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Current practices for treatment of respiratory syncytial virus and other non-influenza respiratory viruses in high-risk patient populations: a survey of institutions in the Midwestern Respiratory Virus Collaborative

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Abstract: *Background.* The optimal treatment for respiratory syncytial virus (RSV) infection in adult immunocompromised patients is unknown. We assessed the management of RSV and other non-influenza respiratory viruses in Midwestern transplant centers.
Methods. A survey assessing strategies for RSV and other non-influenza respiratory viral infections was sent to 13 centers.
Results. Multiplex polymerase chain reaction assay was used for diagnosis in 11/12 centers. Eight of 12 centers used inhaled ribavirin (RBV) in some patient populations. Barriers included cost, safety, lack of evidence, and inconvenience. Six of 12 used intravenous immunoglobulin (IVIG), mostly in combination with RBV. Inhaled RBV was used more than oral, and in the post-stem cell transplant population, patients with lower respiratory tract infection (LRTI), graft-versus-host disease, and more recent transplantation were treated at higher rates. Ten centers had experience with lung transplant patients; all used either oral or inhaled RBV for LRTI, 6/10 treated upper respiratory tract infection (URTI). No center treated non-lung solid organ transplant (SOT) recipients with URTI; 7/11 would use oral or inhaled RBV in the same group with LRTI. Patients with hematologic malignancy without hematopoietic stem cell transplantation were treated with RBV at a similar frequency to non-lung SOT recipients. Three of 12 centers, in severe cases, treated parainfluenza and metapneumovirus, and 1/12 treated coronavirus.
Conclusions. Treatment of RSV in immunocompromised patients varied greatly. While most centers treat LRTI, treatment of URTI was variable. No consensus was found regarding the use of oral versus inhaled RBV, or the use of IVIG. The presence of such heterogeneity demonstrates the need for further studies defining optimal treatment of RSV in immunocompromised hosts.

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Although respiratory syncytial virus (RSV) infection often presents as a self-limited upper respiratory tract infection (URTI) in healthy adults, immunocompromised patients have higher rates of progression from URTI to lower respiratory tract infection (LRTI). Further, the mortality rate associated with LRTI is as high as 20–40% in hematopoietic stem cell transplant (HSCT) recipients (1–3). After lung transplantation, infection with community respiratory viruses, including RSV, is associated with the development of bronchiolitis obliterans syndrome, and the mortality rate for RSV infection in this population has been reported to be as high as 10–20% (4, 5).

Ribavirin (RBV) and intravenous immunoglobulin (IVIG) are used for treatment of RSV infection, despite the absence of large, prospective, randomized controlled trials demonstrating efficacy of any treatment in adult immunocompromised patients (6, 7). Non-randomized data suggest, however, that inhaled and oral RBV may reduce progression of URTI to LRTI and reduce mortality (2, 6, 8, 9). These agents have significant limitations including high cost, poor tolerability, and potential toxicity. Moreover, no guidelines exist for the treatment of RSV in immunocompromised adults. In the absence of clear evidence, and given the potential drawbacks of available treatments, we sought to assess how large transplant centers manage RSV as well as other non-influenza respiratory viral infections in immunocompromised adults.

Methods

The Midwestern Respiratory Virus Collaborative (MRVC) is a co-operative effort among 13 large Midwestern transplant centers to study respiratory virus infections in transplant patients. A survey (see Supplementary Data S1) was designed to gather descriptive information about each center including the following: center size, number of adult stem cell transplantations performed in 2013, types of solid organ transplants (SOTs) performed, the diagnostic methods for respiratory viral infection, availability of inhaled RBV, and dose and interval used for inhaled and oral RBV at each institution. The number of adult SOTs performed at each institution in 2013 was obtained from optn.transplant.hrsa.gov. We also assessed the use of IVIG products.

The survey gathered information regarding usual treatment practices for RSV URTI and LRTI in the following scenarios: pre-engraftment autologous and allogeneic HSCT recipients, post-engraftment autologous HSCT recipients within 3 months of transplant, post-engraftment autologous HSCT recipients >3 months from transplant, post-engraftment allogeneic HSCT recipients with and without graft-versus-host disease (GVHD) <3 months from transplant, allogeneic HSCT recipients with and without GVHD >3 months from transplant, lung transplant recipients, non-lung SOT recipients, and patients with hematologic malignancy. In addition, we asked about the management of other non-influenza/non-RSV respiratory viruses: parainfluenza, human metapneumovirus, coronavirus, and adenovirus, including preferred treatment and populations that would routinely be treated. Descriptive statistics are presented.

Results

Surveys were sent via email to transplant infectious disease physicians at 13 transplant centers participating in the MRVC. Twelve of 13 centers responded (characteristics in Table 1). Most (11 centers) use multiplex polymerase chain reaction (PCR) for diagnosis of respiratory viral infections (2 only used PCR for immunocompromised patients and 1 limited its use to the inpatient setting). One center primarily used rapid antigen testing for diagnosis.

Table 2 describes RBV usage and dosing for treatment of RSV infection. Inhaled RBV was not used for outpatients at any center, but was used for inpatients in 8 centers. In the 4 centers that did not use inhaled RBV, reasons included cost, inconvenience, safety concerns regarding teratogenicity, and lack of efficacy. Three of these 4 stated a specific preference for oral RBV. Six centers used both oral and inhaled RBV depending on the clinical situation: 2 preferentially utilized inhaled RBV; the remaining 4 utilized inhaled or oral RBV on a case-by-case and/or service-specific basis. One of these centers noted that inhaled RBV was used in more severe cases. One center did not routinely use inhaled or oral RBV, but used IVIG as monotherapy in some circumstances. In the 5 other centers that used IVIG, it was given in combination with inhaled or oral RBV. IVIG was not used for treatment of URTI by any center, and 2 centers used IVIG only in cases where the patient was hypogammaglobulinemic. No center used palivizumab, with 1 center reporting in follow-up communication that palivizumab was too expensive for use in adult patients.

Likewise, variation was found in management strategy by patient population (Fig. 1). Treatment strategies were excluded from 1 center, as management was "dependent on symptoms." HSCT recipients with LRTI, GVHD, and more recent transplantation were more

Center characteristics and diagnostic method

Characteristics	Number of centers (n = 12)
Hospital size, *n* (%)	
501–1000	9 (75)
>1000	3 (25)
Number of SCT performed in 2013, *n* (%)	
51–100	1 (8.3)
101–150	3 (25)
151–200	2 (16.7)
>200	6 (50)
Number of adult SOT performed in 2013, *n* (%)	
101–200	2 (16.7)
201–300	5 (41.7)
301–400	3 (25)
>400	2 (16.7)
Type of SOTs available, *n* (%)	
Heart	10 (83.3)
Intestine	3 (25)
Kidney	12 (100)
Liver	12 (100)
Lung	9 (75)
Pancreas	12 (100)
Diagnostic method used, *n* (%)	
Multiplex PCR	11 (91.7)[1]
Rapid antigen test	1 (8.3)

[1]In 3 centers, influenza-/RSV-specific RT-PCR assays were used for non-immunocompromised patients (2) or ambulatory patients (1). SOT data obtained from optn.transplant.hrsa.gov. SCT, stem cell transplant; SOT, solid organ transplantation; PCR, polymerase chain reaction.

Table 1

Ribavirin availability, dose, and interval

	Ribavirin dose and interval	
Center	Oral ribavirin	Inhaled ribavirin
1	600–800 mg 2× daily	Not used
2	20–30 mg/kg/day	Continuous inhalation × 18 h daily
3	600–800 mg 2× daily	Not used
4	Not used	Not used
5	600 mg twice daily	2 g given 2 h q 8 h, or 6 g over 12–18 h
6	Not used	2 g q 8 h
7	Not used	2 g given 2 h q 8 h, or 6 g over 12–16 h
8	600 mg 3 × daily	2 g over 2 h q 8 h
9	400 mg q 8 h (10–20 mg/kg)	Not used[1]
10	15–20 mg/kg 3× daily	2 g q 8 h
11	600 mg 3× daily	2 g over 2 h q 8 h
12	200 mg 4× daily	6 g × 10 h overnight

[1]Once in 5 years.
q, every.

Table 2

likely to receive antiviral treatment, and inhaled RBV was used at higher rates than oral RBV.

All 10 centers that had experience with lung transplantation treated LRTI in these patients with either oral or inhaled RBV. One center used prednisone in combination with RBV. One center used inhaled RBV to treat URTI in patients with hematologic malignancy; URTI was otherwise not typically treated in this group or in non-lung SOT patients. Treatment of LRTI in these populations is described in Figure 1.

Survey recipients were also asked about the management of non-influenza, non-RSV respiratory viruses. Three of 12 centers treated severe parainfluenza and metapneumovirus; 1 of 12 treated coronavirus. Treatments included RBV, IVIG, and the investigational drug DAS181 in parainfluenza infection. All 12 centers would treat LRTI or disseminated adenovirus infections with intravenous cidofovir or the investigational agent CMX001 when available.

Discussion

To our knowledge, this is the first survey documenting management strategies for RSV infection in adult immunocompromised patients. In the absence of strong evidence of effectiveness for any particular treatment, it is not surprising that treatment strategies differed widely among centers. While no consensus existed regarding management, some trends were observed.

Diagnostic strategy was the most uniform aspect of management. Most centers utilized multiplex PCR, which provides several potential advantages over traditional diagnostic methods, including rapid turnaround time and the capability to identify multiple respiratory pathogens. In addition, PCR appears to be more sensitive than culture and antigen testing (10).

Treatment strategies varied significantly from center to center. Aspects of treatment as fundamental as dose, frequency, and route of administration of RBV were

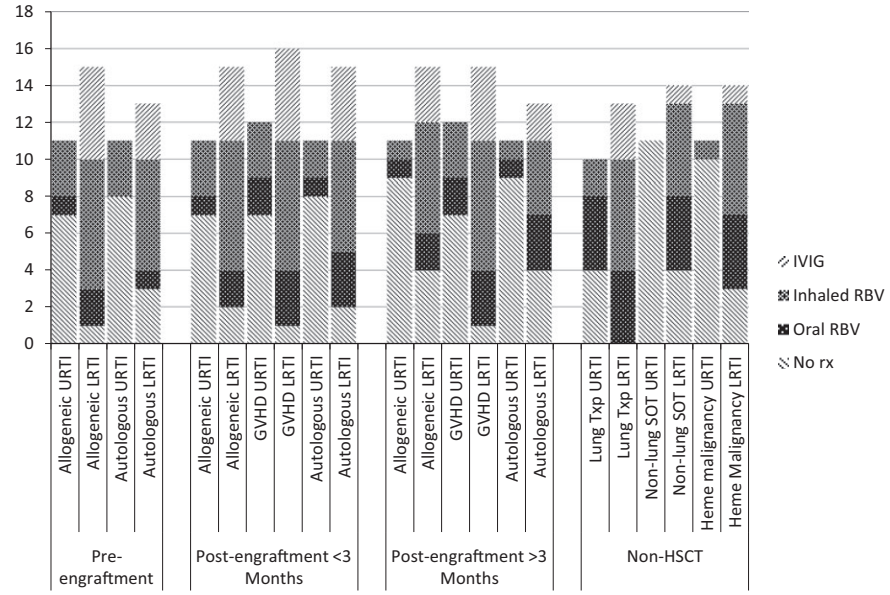

Fig. 1. Treatment patterns for respiratory syncytial virus infection in adult allogeneic and autologous hematopoietic stem cell transplant (HSCT), lung and non-lung solid organ transplant (SOT), and hematologic (Heme) malignancy patients. Responses are from 11 centers; 10 centers responded with management in lung transplants. In some scenarios, individual centers treated patients with oral or inhaled ribavirin (RBV) depending on clinical circumstances, which is why the denominator exceeds 11 in certain scenarios. Intravenous immunoglobulin (IVIG) was used as monotherapy by 1 center in pre-engraftment allogeneic and autologous HSCT patients with lower respiratory tract infection (LRTI), post-engraftment allogeneic and autologous HSCT patients with LRTI within 3 months of transplant, and in patients with graft-versus-host disease (GVHD) and LRTI. IVIG was otherwise given in combination with oral or inhaled RBV. URTI, upper respiratory tract infection; rx, treatment.

wide ranging. For oral RBV, dosing ranged from 800 to 1800 mg daily; for reference, recommended dosing for hepatitis C virus ranges from 800 to 1400 mg daily (weight-based dosing). Oral RBV for RSV therapy is an off-label use, and little information is available to define the appropriate dose. In the available literature, dosing strategies vary, and include non-weight-based and weight-based regimens ranging typically from 15 mg/kg/day to 22.5 mg/kg/day (4, 10–13). Inhaled RBV is approved for use in children at a dose of 6 g aerosolized over 12–18 h. This long duration of nebulization can be difficult to tolerate and often disrupts other patient care activities. Limited data suggest than an intermittent dosing schedule is equal, in terms of safety, and may be superior in preventing progression to LRTI (14). This alternative intermittent dosing schedule of 2 g aerosolized every 8 h (typically for a 2-h period with each administration) was the most commonly used regimen in our survey.

Inhaled RBV was used more frequently than oral in most of the scenarios that were presented, and particularly in scenarios involving LRTI. Of the available treatments, inhaled RBV has been the most studied. A systematic review suggested benefit in terms of decreased progression to LRTI and mortality with administration of inhaled RBV plus monoclonal (palivizumab) or polyclonal antibody preparations (IVIG, RSV-IVIG) (8). Other retrospective studies in HSCT populations have shown similar results (2, 9). Evidence for the efficacy of oral RBV is more limited; however, some retrospective studies suggest that it is well tolerated in HSCT and lung transplant recipients (4, 10, 11, 13). In the same systematic review noted above, oral RBV in combination with IVIG and/or palivizumab was associated with lower rates of progression to LRTI and mortality, although the effect was not as pronounced as that seen with inhaled RBV combined with immunomodulators (IVIG, RSV-IVIG, and/or palivizumab) (8). Of note, RSV-IVIG is no longer commercially available. A study aimed at determining the efficacy of RSV-IVIG for prophylaxis of RSV infection in allogeneic HSCT recipients was unable to determine benefit (15). Likewise, palivizumab is costly and has not proven to be efficacious in preventing progression of URTI to LRTI, or reducing mortality in adult allogeneic HSCT recipients (6, 16).

Centers were less likely to treat URTI despite available evidence that treatment at the URTI stage can prevent progression to LRTI (6). For inhaled RBV, the main limitations for outpatient administration

include cost (a treatment course of inhaled RBV typically costs $14,000–$23,000 compared with a course of oral RBV, which is $300–$700) and difficulty of administration. Tents are necessary because of concern for environmental contamination and potential teratogenicity to healthcare workers (11).

Lung transplant patients had the highest rates of treatment at the URTI stage and were the only patient population where unanimity existed regarding the decision to treat LRTI. A multidrug regimen of inhaled RBV, IVIG, corticosteroids, and palivizumab showed efficacy in maintaining allograft function after RSV infection (17). Furthermore, studies evaluating the use of oral RBV suggest that it is equivalent to inhaled RBV for treatment of RSV in lung transplants (4). In non-lung SOTs and in patients with hematologic malignancy, most centers would not treat URTI, which is consistent with Infectious Diseases Society of America guidelines recommending against routine treatment of RSV URTI in neutropenic patients (18). LRTI was treated at higher rates; however, studies evaluating the incidence and spectrum of RSV infection in these populations are scarce.

Our study has a number of limitations. As our data were collected via survey forms, the possibility of recall bias exists. In institutions without a set protocol, treatment strategies may vary between treating physicians. In addition, surveyed institutions were all located in the Midwest, and regional differences in management may exist.

From our survey, it is apparent that treatment strategies varied greatly among institutions. Although many centers do treat LRTI, treatment of URTI was more variable. While inhaled RBV was used more commonly, no consensus existed regarding its use compared to oral RBV or regarding the use of IVIG. Given the potential severity of RSV infection in adult immunocompromised patients, this variability demonstrates the critical need for well-designed studies examining currently used and novel agents. Attempts at randomized studies examining the efficacy of inhaled RBV in the past have not been successful owing to poor enrollment and perhaps reluctance to accept a placebo arm, and we would not advocate repeating that effort. Larger multicenter non-interventional trials could better identify risk factors for poor outcomes and identify populations most likely to benefit from expensive and potentially toxic therapies such as inhaled or oral RBV. The issue, however, may be solved as new therapies are tested and approved. ALN-RSVO1, a topically administered small interfering RNA; GS-5806, an oral fusion inhibitor; and MDT-637, an inhaled viral fusion inhibitor, are in various stages of development and provide hope that a proven effective treatment will soon be available (6, 19–21). For the present, our study provides insight into current practices in large transplant centers.

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Supporting Information

Additional Supporting Information may be found online with this article:

Data S1. Survey.