

Community-acquired respiratory viruses

Epidemiology

Community-acquired respiratory viruses are common causes of upper and lower respiratory tract disease both in the immunocompetent and immunosuppressed host. A diverse group of viruses are responsible for these diseases including respiratory syncytial virus (RSV), parainfluenza virus (PIV), influenza virus, adenovirus, rhinovirus, coronavirus and enterovirus. With the exception of adenovirus (which is discussed in a separate section of these guidelines), all of these microbial organisms are single stranded RNA viruses. Community-acquired respiratory viruses cause a variety of clinical manifestations and disease severity ranging from mild congestion and rhinorrhea to more severe tracheobronchitis, bronchiolitis and pneumonia. They are increasingly recognized as a cause of illness after both solid organ and bone marrow transplantation, particularly in children. All are potential nosocomial pathogens which can be potentially spread by staff or visitor with mild upper respiratory illness. However, few large series are available (especially among solid organ transplant recipients) to help define the full scope of this problem as well as the best preventive or treatment strategies. To a large extent this is due to a lack of surveillance and diagnostic studies, particularly when patients are at home, often at a site distant from the transplant center. Data emerging from retrospective series or those looking at patients early after transplantation will be weighted towards identifying patients with more severe illness as extensive diagnostic evaluations are unlikely to be performed in individuals with mild symptoms.

While a number of different species of viruses cause upper and lower respiratory infections in transplant recipients, some similarities exist between these pathogens. In general, transmission of all of these viral pathogens occurs by spread from person to person through direct or close contact with contaminated secretions which may involve droplets or fomites. In addition, influenza virus may be spread by small particle aerosols. Accordingly, attention to good hygienic practices, in particular hand washing, should be part of infection control and prevention both in and out of the hospital. Supportive care is a mainstay of treatment. Specific antiviral agents are not available for coronavirus and parainfluenza. Specific data on RSV, influenza and PIV in the transplant population are discussed in more detail.

Respiratory syncytial virus

The RNA virus is a cause of seasonal annual epidemics worldwide. In temperate climates RSV strikes in the fall,

winter and early spring. By 2 years of age, virtually all children have experienced a primary infection. In recent years it is has become clear that re-infection can occur throughout life. While symptoms of RSV infection tend to be milder in older children and adults, these individuals may serve as a reservoir for transmission to more susceptible hosts. RSV has been recognized as a cause of severe disease after bone marrow transplantation (BMT) (1–4). Likewise, it is recognized as a cause of respiratory disease after pediatric solid-organ transplantation and is being increasingly recognized in adult recipients (3,5–9). Risk-factors for development of lower respiratory tract disease in BMT recipients with RSV infection include lymphocytopenia and neutropenia (4). As many as 60% of BMT recipients infected with RSV will develop lower respiratory tract disease. Once lower tract disease is present, mortality rates ranging from 30 to 80% have been reported (1,4,7,10). Risk factors for more severe disease after organ transplantation include infection in children under a year of age or with underlying lung disease (5–9). Early acquisition of RSV after transplantation or after augmented immunosuppression has been associated with increased severity of disease in some but not all studies (3,5–9,11–13).

Diagnosis of RSV

Definitive diagnosis is made by growth of RSV in cell lines such as HeP-2. However, the virus is quite labile and sensitivity diminishes quickly if specimens are not inoculated promptly onto cell culture lines. A number of commercial rapid antigen detection kits and shell vial assays are available that permit the diagnosis to be made quickly and with increased sensitivity compared to culture in children (14). However, adults (including immunocompromised patients) may have low titers of virus in the upper respiratory tract so that the sensitivity of antigen detection in adults is lower than seen for children. Polymerase chain reaction assays (PCR) are also available in some laboratories and one commercial multiplex assay (Hexaplex, Podesse, Inc; Waukesha, WI, USA.) is approved by the Food and Drug Administration (FDA). Nasal washes or aspirates have been shown to be superior to nasal swab specimens for the diagnosis of RSV. Bronchoalveolar lavage is recommended for assessment in adults with suspected lower respiratory tract disease. A review of the diagnosis of RSV is provided in Table 1.

Treatment of RSV

Supportive care is recommended (BIII). The role of specific antiviral treatment is controversial. Ribavirin has been

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Table 1: Overview of the diagnosis and treatment of common community acquired respiratory viral infections in solid organ transplant recipients

| Virus | Diagnostic test (s) | Treatment (s) |
|-----------------------------|--|---|
| Respiratory syncytial virus | Antigen detection Nucleic acid detection Viral culture Shell vial culture | Upper respiratory tract & no risk factors: Supportive care Upper respiratory tract & risk factors or Lower respiratory tract: Aerosolized ribavirin in combination with RSV IVIG or palivizumab should be considered (BIII) |
| Influenza | Viral culture Shell vial culture Antigen detection | Influenza A infection: amantadine, rimantadine, zanamivir and oseltamivir (BIII) Influenza B infection: zanamivir and oseltamivir (BIII) Consider addition of aerosolized ribavirin for severe lower respiratory tract disease (CIII) |
| Parainfluenza | Viral culture Shell vial culture Antigen detection Nucleic acid detection | Upper respiratory tract infection: Supportive care Lower respiratory tract infection: Supportive care Consider aerosolized ribavirin (CIII) as no other options but experience to date provides little evidence for likely efficacy |

shown to have *in vitro* activity against RSV and the aerosolized form of this drug has been approved for the treatment of lower respiratory tract disease due to RSV in certain at-risk populations. Despite its FDA approval, convincing data describing the clinical efficacy of this agent are lacking and a consensus on the utility of this drug in the treatment of RSV disease does not currently exist. Published data on the treatment of RSV disease in solid organ transplant recipients is very limited. However experience from the treatment of BMT recipients may provide guidance for the treatment of RSV disease in solid organ transplant recipients. BMT recipients have a high mortality rate from RSV pneumonia even with the use of aerosolized ribavirin (1–3,7,10,11) prompting the clinical investigation of additional therapeutic options in this patient population. A noncontrolled study using a combination of ribavirin with IVIG with higher RSV titers (RSV-IVIG, Respigam) was performed which appeared to demonstrate a benefit when used early after symptoms developed in BMT recipients (15,16). The high mortality rate in this patient population would lead many to recommend early therapy (BII). Combinations of aerosolized ribavirin and RSV IVIG (15,16) or palivizumab (17) (Synagis, MedImmune, Inc; Gaithersburg, Maryland.), an RSV-specific monoclonal antibody, appear to be beneficial in some BMT recipients even when they present with lower respiratory tract disease. Based on these experiences, many experts would recommend the use of the combination of aerosolized ribavirin and either RSV IVIG or palivizumab for the treatment of RSV upper respiratory tract or lower respiratory tract infection in BMT recipients (BII).

Combining this experience with the limited published experience of treatment of RSV disease in solid organ transplant recipients provides support for the following recommendations (Table 1). Aerosolized ribavirin use in the treatment of some solid organ transplant patients with lower tract disease has been reported with seeming benefit (7,13) (BIII). However, these studies report retrospective experiences. Based upon published experience from pediatric organ transplant recipients, patients without risk factors for severe disease and with only upper respiratory infections are unlikely to benefit from aerosolized ribavirin (DII). For patients with upper respiratory tract disease and the presence of risk factors, and for those organ transplant recipients with lower respiratory tract disease the use of aerosolized ribavirin in combination with RSV IVIG or palivizumab should be considered (BIII).

Prevention of RSV

Prophylaxis with the RSV-specific monoclonal antibody (Palivizumab) or high titer RSV-IVIG has been shown to be effective for specific groups of high-risk infants and young children (18) (A1). However, no studies have been conducted to evaluate their use in the solid organ transplant setting and the cost of the weight adjusted dosing of these products in adults would be extremely high. The unexpected increased risk of death in children with cyanotic heart disease who received RSV IVIG shows the inability to generalize the use of this immunoprophylaxis from one population to another without study. Despite this, some experts would support the use of immunoprophylaxis for

children less than 1 year of age who receive their transplant during the RSV season (CIII). While specific prophylaxis is not proven for transplant recipients, aggressive infection control policies (e.g. contact precautions and cohorting of patients) are shown to decrease transmission of RSV and other community respiratory viruses in the hospital (7,19) (BII).

Future studies

Studies are necessary to define risk factors for severe disease in adult solid-organ transplant recipients and to develop more sensitive rapid diagnostic assays for use in adults. The utility of immunoprophylaxis in recipients of transplantation also requires evaluation. Finally, trials are also needed to confirm the utility of aerosolized ribavirin, alone or in combination with RSV-IVIG in the treatment of patients at risk of progressing to or who present with lower respiratory tract disease.

Influenza virus

Influenza virus, an orthomyxovirus, is considered one of the most important community-acquired viruses leading to substantial morbidity and mortality worldwide. Antigenic variability gives this virus a survival advantage allowing for its continued virulence during yearly epidemics. Few studies have examined the prevalence of influenza virus infection prospectively in organ transplant recipients (12). Retrospective studies demonstrate the potential for substantial disease in pediatric recipients after influenza infection (20,21). Reviews of influenza virus infection after adult organ transplantation document variable levels of severity (6,12,22–24) which may be due to different levels of immunosuppression, type of transplantation, and seasonal variation of influenza virulence. In addition, differences in prevention through vaccination policies or disparate response rate to vaccination of patients of different ages or under different immunosuppressive regimens undoubtedly affect the disease severity (25).

Diagnosis of influenza

Diagnosis of influenza infection is proven by isolation of the virus in culture. Other rapid methods, such as shell vial culture, antigen detection, or detection of neuraminidase activity are relatively sensitive and specific, depending on the specimen and patient source, and are commercially available. Some of these rapid tests can be used for office-based diagnostic testing. Adequate specimen collection and timing of sampling also play important roles in identifying pathogens. When viral cultures are performed, specimens should be obtained during the first few days of illness to maximize yield as viral load may decrease rapidly thereafter. Cultures typically turn positive within 2–6 days. Rapid diagnostic tests for identification of influenza A and B antigens are commercially available. A nasopharyngeal aspirate specimen is considered optimal. Use of throat swabs or nasopharyngeal swab has tended to result in lower levels of sensitivity. A review of the diagnosis of influenza is provided in Table 1.

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Treatment of influenza

Prompt treatment of influenza A infection with amantadine, rimantadine, or the newer neuraminidase inhibitors, zanamivir and oseltamivir has been effective in studies on healthy adults. Only the latter two drugs have efficacy against influenza B; early treatment of influenza with inhaled zanamivir or oral oseltamivir appears to reduce the likelihood of lower respiratory tract complications (e.g. bronchiolitis, pneumonia) but none of the drugs has been proven to be efficacious in preventing serious complications from influenza (26). Retrospective analysis indicates that early antiviral treatment with amantadine or rimantadine reduces the likelihood of developing pneumonia in patients with acute leukemia or who have undergone BMT. A review of recommendations for the treatment of influenza virus infections in solid organ transplant recipients is provided in Table 1. Despite the absence of data in organ transplant recipients, most transplant physicians would recommend the use of an antiviral agent for the treatment of organ transplant recipients with influenza virus infections (BIII); many experts would consider the use of a neuraminidase inhibitor either alone or in combination with another drug because of the concern of acquisition of resistance associated with the use of amantadine or rimantadine which may exceed a rate of 30% in these patients. Finally, ribavirin also has *in vitro* activity against influenza virus and anecdotal reports of its use in immunocompetent hosts with severe influenza infections suggested possible activity (27). Accordingly some would advocate the addition of aerosolized ribavirin to one of the antiviral agents for a transplant patient with serious influenza infection (CIII).

Prevention of influenza

The use of influenza vaccine in high-risk individuals (including transplant recipients) >6 months of age is strongly recommended (BII). Influenza vaccine should also be administered to people who have contact with high-risk patients such as health care workers and household contacts (BIII). The response to influenza vaccine has been studied in a number of transplant settings (25). While the vaccine year, specific influenza strain, and recipient type lead to variations in antibody response, several conclusions can be made. First, transplant recipients do not have as strong a response to vaccine as healthy controls. Despite this, 30–100% of patients achieved protective hemagglutination-inhibiting serum antibody titers. Accordingly, yearly vaccination should be strongly considered (AII). Yearly vaccination should likewise be recommended for all health care workers and household contacts. Chemoprophylaxis with antiviral agents can be used effectively in at-risk populations who have not received vaccine or who have not had an opportunity to respond to recent vaccination during the

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time when influenza is already circulating in the community (BIII). However, failure of amantadine or rimantadine may occur on the basis of antiviral resistance in communities where prophylactic or therapeutic use of these agents is high.

Parainfluenza

Parainfluenza types 1 and 2 tend to circulate sporadically in fall and winter months in temperate areas while type 3 occurs year round. Transmission occurs via person-to-person spread by direct contact with infectious secretions or fomites. Disease can be serious in pediatric transplant recipients and lung transplant recipients of any age (2,3,6–9,21). The type of organ transplanted did not affect symptoms, severity of illness or survival in one relatively large series of pediatric organ transplant recipient with parainfluenza virus infections. Clinical manifestations can range from minimal upper respiratory tract symptoms to respiratory failure and death. Parainfluenza viral infections have been associated with the presence of copathogens, particularly in recipients of lung transplantation. Of interest, several series have documented an association between parainfluenza virus infection and the development of acute rejection and bronchiolitis obliterans in lung transplant recipients.

Diagnosis of parainfluenza

The diagnosis of parainfluenza relies on viral isolation, shell vial assays or the use of rapid antigen detection using fluorescent antibody staining techniques directly on specimen or the cultured cells. In addition, RNA detection techniques have recently become available. Prolonged viral shedding can occur in immunosuppressed hosts. An overview of the diagnosis of parainfluenza virus is provided in Table 1.

Treatment of parainfluenza

Specific antiviral treatment is not available for PIV infection but ribavirin has *in vitro* activity and has been used to treat lung transplant recipients with lower tract disease (8). Because no other therapeutic options are currently available, consideration can be given to the use of aerosolized ribavirin for high-risk patients with PIV-associated severe lower tract disease (CIII) (Table 1). However, analysis of uncontrolled studies of aerosolized ribavirin in BMT recipients with parainfluenza virus disease found little evidence of for antiviral effects or clinical benefit (11). Similarly, the early use of oral ribavirin was of little benefit in preventing the progression from asymptomatic or mild upper respiratory tract symptoms to lower respiratory tract disease.

Prevention of parainfluenza

No specific prophylaxis is available for PIV. As noted above, good attention to infection control practices is necessary to prevent nosocomial transmission (19). Outside the hospital setting infection control methods can be challenging. Educating recipients and their families about the risk of

community-acquired viruses and methods of their spread will allow them to avoid some exposures.

Future studies

Studies defining the potential therapeutic role of ribavirin in the treatment of PIV disease are necessary. In addition, multicentered-studies aimed at identifying the potential prophylactic benefit of polyclonal IVIG (containing antibodies against PIV and other respiratory viruses) would also be of benefit.

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