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Viral Pneumonias Other Than Cytomegalovirus in Transplant Recipients

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Community-acquired respiratory viruses (CARVs) are frequent causes of upper respiratory infection (URI) in adult and pediatric populations, usually occurring in seasonal outbreaks. In healthy outpatients, the morbidity caused by these infections is minimal, because progression to lower respiratory tract infection (LRTI) is rare, and most infections are self-limited in duration.

Although case reports of viral pneumonia complicating hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT) have been described for decades, it is only in recent years that larger case series and therapeutic trials have been conducted and reported, providing greater insight into the impact of CARV on these immunosuppressed hosts. After some general observations about CARV infections, this article focuses on this important recent literature and specifically on the four most common pathogens, respiratory syncytial virus (RSV), influenza virus, parainfluenza virus (PIV), and adenovirus. It concludes by briefly touching on several less commonly reported causes of viral pneumonia, including some potentially important emerging pathogens.

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General observations

Epidemiology

Although dozens of published studies have described the epidemiology of some or all of the CARVs, their findings are often widely disparate. This differences in part result from the nature of the diseases, because both their seasonality and relative frequencies may vary depending on the climate of the reporting institutions. Similarly, studies that track only a single year's incidence of the CARVs may over- or underestimate the general relative frequency of the pathogens based on a particularly widespread epidemic of a single viral pathogen, as might be seen in a year with an especially widespread influenza epidemic. Table 1 reviews the relative frequencies of the CARVs in several recent reports. Depending on the center and the year, RSV, PIV, or influenza has been the most common pathogen, whereas adenovirus generally accounts for fewer than 10% of CARV infections [1–8]. Finally, studies that include children may report higher rates of CARV infections than those focusing on adult populations, probably reflecting in part the higher carriage of CARVs in children.

Most commonly, investigators have employed two major strategies to gain an understanding of the general epidemiology of respiratory virus infections. In the first, consecutive tranplant recipients have been screened at regular intervals, usually in the first 6 to 18 months after transplantation, regardless of symptomatology. Results of such studies have shown overall incidence rates of CARV infection in HSCT

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Table 1
Frequency of respiratory viruses in recent published case series

Reference	No. of patients	No. of culture-positive episodes	RSV[a] (%)	PIV[a] (%)	Flu[a] (%)	Adeno[a] (%)	Other[a] (%)
Ljungman [1]	545 HSCT	39	21	21	38	21	0
Raboni [2]	722 HSCT	62	48	11	37	3	0
Hassan [3]	626 HSCT	29	27	13	17	0	37 Rhino 7 Entero
Machado [4]	179 HSCT	68	33	15	52	0	0
Chakrabarti [5]	89 HSCT	25	37	49	14	0	0
Roghmann [7]	62 HSCT	22	46	21	21	0	13
Lujan-Zilbermann [6]	281 HSCT	32	14	47	17	19	0
Khalifah [8]	259 lung transplant	21	38	33	19	10	0

Abbreviations: Adeno, adenovirus; Entero, enterovirus; Flu, influenza virus; HSCT, hematologic stem cell transplant; PIV, parainfluenza virus; Rhino, rhinovirus; RSV, respiratory syncytial virus.

[a] Percentages are percent of all isolates; may not add to 100 because of rounding.

recipients ranging from 11% to 65% [5–7,9]. In contrast, a recent prospective surveillance study in SOT recipients showed only a 4% incidence of CARV in adult liver transplant recipients during the first 12 weeks after transplantation, although interpretation of this study is limited by the investigators' use of throat swabs alone to detect CARV infection [10]. More frequently published are large retrospective case series of CARV infections. Because these series do not include patients who had asymptomatic infection, overall reported rates of CARV infection are predictably lower, ranging from 4% to 27% in HSCT recipients [1–3,11] to 8% to 21% in lung transplant recipients [8,12,13]. Although these larger reported series represent the best estimates of the CARV disease burden in the general transplant population, it is important to remember that the reports are biased by the seasonal occurrence of CARV in both nosocomial and community settings and the potentially devastating impact of these infections on HSCT and SOT patients [14].

Diagnosis

A major limiting factor in the understanding of CARV infection has been the limited sensitivity of what currently are the most widely used diagnostic tests. In three patient series involving more than 1500 episodes of symptomatic URI in HSCT recipients [2,4,11], fewer than half the patients had a virus isolated from clinical specimens. Most studies (and clinical centers) use a combination of direct (DFA) or indirect (IFA) fluorescent antibody testing and viral culture. Results of fluorescent antibody testing are typically available in about 24 hours, but viral culture may not be positive for 7 to 14 days. In children, these tests are often performed on samples from nasopharyngeal lavage. In adults, swabs from the nasopharynx or throat often are substituted. Whereas the DFA or IFA tests may have a sensitivity of up to 90% for CARV infection in immunocompetent hosts, two studies comparing IFA and viral culture in HSCT recipients have shown a composite IFA sensitivity of 52% [2–4,11,15]. Palmer and colleagues [16] reported a DFA sensitivity of 20% in their series of lung tranplant recipients who had CARV infections. Both fluorescent antibody testing and viral culture probably have higher yields when the sample is obtained from the lower respiratory tract. In one recent study, two thirds of CARV diagnoses were made from bronchoalveolar lavage (BAL) samples [17]. Recently, two series have used real-time polymerase chain reaction (PCR) assays to test for CARV infections in HSCT recipients [9,15]. In one series of 72 adult HSCT recipients being monitored with routine nasal and throat swabs over a 6-month period, real-time PCR was positive in 33 patients, whereas viral culture was positive in only 11 [9]. Many of the additional positive tests were asymptomatic patients who had rhinovirus infection. Bredius and colleagues [15] tested 39 children with symptomatic respiratory tract infection; IFA was positive in 5; viral culture was positive in 10; and real-time PCR was positive in 13.

Viruses, perhaps especially PIV, are often copathogens with other bacterial or fungal infections [18,19]. Infection with both a CARV and cytomegalovirus, *Aspergillus* species, or *Pneumocystis jiroveci* have been described in up to 53% of CARV pneumonias [18,19]. Conversely, because providers may halt a diagnostic work-up after isolation of a single bacterial or fungal pathogen, it is not known how often infection with these more traditionally oppor-

tunistic pathogens is complicated by coinfection with a CARV.

Outcomes

The overall reported mortality from CARV infection has varied widely in published series. Probably no mortality is associated directly with CARV infection limited to the upper respiratory tract. In older case series of predominantly hospitalized HSCT or SOT recipients who had LRTI, mortality was frequently greater than 50% [1]. It can be difficult to compare some series based on varying definitions of LRTI: in some series, a positive chest radiograph is required to define LRTI or pneumonia, whereas in others series physical examination findings (eg, rales, hypoxia) consistent with lower tract disease have sufficed.

Most recent series in HSCT recipients have included more outpatients who have URI and have shown much lower mortality, ranging from 2% to 18% [4,6,11,20]. Raboni and colleagues [2] in Brazil reported 37% mortality from CARV infection in a cohort of patients. Many of these patients had received allogeneic bone marrow transplants within the previous year. Fewer case series exist in SOT recipients. Palmer and colleagues [16] reported 20% mortality in their series of CARV in lung transplant recipients , but case series in renal and liver transplant recipients showed no mortality from the infection [10,17].

Of particular recent interest has been the possible link between CARV infection and the development of chronic rejection in lung transplant recipients. This link is supported by a mouse model in which PIV infection aggravated chronic rejection of lung allografts [13]. Epidemiologically, the possibility that CARV infection contributes to chronic lung transplant rejection manifesting as bronchiolitis obliterans syndrome (BOS) has been supported by the observation that BOS may have a seasonal pattern of onset [17]. This observation has not been true in all studies, however [13]. Although BOS occurs in up to 60% to 80% of lung transplant recipients after 5 years [21], the overall incidence rates for each of the four most commonly reported CARVs generally have not exceeded 5% in lung transplant cohorts [8,13, 21–23]. As noted previously, this percentage may reflect a limitation in current diagnostics rather than a lower incidence of these infections.

CARV infection may produce wheezing and bronchospasm in immunocompetent adults, so it is not surprising that case series of CARV infections in lung transplant recipients report a decline in performance on pulmonary function tests during the acute illness [22,24]. In two reports that have followed serial pulmonary function tests for several months after CARV infection, there have been no significant changes in the pulmonary function testing after a few months' follow-up [24,25], although one investigator reported impairment of pulmonary function persisting beyond 90 days in 21% of patients [25]. Three reports demonstrated marked variability in rates of acute rejection at the time of CARV infection. Vilchez and colleagues [23] reported allograft rejection in 18 (82%) of 22 patients who had PIV infection, whereas two other series reported acute rejection in 0 (0%) of 11 and 1 (7%) of 14 patients, respectively, at the time of CARV infection [24,25]. Further study is needed to clarify this important disparity.

Two larger series specifically designed to investigate the link between any CARV infection and BOS bear closer analysis. Khalifah and colleagues [8] followed 259 adult lung transplant recipients prospectively and identified 21 CARV infections. Nearly all were lower respiratory infections found on bronchoscopy performed either for surveillance or in response to a new clinical syndrome. Patients who had any history of CARV infection in this cohort were more likely to develop severe BOS (38% versus 14%), to die from BOS (29% versus 9%), or to die from any cause (43% versus 23%) than were patients who had no history of CARV infection [8]. Additionally, the authors note that of eight patients who had RSV infection, three who were treated with antiviral agents did not develop BOS, whereas four of five patients not treated with antiviral agents did develop BOX. Billings and colleagues [13] followed 219 adult lung transplant recipients and found 40 CARV infections in 33 patients over an 11-year follow-up period. Again, the majority of identified CARV infections in this series were LRTI, and many were identified from bronchoscopy specimens when bronchoscopy was performed for surveillance or follow-up of treatment for rejection. In this series, CARV LRTI was found to be predictive of severe (grade 3) BOS, but not of moderate (grade 2) BOS. The authors noted that BOS was clearly a risk factor for CARV [13]. It is possible that the chronic rejection facilitates colonization, infection, or progression to LRTI by CARVs. It is also probable; however, that patients who have BOS undergo more frequent bronchoscopy, making it more likely that CARV infection will be identified. Taken together, the reports from Khalifah [8] and Billings [13] strongly suggest an association between CARV infection and BOS. The significance and directionality of this association remain to be determined.

Respiratory syncytial virus

Epidemiology

RSV occurs annually in late autumn or winter outbreaks in the general population, with a low level of persistent year-round activity. These same seasonal patterns have been found in HSCT recipients [26,27]. Like most CARVs, RSV affects children more than adults, and this observation has been confirmed in single-center analyses where adult and pediatric HSCT programs coexist [28]. The epidemic nature of RSV infections must be stressed, because these outbreaks have been responsible for significant morbidity and mortality [14]. Several important factors may contribute to RSV outbreaks among HSCT or SOT recipients. On inpatient units, HSCT or SOT recipients tend to be housed on dedicated wards, thus exposing them to each other and also to a common group of hospital staff and care providers. In fall or winter seasons, 15% to 20% of these providers may shed RSV asymptomatically, and that number may increase to 50% during community outbreaks [29]. Additionally, HSCT or SOT recipients are more likely than immunocompetent patients to have prolonged shedding of RSV, thus introducing the potential for a single index case to infect many other patients [10,29,30]. Together, these factors may explain why multiple reported series of RSV infection note that more than 50% of cases were nosocomially acquired [27,30,31].

Among HSCT and SOT recipients, RSV is the most commonly reported CARV in most series (see Table 1). Large series of RSV infection have been reported in recipients of allogeneic HSCT [28,32–34], autologous HSCT [28,31], liver transplants [12], and lung transplants [12,21], in addition to case reports or small series from nearly all other transplant types. It is difficult, however, to compare the incidences reported in these trials directly, because study designs include longitudinal studies, single-year surveys, and prospective surveillance data. McCarthy and colleagues [32] reported a cumulative RSV incidence of 6.3% in allogeneic HSCT recipients over a 5-year period. Small and colleagues [28] reviewed consecutive HSCT recipients over a 6-year period and demonstrated an incidence of 8.8% in allogeneic HSCT recipients as compared with 1.5% in autologous HSCT recipients. Other reports have confirmed this higher rate in allogeneic HSCT recipients, including a multicenter European study that showed a single-year incidence of symptomatic RSV of 3.5% in recipients of allogeneic HSCT and of 0.4% in autologous HSCT recipients [34]. Longitudinal studies of pediatric liver transplant recipients and adult lung transplant recipients showed incidence rates similar to the longitudinal studies, at 3.4% and 5% to 10%, respectively [12,21].

Clinical features and diagnosis

RSV infection begins in the upper respiratory tract, with cough present in 87% to 100% of immunocompromised patients [35]. Most patients also report rhinorrhea or sinus congestion, and nearly half report subjective wheezing [35]. Although fever may be present in most immunocompromised patients, the prevalence of fever in HSCT and SOT recipients has not been well clarified; in one series, only 35% of patients who had RSV LRTI were febrile [25].

Morbidity and mortality from RSV are directly attributable to progression of the infection to pneumonia. Although bacterial infection may occur coincidentally with other CARV infections, it is not seen frequently with RSV in HSCT or SOT recipients [36]. Many recent series have documented that about 50% of patients who have RSV infection develop pneumonia; some present with pneumonia, and others develop pneumonia after initial presentation with URI (Table 2). Nearly all patients who present with pneumonia give a history of several days of antecedent URI symptoms. Once the infection progresses to pneumonia, mortality rates are high. The results of several recent reports are presented in Table 2 and show that 66 (41%) of 161 HSCT recipients who had RSV pneumonia died [1,4–6,11,27,28,32,34,37,38].

Diagnosis of RSV infection at most centers is done primarily by fluorescent antibody testing because of the wide availability of the tests (IFA or DFA) and the rapid turnaround time. In immunocompetent hosts, DFA or IFA for RSV may be up to 90% sensitive, whereas culture is only 33% to 67% sensitive [35]. Englund and colleagues [39], however, reported concerning data in immunocompromised adults who had hematologic malignancies, in whom DFA testing on specimens from throat swabs and nasopharyngeal washing had a sensitivity of only 15%. When applied to specimens from BAL, the DFA was 70% to 90% sensitive [39]. These results parallel those reported by Billings and colleagues [17], in which 67% of RSV diagnoses were made from BAL samples. The poor yield of DFA on easily obtained samples highlights the need for newer diagnostic tests or strategies. Preliminary data suggest that real-time PCR may have a sensitivity of greater than 90% for RSV infection [35]. There are no large series employing this diagnostic modality, however.

Table 2
Outcomes of respiratory syncytial virus infection in case series of hematopoietic stem cell transplant recipients published from 1997 to 2003

Reference	No. of cases	No. LRTI (%)	No. of deaths in LRTI (% of LRTI)	Treatment?
Ljungman [34]	46	27 (59)	11 (41)	No
Abdallah [27]	8	4 (50)	2 (50)	No
McCarthy [32]	26	15 (58)	5 (33)	No
Bowden [37]	88	35 (40)	24 (69)	No
Machado [4]	18	10 (55)	1 (10)	Yes
Small [28]	58	25 (43)	3 (12)	Yes, in majority
Whimbey [11]	33	20 (61)	12 (60)	No
Lujan-Zilbermann [6]	5	0 (0)	0 (0)	No
Ljungman [1]	19	15 (79)	6 (40)	No
Chakrabarti [5]	13	6 (46)	0 (0)	Yes
Sparrelid [38]	6	4 (67)	2 (50)	Yes
Total not treated	**225**	**116 (52)**	**60 (52)**	**No**
Total treated	**95**	**45 (47)**	**6 (13)**	**Yes**
Total	**320**	**161 (50)**	**66 (41)**	**[Mixed]**

Abbreviation: LRTI, lower respiratory tract infection.

As with other PCR testing, there may be issues with false-positive tests (in this case, defined as a positive PCR for RSV when RSV is not the true cause of the patient's symptomatology), and the definition of an appropriate criterion standard test may prove difficult in future studies. One recent series used real-time PCR on all samples, and found four cases of RSV, three of which were missed by viral culture and were found only by real-time PCR [7]. Serology has a reported sensitivity of up to 80% but is not commercially available [35].

Treatment

Ribavirin, a synthetic guanosine analogue, is an antiviral agent with activity against RSV. Its exact role in the treatment of HSCT or SOT recipients who have RSV infection remains unclear, however. Dozens of studies using ribavirin in various forms—intravenous, oral, or aerosolized—and at different points in the illness now have been reported. Although generalization of so many studies is difficult, the preponderance of data suggests a benefit to ribavirin therapy, which may be augmented by the addition of nonspecific or RSV-specific intravenous immune globulin. This benefit has been demonstrated best in trials using aerosolized ribavirin, in contrast with decidedly mixed evidence for oral or intravenous ribavirin. This combination therapy is now endorsed in several sets of consensus guidelines [40,41], although most of the data on which this recommendation is made are from experience in treatment of HSCT recipients. The reader is referred to the excellent review by Englund and colleagues [36] for a detailed summary of 17 years of ribavirin trials for RSV infection through 1996.

Despite the recommendations in favor of ribavirin therapy for RSV, the patient population that might benefit most from the therapy has not been identified definitively. As noted previously, morbidity and mortality from RSV are linked to progression of infection to the lower respiratory tract. Several investigators, therefore, have sought to use ribavirin-based therapy for the treatment of documented RSV URI. Recent series by Ghosh and colleagues [42] and Small and colleagues [28] have demonstrated low rates of progression to pneumonia in HSCT recipients who had RSV URI and who received early therapy with ribavirin and intravenous immune globulin. Antiviral treatment of RSV URI is specifically not recommended by the American Society of Transplantation, however [40]. In the Ghosh [42] and Small [28] series, those patients progressing to pneumonia while receiving therapy also had low mortality rates in comparison with historical controls. Interestingly, the benefit of therapy for established pneumonia, which is recommended in the guidelines, has not been as clear in the literature [40]. Mortality rates in SOT or HSCT recipients who had respiratory failure caused by RSV pneumonia have been estimated at 90%, however [36], and at least one consensus group does not favor treatment at that late stage [41].

It is important to highlight the potential difficulties of administering aerosolized ribavirin, which requires a small-particle nebulizer machine that may not be present in all hospitals. In addition, ribavirin is tera-

togenic, so pregnant women may not enter the room of a patient receiving the therapy. Those who do enter the room (including the patient) may develop a number of bothersome side effects from exposure to the drug, including headache, rash, and conjunctivitis [41]. These potential barriers to drug delivery are best addressed in advance if a provider group wishes to ensure timely administration of the drug when a patient is identified.

Parainfluenza virus

Epidemiology

PIV and RSV are both members of the paramyxovirus family, but, unlike RSV, there are four major serotypes of PIV that cause disease in humans. PIV-1 and PIV-2 cause annual winter outbreaks in a pattern similar to RSV or influenza, whereas PIV-3 circulates in low levels year-round, with epidemic spread frequently seen in the spring or summer [19]. PIV-1 and PIV-2 are the classic causes of childhood croup, whereas PIV-3 is more associated with adult disease and with LRTI or pneumonia. The epidemiology of PIV-4 is not clearly defined, because it is the least commonly isolated serotype. As in the case of RSV, epidemics of PIV are frequently reported both in the community and in dedicated HSCT units and have been the cause of significant morbidity and mortality [14,43]. Data on factors contributing to epidemics in these settings are limited; one series reported PIV shedding for 4 months in two HSCT recipients [18].

PIV infections account for 10% to 50% of CARV infections in recent case series of HSCT and SOT recipients (see Table 1) [1–8]. Two excellent longitudinal surveys of PIV infection in HSCT recipients were published in 2001 [18,19]. Nichols and colleagues [19] at the Fred Hutchinson Cancer Research Center reviewed 3577 HSCT recipients who received transplants between 1990 and 1999 and found 253 (7.1%) PIV infections. Of these, PIV-3 accounted for 90%, PIV-1 for 6%, and PIV-2 for 4%. Elizaga and colleagues [18] in London similarly reviewed 456 HSCT recipients from 1990 to 1996 and found 24 (5.3%) with PIV-3 infection. Unlike most reports of RSV in HSCT recipients, PIV was found with similar frequency in recipients of allogeneic (5.2%) and autologous (5.5%) HSCT [18]. Among SOT recipients, case series of PIV have been reported in renal transplant [17] and lung transplant recipients [21–23]. Between 1.6% and 11.9% of lung transplant recipients may develop PIV infection, although some may be asymptomatic infections detected during frequent bronchoscopies [22]. In lung transplant recipients, PIV-3 accounted for 63% of PIV isolates, PIV-1 for 29%, and PIV-2 for 8% [23].

Clinical features and diagnosis

Cough is the hallmark symptom of PIV infection, but other URI symptoms (eg, rhinorrhea) may be absent. Fever is uncommon: in lung transplant recipients who have PIV LRTI, only 17% to 35% are febrile [23,25].

The frequency of LRTI in recent series of PIV infection in HSCT recipients is reviewed in Table 3 [1,5,11,18–20,37,38,43]. Overall, LRTI (as either the presenting syndrome or as progression from URI) is reported in one third of patients, and half of those with LRTI die, but considerable variability exists among series. Of patients in series with at least 10 cases of PIV infection, rates of LRTI vary from 18% to 77%, and mortality among patients who have LRTI varies from 15% to 73%. Importantly, both large reviews of PIV infection in HSCT recipients demon-

Table 3
Outcomes of parainfluenza virus infection in case series of hematopoietic stem cell transplant recipients published from 1997 to 2003

Reference	No. of cases	No. LRTI (%)	No. of deaths in LRTI (% of LRTI)
Nichols [19]	253	56 (22)	41 (73)
Elizaga [18]	24	14 (58)	8 (57)
Chakrabarti [5]	17	13 (76)	2 (15)
Whimbey [11]	45	26 (58)	10 (38)
Ljungman [1]	13	10 (77)	2 (20)
Sparrelid [38]	3	3 (100)	0 (0)
Chakrabarti [20]	5	4 (80)	0 (0)
Hohenthal [43]	5	2 (40)	0 (0)
Bowden [37]	38	7 (18)	4 (57)
Total	403	135 (33)	67 (50)

Abbreviation: LRTI, lower respiratory tract infection.

strated a 50% rate of bacterial or fungal coinfection in patients who have PIV pneumonia, emphasizing the need for comprehensive diagnostic testing in this population [18,19].

The diagnosis of PIV infection usually is made with IFA or DFA testing of respiratory secretions, along with viral culture. It is notable that most widely available fluorescent antibody tests for PIV do not test for PIV-4, which may explain in part why there has been only one reported case in an HSCT recipient [44]. Although real-time PCR testing is being developed, there are not yet sufficient data to permit comment on its relative usefulness in comparison with conventional testing.

Treatment

Ribavirin has activity against PIV, and a number of smaller recent reports in which ribavirin was given to all HSCT recipients who had PIV have demonstrated LRTI and mortality rates lower than historical controls [5,20,25,38,43]. The two largest series, however, demonstrated no benefit of ribavirin given alone or in combination with intravenous immune globulin [18,19]. Furthermore, Nichols and colleagues [19] demonstrated a failure of ribavirin therapy to shorten duration of shedding time. A recent consensus statement from the Infectious Disease Community of Practice of the American Society of Transplantation recommends for PIV LRTI that providers ''consider aerosolized ribavirin as no other options exist but experience to date provides little evidence for efficacy'' [40].

Influenza virus

Epidemiology

Influenza, an orthomyxovirus, is one of the most common community-acquired respiratory viruses and is a significant cause of morbidity in transplant recipients. The actual incidence of influenza in transplant recipients is unknown; many cases are likely undiagnosed, and case reports of influenza illness probably overestimate the severity of illness in this population. Although most cases of influenza are acquired in community settings, nosocomial acquisition has been noted in both SOT and HSCT units. Because nosocomial acquisition often is associated with earlier acquisition after transplantation, these cases are more likely to result in worse outcomes.

Influenza occurs on a seasonal basis, with the vast majority of cases occurring during winter months. Both influenza A and B have been described in transplant recipients; the distribution of these infections mirrors community patterns of infection. Influenza virus has been reported to be a significant pathogen in both HSCT and SOT recipients; among SOT recipients, lung transplant recipients may be at special risk for infection [45,46]. Transplant recipients have been documented to have persistent influenza viral shedding, serving as a potentially significant reservoir of virus that can spread to others in both community and institutional settings [47,48].

Clinical features and diagnosis

The timing of influenza infection with respect to transplantation significantly affects the outcome of infection, with more severe infection occurring in the earlier posttransplantation period. In most cases, upper respiratory tract symptoms predominate. Lower respiratory tract involvement is uncommon. Other complications of influenza include bacterial superinfection, central nervous system involvement, myocarditis, and transplant rejection [49,50]. Influenza mortality remains low.

Influenza should be suspected in any individual presenting with fever, rhinorrhea, coryza, myalgia, and headache during the winter months. Diagnosis of influenza typically relies on isolation of the virus, either by fluorescent antibody techniques (DFA or IFA) or by viral culture of nasal and oropharyngeal epithelial cell samples obtained by nasal lavage (in pediatric patients) or swab sampling [40,51]. Alternatively, BAL specimens can be assayed. Serologic diagnoses are retrospective and may be limited by impairment of humoral responses in recent HSCT recipients or SOT recipients, especially those receiving mycophenolate mofetil.

Treatment

There are several antiviral agents with demonstrated efficacy against influenza, most of which have been used to varying degrees in transplant recipients [46,52]. Amantadine and rimantadine have antiviral activity limited to influenza A; oseltamivir and zanamivir have activity against both influenza A and B. To date, no significant drug interactions have been reported with any of these medications and immunosuppressive therapies including calcineurin inhibitors. The recommended dosages and duration of treatment are the same as those for the normal host. Antiviral resistance has been reported rarely in transplant recipients [47], but there are currently no specific recommendations for altering antiviral therapy.

Adenovirus

Epidemiology

There are several fundamental differences between adenovirus infection and infection with the other common CARVs. Adenovirus may be acquired by person-to-person transmission as a primary respiratory tract infection, as is the norm for RSV or PIV. Most adenovirus disease in immunocompromised patients, however, is probably reactivation of latent infection. In addition, adenovirus infection can produce a wide variety of clinical syndromes—gastroenteritis, hepatitis, and hemorrhagic cystitis—in addition to respiratory tract illness. These patterns of illness may vary by host and by adenovirus serotypes [53].

Adenovirus infections account for 0% to 21% of CARV infections in recent large case series (see Table 1) [1–8]. In general, adenovirus is more common in children, in whom infection with a new serotype may be primary infection and more likely to produce true clinical disease. Although adenovirus may be the least commonly reported of the four main CARV infections in these series, it is important to recall that most of these series test patients who had symptomatic URI; the true incidence of adenovirus infection in these patient populations probably would be higher if other clinical manifestations were included.

Clinical features and diagnosis

In general, three patterns of adenovirus infection are described in HSCT and SOT recipients who have positive sputum testing for adenovirus infection: (1) asymptomatic; (2) symptomatic respiratory tract infection; and (3) disseminated disease, with or without respiratory tract involvement. Mortality from adenovirus clearly is tied to dissemination of the infection, but dissemination does not require progressive respiratory tract infection. Therefore, unlike RSV or PIV infections, many cases of fatal adenovirus infection are reported in patients who have adenovirus isolated from the upper respiratory tract only and without radiographic evidence of pneumonia or positive testing from lower respiratory tract samples [11,15].

Outcomes from adenovirus respiratory tract infection after HSCT have been poor. Four recent series describe mortality rates ranging from 38% to 100%, with a cumulative mortality of 56% (30 of 54 cases) [1,2,11,15]. Although mortality from adenovirus pneumonia is high, it is noteworthy that one third of these deaths occurred in patients who had adenovirus URI without evidence of pneumonia.

Fewer cases of adenovirus infection have been reported in SOT recipients, but details presented in some reports shed important light on the nature of the disease in this population. McGrath and colleagues [54] performed the largest review of adenovirus infection in adult liver transplant recipients and showed an overall incidence rate of 5.8%. Four (36%) of their 11 patients who had positive cultures were asymptomatic. Of the seven who had clinical disease, three had pneumonia, but all had evidence of disseminated disease, making it unclear if the pneumonia was a primary event or the result of dissemination of uncontrolled infection. Therefore, it is unclear if any patients in this series had a true, newly community-acquired respiratory tract infection with adenovirus.

Several papers have reviewed the potential significance of adenovirus infection in lung transplant recipients. Approximately 1% to 3% of lung transplant recipients may develop adenovirus infection in longitudinal studies [16,21,55,56]. In many of these patients, adenovirus has been tied closely to graft failure and to acute and chronic rejection, but the numbers of patients involved prevent rigorous statistical analysis or the ability to draw a firm conclusion. In the two largest recent series examining the potential link between BOS and CARV infection, for example, adenovirus accounted for only 2 of 61 isolates [8,13].

Adenovirus infection may be diagnosed using the widely available immunofluorescent antibody kits. This test is insensitive for adenovirus in sputum, however, with a reported sensitivity of perhaps 50% in immunocompetent hosts. Given that DFA and IFA are the most commonly used assays, this lack of sensitivity may explain, in part, the relative infrequency of adenovirus in some surveys of CARV infection. The virus can be cultured as well and is identified readily by characteristic smudge cells on histopathology. Because adenovirus frequently may be a reactivation disease, more sensitive assays, perhaps PCR based, may detect the infection more frequently. Further study is needed to determine whether patients who have more indolent adenovirus replication actually have clinical disease, or whether another pathogen is responsible for the clinical presentation.

Treatment

The widely reported high mortality rates from adenoviral infection, particularly in the early post-transplantation period, have prompted many clini-

cians to push for early and aggressive treatment of documented adenovirus infections in HSCT and SOT recipients. Unfortunately, there are limited data to support the efficacy of available therapeutics. Recently cidofivir has been shown to improve outcomes in small studies of children after HSCT and has had anecdotal reports of success in adults. Because of the significant risk of nephrotoxicity associated with cidofivir, this agent should be used with caution in transplant recipients who may be at increased risk for renal impairment. Although both have been tried in the past, neither ribavirin nor ganciclovir has demonstrated significant efficacy; consequently, neither agent is recommended [53].

Two recent articles have questioned the need for treatment in all patients who have documented adenovirus infections. Walls and colleagues [57] recently reported the results of retrospective testing for adenovirus in 26 consecutive pediatric HSCT recipients. In this series, 11 children had at least one positive test for adenovirus, but 7 of the 11 spontaneously cleared the infection without antiviral therapy. Two children died of disseminated disease, and each first tested positive in the first 2 weeks after HSCT. A recent prospective monitoring study by van Kraaij and colleagues [9] in HSCT recipients also demonstrated several cases of early but asymptomatic adenovirus infection.

Miscellaneous respiratory viruses

Rhinovirus

The rhinoviruses (comprised of more than 100 serotypes) are among the most common causes of the common cold in immunocompetent adults and children. Only a few studies have addressed their potential role as respiratory pathogens in SOT and HSCT recipients, but the available data suggest that rhinovirus infection may be underappreciated. Four studies of prospective active surveillance for CARV infection—one in adult lung transplant recipients [56], one in pediatric HSCT recipients [15], and two in adult HSCT recipients [7,9]—noted rhinovirus infection in their cohorts; in two studies, rhinovirus was the most common isolate. In these groups, most rhinovirus infections were asymptomatic, but, taken together, three other longitudinal studies of HSCT recipients who had symptomatic respiratory tract infection identified rhinovirus in a total of 42 (27%) of 157 isolates [3,37]. Of these 42 reported cases of symptomatic rhinovirus respiratory tract infection, 7 (17%) progressed to LRTI, and two (29% of LRTI) deaths were attributed to rhinovirus pneumonia. Several of these series used real-time PCR for viral surveillance; as this newer diagnostic technology becomes more widely used, the true epidemiology and impact of rhinovirus infections in HSCT or SOT recipients will become clearer. At present, there is no specific antiviral therapy available for the treatment of rhinovirus infections.

Coronavirus

Coronaviruses, like rhinoviruses, are frequent causes of benign URI occurring in annual wintertime community outbreaks. Laboratory isolation of these agents is difficult, so no systematic study of their possible role in LRTI in HSCT or SOT recipients has been undertaken [11]. The recent experience with the newly identified causative agent of severe acute respiratory syndrome (SARS), SARS coronavirus, bears mention. Kumar and colleagues [58] in Toronto reported a liver transplant recipient who died from SARS. A study of tissue obtained at autopsy revealed that a dramatically higher concentration of the SARS coronavirus was present in this patient's tissues than in those of other case patients, suggesting both a reason for the fatal course and the possible role of immunosuppressed patients as 'super-spreaders' of the epidemic.

Herpes viruses

Nearly all viruses in the herpes virus family have been reported as occasional causes of pneumonia in HSCT and SOT recipients. Herpes simplex virus type 1 (HSV-1) will reactivate almost universally after HSCT or SOT in the 70% to 80% of adults with latent infection, and several reports have documented pneumonia, occasionally fatal, from this pathogen [56,59–61]. HSV-1 is suppressed effectively by agents used for cytomegalovirus prophylaxis, however, and reports of HSV-1 pneumonia have greatly decreased in the era of universal prophylaxis. At most centers, prophylactic acyclovir is given to suppress reactivation of herpes simplex disease even when the recipient and the donor are cytomegalovirus negative. Similarly, acyclovir and ganciclovir are active against varicella-zoster virus (VZV), which has been reported as a rare cause of pneumonia in SOT or HSCT recipients [56,59,61]. VZV may reactivate at any point in the posttransplantation course, and shingles is a common disease in all immunosuppressed populations. Because most cases of VZV pneumonia in HSCT or SOT recipients are preceded by the characteristic vesicular skin rash [61], and because

VZV pneumonia is rare, it is assumed that prompt antiviral therapy with acyclovir can abort the progression of reactivation disease to pneumonia. VZV pneumonia may be more of a concern in children or adult patients who have no innate immunity to VZV from either natural exposure or previous vaccination, because primary VZV infection is more likely to cause pneumonia.

Finally, the roles of human herpesvirus 6 and human herpesvirus 7 (HHV-7) as pulmonary pathogens remain poorly understood. Active replication with both viruses can be detected, probably as reactivation of latent infection, in 20% to 50% of HSCT or SOT recipients [62]. Several authors have reported isolation of human herpesvirus 6 from sputum or lung tissue in patients who have otherwise idiopathic pneumonia after HSCT [62–64]. The overall data, however, conflict as to whether a causative role can be established [62,65]. Ross and colleagues [66] have reported HHV-7 in seven (100%) of seven lung transplant recipients who had early bronchiolitis obliterans with organizing pneumonia and in three (75%) of four patients who had diffuse alveolar damage. In this series, HHV-7 was detected in 5 (19%) of 26 lung transplant recipients who had no pathology on biopsy and in 2 (14%) of 14 patients who had acute or chronic rejection (ie, BOS). These findings are thought-provoking and confirm the need for further research into the potential role of HHV-7 as a single or copathogen for certain patterns of pulmonary disease.

Prevention of community-acquired respiratory virus infection

Given that CARV infections in HSCT or SOT recipients occur frequently and are associated with poor outcomes, attention must be given to the prevention of CARV infection. Recommendations for a multifaceted approach to the prevention of morbidity and mortality from these infections are presented in Box 1.

Any approach to the prevention of CARV infection must start with appropriate hand hygiene. With the possible exception of influenza [67], which may be transmitted in part by aerosolized droplets, CARV infections are transmitted by larger droplet particles that are introduced to the host oropharynx from the hands. Regular hand washing with attention to hand washing before food preparation or meals significantly reduces the incidence of CARV infection. In the inpatient setting, the widespread availability of alcohol-based hand-washing products has reduced the transmission of most hospital-acquired infections.

Additional infection control measures are recommended to prevent the spread of CARV infections on inpatient units. The Centers for Disease Control and Prevention recommend contact isolation for all patients who have CARV infection [67]. In addition, droplet precautions should be taken in the rooms of patients who have adenovirus or influenza respiratory tract infections. Importantly, patients should be placed under special precautions when the infections are first suspected, not when they are first confirmed, to limit the exposure of other patients and staff to infectious droplets [67]. These measures have been used successfully on a number of occasions to limit nosocomial spread of CARV infections. One group reported an 81% reduction in RSV cases on a HSCT unit with institution of droplet precautions and with cohorting case patients [30]. Many authorities, including the Centers for Disease Control and Prevention, advocate strongly for restricting visitors during the winter months as well [29,67].

Infection with many CARVs produces a measurable, type-specific antibody response. This response is neither long lasting nor protective [17]. Unfortunately, trials of active vaccination for RSV or PIV have been disappointing, including trials of subunit vaccines and live attenuated viruses [36]. Cortez and colleagues [68] recently reported on the use of passive vaccination (pavilizumab) in 54 allogeneic bone marrow transplant recipients. Although titers of RSV-specific immune globulins were increased, no difference in the rates of RSV infection were observed.

Prevention of influenza in transplant recipients has been focused on vaccination, and transplant recipients are among the immunosuppressed hosts targeted for influenza vaccination [69]. The standard inactivated vaccine is composed of two influenza A and one influenza B strain. Vaccine composition varies annually based on predicted antigenic drifts and shifts in circulating virus; consequently, annual reimmunization is recommended for optimal protection. Live attenuated intranasal influenza vaccine is not recommended for immunosuppressed hosts, including transplant recipients, or for family or health care providers who are in close contact with the patients. Numerous studies over several decades have examined vaccine responses in transplant recipients and have demonstrated conflicting results. In general, both humoral and cellular vaccine responses seem to be suboptimal when compared with healthy controls and cannot be reliably predicted based on the level of

Box 1. Approaches to reducing morbidity and mortality from community-acquired respiratory virus infections in hematopoietic stem cell transplant or solid organ transplant recipients

Prevention of CARV infection

- Careful hand hygiene, especially during fall and winter months
- Vaccination of patients and close contacts (particularly for influenza)
- Avoidance of contact with patients who have symptomatic URI
- Patient education (eg, how CARV infection is spread, how to avoid sick contacts, how to perform appropriate hand hygiene)

Diagnosis of CARV infection

- Combination nasal/throat swab fluorescent antibody testing in early URI
- Consideration of bronchoscopy for BAL sample if symptoms progress or in any HSCT or SOT patient with an unexplained LRTI or pneumonia
- Routine testing for CARV infection in all SOT or HSCT recipients presenting with pneumonia, including those patients who have an already identified bacterial or fungal pathogen
- Expanded use of newer diagnostic tools (eg, real-time PCR)
- Awareness of seasonal patterns of CARV infection and of circulating viruses in the local community
- Patient education (eg, regarding need to contact a physician when URI symptoms occur)

Prevention of CARV LRTI

- Consideration of pre-emptive antiviral therapy for RSV or PIV URI in the early posttransplantation period
- Specific antiviral therapy for influenza

Treatment of established CARV LRTI or pneumonia

- Specific antiviral therapy for influenza
- Aerosolized ribavirin therapy for RSV, possibly in combination with intravenous immune globulin
- Appropriate therapy for bacterial or fungal coinfections

Prevention of CARV outbreaks

- Strict adherence to infection-control guidelines in hospitals, including attention to hand hygiene and contact, droplet, or aerosol isolation as dictated by accepted guidelines
- Consideration of cohorting patients on inpatient units
- Active surveillance or case finding by infection control personnel
- Careful monitoring of staff and visitors for symptoms of URI, particularly during times of heightened CARV prevalence in the community
- Separation of sick from healthy patients in outpatient waiting areas

immunosuppression [70–73]. Anecdotal reports have suggested a potential linkage between vaccination and organ rejection; however, this association has not been supported by the majority of studies examining the immunogenicity of vaccine in SOT recipients. Current recommendations support annual vaccination of all SOT recipients, although it is likely that those with more recent transplants may be less likely to respond to vaccine. HSCT recipients may be especially poor vaccine responders within the first 2 years after transplantation [46]. Prophylactic administration of licensed antiviral agents (including oseltamavir and zanamavir) may serve as an alternative preventive measure for individuals who are unable to receive influenza vaccination (eg, those with egg allergy) or who are anticipated to be especially

unlikely to respond to vaccine [74]. Although not specifically studied in transplant recipients, these antiviral agents have been demonstrated to be effective in preventing the acquisition of influenza when administered to immunocompetent individuals during periods of peak influenza activity [69]. Because transplant recipients may be suboptimal vaccine responders and are at increased risk for adverse outcomes from influenza, consideration should be given to immunization of household contacts before the influenza season.

Summary

CARVs are frequent causes of both URI and LRTI in HSCT or SOT recipients. In most series, RSV and PIV are the most common CARVs. Significant morbidity and mortality are associated with these infections, particularly when they progress to LRTI. Outcomes are also poor with adenovirus, frequently reflecting disseminated infection. Efforts to prevent morbidity and mortality from CARV infection should focus on prevention, because treatment options are limited, with inconclusive data to support their efficacy.

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