at the highest risk for influenza virus infection [46]. The initial presentation in these patients may not always be in the respiratory tract, as illness can present with nonspecific gastrointestinal symptoms; however, patients who required hospitalization always presented with pneumonia [47]. Progression to bronchiolitis obliterans, which is a characteristic of chronic lung rejection after infection, was also reported. In patients postrenal transplantation, influenza pneumonia is often acute, with high fever, cough, dyspnea, cyanosis, leukopenia, and thrombocytopenia [48].

Diagnosis

Influenza infection can only be diagnosed clinically in persons exhibiting the classic syndrome during an epidemic. However, because other viruses can produce the same syndrome and influenza infection can produce other respiratory syndromes, a confirmatory test detecting the virus or viral antigens in nasal washes, throat swabs, respiratory tract secretions, or bronchoalveolar lavage specimens is needed in sporadic cases and in immunocompromised patients. Viral culture remains the gold standard for diagnosis, but can take up to 72 h to yield results [49]. Sputum and nasal washes or nose swabs are superior to throat swabs for diagnosis [50]. Rapid antigen testing using immunofluorescence assays, enzyme immunocassays, and PCR-based testing are used frequently in clinical settings [51]. The results of these tests can be obtained in hours and can have good sensitivity (72–95%) and specificity (76–84%) if obtained early from those with more severe illnesses [52]. PCR-based assays are more sensitive than rapid antigen testing for diagnosing influenza A and B, but are not often used because of availability and cost [51]. Samples should be obtained within 24–48 h of the appearance of symptoms for the most accurate results.

Treatment

Two classes of drugs are available to treat influenza infections [53]: the neuraminidase inhibitors, zanamivir and oseltamivir, which are active against influenza A and B viruses; and the M2 inhibitors, amantadine and rimantadine, which are only active against influenza A viruses [54]. Amantadines are not effective against influenza B and resistance has been reported for 2009 novel H1N1 virus; resistance to oseltamivir has increased for the seasonal H1N1 virus (Table 32.2) [55, 56]. Therapy should be initiated as early as possible, preferably within 48 h after symptom onset [57]. Zanamivir and oseltamivir have been used extensively to treat both influenza A and B; both were shown to reduce the mean duration of symptoms by 1 day when used within 48 h of symptom onset [58]. Both neuraminidase inhibitors have been shown to significantly decrease the incidence of complications associated with influenza such as development of pneumonia when compared to placebo [59]. The most common side effects of oseltamivir are nausea and vomiting, although other toxicities have been reported. Central nervous system side effects such as anxiety, insomnia, impaired thinking, confusion, lightheadedness, and hallucinations have been reported with amantadine use. Newer NI inhibitors including parenteral preparations are under development [60].

Prevention/Vaccination

The mainstay of influenza prophylaxis in the general population is the administration of influenza vaccine. Annual vaccination has been recommended for many years for people at high risk for complications, including those older than 65 years, residents of nursing homes or other facilities, adults and children with chronic pulmonary or cardiovascular conditions, adults and children hospitalized during the previous year, women in the second and the third trimesters of pregnancy, immunocompromised patients, healthcare workers, and family member of those at high risk prior to the onset of influenza season [41]. The American Committee on Immunization Practices has recently recommended vaccination for all persons for whom there is no contraindication [61].

Currently, there are two types of vaccines available, an intramuscular (inactivated virus vaccine) and an intranasal (attenuated virus vaccine). The intranasal form is to be used only in healthy individuals between the ages of 2 and 49 years;
it should not be used to vaccinate immunocompromised patients [62]. Individuals with a significant allergy to eggs or those with acute febrile illness should not be given vaccine [63]. The Advisory Committee on Immunization Practices recommends that immunocompromised individuals be vaccinated prior to influenza season and receive daily chemoprophylaxis with an antiviral medication during community outbreaks [41].

Influenza chemoprophylaxis may be used in patients at high risk for complications if the vaccine is contraindicated or not likely to be completely protective. Antiviral drugs should be administered to patients within the first 6 months of HSCT, those with documented graft-versus-host disease, unvaccinated healthcare workers who care for immunocompromised individuals, and residents of long-term care institutions during outbreak periods [64]. The American Society for Blood and Marrow Transplantation (ASBMT) 2009 guidelines [65] for prevention of infection in HSCT recipients recommend annual inactivated influenza vaccine before the beginning of the season and before stem cell transplant. The vaccine may be given 4–6 months after HSCT. They also recommended prophylaxis and preemptive treatment during community and nosocomial outbreaks of influenza A for HSCT recipients regardless of the vaccination status in those who are within 24 months of the transplant or in those with more than 24 months posttransplant, but have GVHD and/or are on immunosuppression. The drug to be used for chemoprophylaxis depends on the susceptibility pattern of the outbreak virus.

Infections in Immunocompromised Patients

Immunocompromised individuals are at risk for a PIV infection that can progress to pneumonia. A study at our institution found a higher rate of progression among leukemia patients than among HSCT recipients [70].

Leukemia Patients and HSCT Recipients

PIV usually presents as an URI. In a large study in HSCT recipients over several years, PIV infections were documented in 7.1% of cases, with 78% being community-acquired [71]. Patients who have undergone HSCT are at particular risk for developing severe PIV-associated pneumonia [71–74]; Wendt et al. [72] reported a mortality rate up to 30%. Coinfections (Aspergillus fumigatus being the most common) and mechanical ventilation were found to be significant risk factors for PIV pneumonia-associated mortality in one study [71]. Other factors associated with progression include neutropenia within 1 month prior to infection, an APACHE II score higher than 15, and pulmonary coinfection; this study also found a mortality rate around 20%, with no difference between those treated and those not treated with aerosolized ribavirin [70].

Solid Organ Transplant Patients

Patients who have undergone solid organ transplantation do not appear to be at increased risk for developing severe PIV illness, but only a few studies have been reported [75, 76]. One of these studies in lung transplant patients found PIV infections in 11% of patients, all of whom developed pneumonia, but the majority (74%) were treated with aerosolized ribavirin and all but one recovered [75].

Diagnosis

Except for croup in young children, the clinical pattern of PIV infection is similar to that of other respiratory viruses and cannot be distinguished on the basis of symptoms alone. During a community outbreak, a presumptive diagnosis can be made; however, confirmation in laboratory tests may be
Respiratory Viruses

appropriate in immunocompromised individuals. The virus can be detected in respiratory tract secretions, nasal washes, nasal swabs, throat swabs, and bronchoalveolar lavage specimens. Viral culture remains the gold standard for diagnosis, but can take days to yield a result [3, 77]. Rapid antigen detection by immunofluorescence or ELISA is most commonly used and can have a sensitivity of as high as 75–95% [78]. Recent PCR-based assays have sensitivities up to 100%, with high specificity [26, 79].

Treatment

Management of PIV infection is mostly supportive as no PIV-directed antiviral therapy has been licensed by the U.S. Food and Drug Administration. Ribavirin has been shown to be active against the virus in vitro and in animal models and has been used occasionally to treat immunocompromised patients with severe PIV infections [80]. One case series reported a decrease in PIV viral loads and clinical improvement after aerosolized ribavirin treatment in children with severe immunodeficiency [81]. Nichols et al. [71] reported that aerosolized ribavirin did not reduce viral shedding or mortality rates in HSCT recipients after the infection had progressed to the lower respiratory tract. Our data also showed no apparent benefit of aerosolized ribavirin on the mortality rate in HSCT recipients and leukemia patients [70]. On the other hand, a combination of methylprednisolone and intravenous or oral ribavirin has, apparently, been used successfully to treat PIV pneumonia in a HSCT and a heart transplant recipient, respectively [82, 83].

Prevention/Vaccination

Currently, no licensed vaccine is available for the prevention of PIV infection. Hence, infection control measures play an important role in containing the spread of the infection. Patients with suspected or confirmed infections should be isolated, and personnel protective equipment should be used.

Adenovirus

Human adenoviruses are DNA viruses belonging to the Mastadenovirus genus of the Adenoviridae family which measure about 70–80 nm in diameter [3, 84]. There are at least 51 known human serotypes divided into subgenera A to F based on the DNA genome and pattern of hemagglutination [84]. Adenovirus infections are reported most frequently in infants and children and can occur throughout the year; however, they may cause serious infections in immunocompromised patients. After a primary infection in childhood, adenoviruses establish latency in adenoidal tissues along with lifelong persistence of specific antibodies [84, 85].

Clinical Presentation

Adenovirus infections are transmitted by either inhalation of aerosolized virus, inoculation of the virus into conjunctival sac, or through the fecal-oral route [3, 84]. Subgroup A, type 31 and various types from subgroups B and C have been associated with pneumonia and hepatitis [86]. Serotypes 4, 7, 14, and 21 are associated with outbreaks of acute respiratory disease in military recruits, mostly in winter and spring [3]. Types 1, 2, 5, and 6 are most common in children and present as an acute upper respiratory tract illness which can progress to lower respiratory disease; types 3 and 7 are less common, but can cause severe disease. In adults, infections due to adenovirus are characterized by sore throat and gradual onset of fever. Cough, coryza, and regional lymphadenopathy are commonly seen. The most common clinical symptoms besides respiratory symptoms are fever and diarrhea [3].

Infections in Immunocompromised Patients

Leukemia Patients and HSCT Recipients

Adenovirus infections are common after HSCT and can occur as a localized illness or as part of a disseminated disease. It has been associated with delayed engraftment and graft failure. Infections due to adenovirus in HSCT recipients have a reported incidence of 0.5–3% [87, 88] and are more commonly reported in allogeneic HSCT recipients than in autologous transplant recipients (6 vs. 0.92%) [87]; however, the mortality rate can be as high as 75% in both groups [87, 89]. Some reports also suggest that the incidence of adenovirus infection in patients after HSCT may be rising due to transplantation practices [90, 91]. Disseminated infection may occur without respiratory tract symptoms and disease can develop in almost any organ causing gastrointestinal disease, hepatitis, nephritis, pneumonia, conjunctivitis, thrombotic thrombocytopenic purpura, pancreatitis, or hemorrhagic cystitis. Viremia may be present, but is not detected in all cases of disseminated disease [92]. Adenovirus is known to be fatal even in the absence of any respiratory tract involvement; however, if pneumonia is present, the mortality has been reported to be higher (80 vs. 50%) [87]. Coinfections with Aspergillus spp. and bacteria such as Nocardia, Legionella spp., and Mycobacterium tuberculosis are frequently seen in this patient population [90, 93]. Risk factors for adenovirus infections include GVHD, unrelated
donor, total body irradiation, T-cell depletion, younger age (<7 years old), chronic disease, and recent transplantation [90, 91, 94, 95]; the degree of T-cell depletion and posttransplant suppression of T-cell function are the most important ones [92]. Adenovirus types 5 and 21 are associated with severe infections in HSCT recipients [95].

Solid Organ Transplant Patients

There are a few reports of adenovirus infections in solid organ transplant patients in whom the virus involved the donor organ and led to pneumonia, hepatitis, hemorrhagic cystitis, nephritis, enterocolitis, or disseminated disease. In patients with previous liver transplantation, adenovirus pneumonia had a reported prevalence of 1.5% with a mortality rate of 66% [96]. Serotype 5 is known to be associated with hepatitis [96, 97], whereas serotypes 1 and 2 are more commonly associated with pneumonia. In lung transplant recipients, one study found adenovirus infection to be an early complication following surgery with a prevalence rate of 1.3% [98]. Progressive adenovirus infections are known to be associated with graft loss, progression to bronchiolitis obliterans, or death [99].

Diagnosis

Adenovirus infection should be suspected in cases of acute respiratory disease in military recruits or during outbreaks. In most cases, infection caused by the virus cannot be differentiated from those caused by other respiratory viruses from the clinical presentation alone [3]. A definitive diagnosis can be established by viral culture or the detection of specific viral antigens.

Viral culture remains the gold standard for identification of adenovirus. Nasopharyngeal aspirate or swab, throat swab, sputum samples, or bronchoalveolar lavage can be used, depending on the site of the infection. A cytopathic effect is seen in human cell lines such as HeLa (cervix), A549 (lung), HEK (human embryonic kidney), and HEP-2 (larynx) by strains of adenovirus except for types 40 and 41. Adenovirus 40 and 41 grow well in HEK 293 cells. Adenovirus-specific Enzyme Immunoassay (ELISA) or immunofluorescence assay can be used to detect the presence of virus in clinical samples. These rapid tests suffer from a sensitivity of only about 50%; PCR-based assays can detect adenovirus DNA from a variety of clinical specimens and has better sensitivity [100, 101]. Viral load quantification is a useful tool to measure prognosis and monitor clinical response [102, 103]. Viral loads higher than 1×10^6 copies/mL have been associated with an increased likelihood of death [104, 105].

Treatment

There have been no randomized clinical trials for the treatment of adenovirus infection in immunocompromised patients. Most patients are managed using symptom-based treatment and supportive therapy. Cidofovir is currently being used in immunocompromised patients since it has been shown to decrease plasma viral loads in HSCT recipients [106]. Although cidofovir is active against all strains of adenovirus in vitro, only retrospective data are available on the efficacy of cidofovir in HSCT [106–109] and solid organ transplant recipients [110]. Nephrotoxicity is commonly encountered with this drug and it should be used with caution. There are two accepted regimens: 5 mg/kg every 1–2 weeks, or 1 mg/kg 3 times per week, with the latter being associated with less nephrotoxicity [110]. Orally active ether lipid-ester prodrugs of cidofovir (S)-HPMPA are under development with some promising results in in vitro experiments and phase I trials [111]. When tested against five adenovirus serotypes, they were shown to be more active than the unmodified parent compounds [111].

Intravenous ribavirin has been used in a few reported cases, but results were conflicting [112–114]. Finally, another treatment option using adenovirus-specific donor T-cells infusion has been shown to be feasible and effective in protecting children from complications due to adenovirus infection and causing a significant decrease in viral loads [115].

Prevention/Vaccination

Currently, there are no vaccines available for adenovirus infection other than the oral partially attenuated vaccines contained in enteric-coated capsules with use restricted to the military [116]. Only routine infection control practices are recommended for civilian populations where special precautions must be taken for contact and droplet exposure. In HSCT recipients at high risk from adenovirus infection, weekly PCR surveillance of viremia and preemptive treatment with cidofovir can be used [92, 117].

Rhinovirus

Rhinoviruses are members of the Picornaviridae family. They are nonenveloped, single-stranded RNA viruses that measure about 15–30 nm. The capsid of the virus is icosahedral and contains 60 copies of four polypeptides each. A canyon on the viral surface contains the attachment site for the host-cell receptor, with most rhinoviruses using this site to attach to the intercellular adhesion molecule-1 receptor expressed on the
surface of host cells [3, 118]. More than 100 serotypes of the virus have been isolated, making a vaccine unlikely in the near future [3, 119, 120].

Rhinoviruses are proven to cause 15–40% of common colds in adults [3]. Each year, adults experience 2 or 3 colds, whereas children may experience 8–12 [3, 120]. Children are the major reservoir for rhinoviruses with infection rates decreasing with age. Although infections occur throughout the year, peaks may occur in the fall and spring. This infection is primarily due to the deposition of the virus on the nasal mucosa. This can occur via self-inoculation or contact with infected secretions such as small- and large-particle aerosols (respiratory droplets) [3, 118, 120].

**Clinical Presentation**

Individuals with rhinovirus infections may be asymptomatic. When symptoms occur, they are typically those of the common cold: most commonly rhinorrhea and sneezing, which are associated with nasal congestion. Infections due to rhinovirus have an incubation period of 1–4 days. Adults characteristically experience sneezing, nasal obstruction and discharge along with cough, and a sore or scratchy throat. Sinuses are commonly involved so that the illness is rhinosinusitis. Symptoms may last for 4–9 days and usually resolve with no complications. Fever is not usually associated with adult illness [3, 121]. Children, on the other hand, may experience fever, cough, and nasal discharge and obstruction. In addition, the duration of symptoms may be longer. Although bronchitis, bronchiolitis, and bronchopneumonia have been reported in children, rhinovirus is not usually a major cause of lower respiratory illness [3, 122]. However, they are an important cause of exacerbations of asthma and chronic obstructive pulmonary disease in children and adults and of LRI in the elderly [3, 119].

**Infections in Immunocompromised Patients**

**Leukemia Patients and HSCT Recipients**

A retrospective study in adults with rhinovirus infections who had undergone HSCT found that 32% of patients developed and eventually died of pneumonia [123]. One patient was found to have a coinfection with *Aspergillus* spp. on autopsy; most of the other patients had interstitial pneumonitis and/or acute respiratory distress syndrome [123]. A study performed at another institution reported that 55% of HSCT recipients with rhinovirus infections developed pneumonia and 33% died [124].

**Other Immunocompromised Patients**

In a study of community-acquired pneumonia in immunocompromised patients (after HSCT or solid organ transplantation, with HIV infection, or receiving steroids or chemotherapy), rhinovirus was responsible for about 12% of cases, with a mortality rate of 18% [125]. These findings suggest that rhinovirus may cause more severe complications in immunocompromised patients than previously thought.

**Diagnosis**

Many viruses cause common cold symptoms, and a definitive diagnosis cannot be made only on the basis of the presenting symptoms but rhinoviruses are most commonly associated with colds. A definitive diagnosis can be made by isolating the virus from nasal washes or other nasal secretion specimens in tissue culture. Newer diagnostic methods such as real-time reverse-transcription PCR (RT-PCR) have been used; however, these tests are not frequently performed given the self-limited nature of most infections.

**Treatment**

No specific antiviral treatment is available for rhinovirus infections. Most cases are managed with supportive care using antihistamines, decongestants, and nonsteroidal anti-inflammatory drugs.

**Prevention**

Given the number of rhinovirus serotypes known to cause infection, an effective vaccine is unlikely to be developed in the near future. Infection control measures such as hand washing and isolating patients who are known or suspected to have rhinovirus infections can help contain the spread of the virus.

**Human Metapneumovirus**

hMPV belongs to the subfamily *Pneumovirinae* of the *Paramyxoviridae* family. The virus was discovered in 2001 and is genetically similar to RSV. hMPV is an enveloped RNA virus that is known to cause URIs and LRIs in all age groups [126]. Although hMPV infections are more common in children, a recent study revealed an infection rate of 4.5% in adults with acute upper respiratory illness; 11% of patients required hospitalization [127].
Clinical Presentation

hMPV usually causes a mild infection of short duration (about 3–5 days) and is self-limiting. The incubation period is 4–6 days [128]. The most common presenting symptoms in adults are cough, nasal congestion, rhinorrhea, dyspnea, hoarseness, and wheezing [127]. Children often present with cough, rhinitis, fever, and wheezing [129, 130].

Infections in Immunocompromised Patients

A recent study of patients with hematologic malignancies revealed a 9% incidence of hMPV infection. Nine of the 22 patients who had undergone HSCT had pneumonia; three of these patients died [131]. Another study in HSCT recipients detected the presence of hMPV in 3% (in 5 out of 163) of bronchoalveolar lavage specimens. These 5 patients presented with fever, cough, nasal congestion, and sore throat within the first 40 days after transplantation. The infection progressed to respiratory failure, pulmonary hemorrhage, and culture-negative septic shock. The mortality rate was 80% (4 of 5 patients) [132].

Diagnosis

hMPV’s growth in culture is slow and unreliable, which makes this method of diagnosis impractical. The presenting symptoms are similar to those of other infections that cause an acute respiratory illness, making clinical diagnosis impossible. PCR-based methods have been used to diagnose the infection in some centers.

Treatment

No specific antiviral therapy exists for hMPV infections. In vitro studies have demonstrated that ribavirin has activity against the virus [133]; however, no clinical studies have been reported. Immune serum globulins may neutralize the virus as demonstrated in one in vitro study [133]. Anecdotally, a lung transplant recipient with respiratory failure secondary to hMPV pneumonia was treated successfully with aerosolized ribavirin [134].

Prevention

The use of general preventive measures for patients with known or suspected hMPV infections can help reduce the rate of transmission. No vaccine is currently available for this virus.

Coronavirus

Coronaviruses are single-stranded RNA viruses that measure about 80–160 nm in diameter. They are enveloped with club-shaped projections, giving them a crown-like appearance – hence the name [3, 135]. Coronaviruses can cause diarrhea in infants and may play a role in demyelinating diseases of the central nervous system [3, 136]. Coronaviruses are difficult to grow in vitro; some strains can only be grown in human tracheal organ cultures. The major antigenic types that cause diseases in humans are 229E, OC43, HK, and NL63 viruses which cause common colds and may also cause lower respiratory tract illnesses in young children, and SARS-CoV, which causes a severe acute respiratory syndrome [3, 137, 138].

Coronaviruses are found in all tropical, subtropical, and temperate climates. Most infections occur in the late fall, winter, and early spring [3, 139]. Cyclical outbreaks of these infections may occur every 2–4 years. Respiratory infections due to HCoV-229E and HCoV-OC43 strains probably spread in a manner similar to rhinovirus, i.e., via direct contact with infected secretions or aerosol droplets [3].

Clinical Presentation

The clinical manifestations of coronavirus infections are similar to those of rhinovirus infections. The most common symptoms are rhinorrhea, throat congestion, and fever. The middle ear may also be affected, leading to effusions and acute otitis media, especially in children [3, 135]. The incubation period is 1–3 days and the duration of the illness is shorter than that of rhinovirus infections, a mean of 6–7 days. The subtype SARS-CoV has a slightly longer incubation period of 4–5 days.

Infections in Immunocompromised Patients

In immunocompromised adults, coronaviruses can cause lower respiratory tract infections [3, 140]. A recent case series found that the infection rate among immunocompromised patients was significantly higher when compared to immunocompetent patients (8.8 vs. 4.5%) [141]. No large studies have been conducted in cancer patients or other immunocompromised individuals, but a few cases have been reported. Folz and Elkordy [140] reported a patient who had undergone autologous HSCT and was diagnosed with a coronavirus LRI. The patient developed a fever, sore throat, cough, and severe hypoxia and was treated successfully using supportive measures. Kumar et al. [142] described a patient who developed a fatal severe acute respiratory syndrome (SARS) after liver transplantation.
Diagnosis

Epidemiologically, these infections should be suspected during the late fall or winter or during an outbreak. However, no practical method is available to confirm the infection except PCR-based tests. These are used to diagnose coronavirus infections at some institutions [3, 143].

Treatment

Similar to rhinovirus, no specific antiviral therapy is available for coronavirus. Most patients respond well to supportive treatment with nonsteroidal anti-inflammatory drugs, decongestants and antihistamines.

Prevention

General preventive measures must be used around patients with coronavirus infections; hand washing, disposing of infected material carefully, and proper disinfection can help prevent the spread of the virus. No vaccine against the virus has been developed.

Enterovirus

Enteroviruses are single-stranded RNA viruses that can multiply in the gastrointestinal tract. They belong to the Picornaviridae family, but are relatively stable at a low pH. The virus is surrounded by an icosahedral capsid comprising four viral proteins. It has no lipid envelope and is not susceptible to alcohol, ether, or detergents. Poliovirus is the prototype of this group, but nonpolio enteroviruses have a wide spectrum of manifestations including acute respiratory illnesses [3, 144].

Enterovirus infections are more common in developing countries and socioeconomically depressed areas and are associated with poor hygiene and sanitation. They can occur throughout the year, but the peak occurs in the summer and fall [3, 145]. They can be transmitted by direct contact with feces during activities such as cleaning and diaper handling.

Clinical Presentation

The clinical picture of enterovirus infections is similar to that of rhinovirus infections; no specific symptoms are associated with the virus.

Infections in Immunocompromised Patients

Immunocompromised patients have been reported to develop central nervous system infections, chronic disseminated infections, and a dermatomyositis-like syndrome with enterovirus infection. In a study of respiratory tract infections in hematologic malignancy patients, 3% of patients had enterovirus infections; most (66%) were HSCT recipients with 33% of these developing pneumonia [131]. A study from Spain reported on four HSCT recipients who developed enterovirus infections, with a mortality rate of 75% (3 of 4) [146]. These findings demonstrate that immunocompromised patients may be at risk for lower respiratory tract infections and death from an enterovirus infection [3, 131, 146].

Diagnosis

Most enteroviruses can be isolated in cell cultures from nasopharyngeal or throat swabs. PCR-based testing is used to amplify the viral RNA from throat swabs, cerebrospinal fluid, and tissues. For diagnosis, isolation of the virus from the throat is more clinically significant than from stool because this virus has a shorter duration of shedding from the throat.

Treatment

Most enterovirus infections are self-limiting and do not require specific treatment. Intensive care may be required for central nervous system, cardiac, and hepatic infections. IVIGs have been used in some patients with severe infections, but no specific antiviral therapies are available [3, 147].

Prevention

General infection control measures must be undertaken around patients with enterovirus infections. Special attention must be paid to hand hygiene. Material in contact with or soiled by feces should be handled carefully and discarded with proper precautions.

Summary Comments

The respiratory viruses as a group are the most common cause of an acute infectious illness in developed societies. The variety of viruses that can cause infection and illness in all age groups and their presence in high frequencies throughout the year describe the risk of exposure of all persons at all
times including immunocompromised persons residing in the community. The immunocompromised state of many cancer patients constitutes the basis for the frequent failure of the host to promote a normal and rapid recovery from an acute respiratory viral infection and results in a more severe and prolonged infection that causes significant morbidity and mortality in these patients. Those respiratory viruses that are most prevalent and most prone to produce lower respiratory illnesses and pneumonia in healthy hosts, RSV, influenza viruses and PIV, are those most likely to cause severe illness and pneumonia leading to hospitalization in immunocompromised persons. However, viruses less prone to produce a lower respiratory illness but that are highly prevalent, such as rhinoviruses, may frequently be associated with severe illness. Although not generally considered respiratory viruses, the Herpes viruses are known to produce respiratory infection and disease, sometimes severe, in immunocompromised patients (Table 32.1). A historically important virus, measles virus, is now rarely encountered because of widespread vaccination.

The limited availability of antivirals and vaccines for the acute respiratory viruses means that these infections will continue to be important for many years and dictate a need for utilizing infection control procedures as much as possible, particularly in hospitals and institutions, so as to minimize spread. Efforts to develop specific vaccines are important as their use could prevent as well as reduce exposure of cancer patients to these viruses. Development of specific antivirals is important for use in immunocompromised patients as normal recovery mechanisms may be seriously impaired.

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