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Letter to the Editor

Impact of Respiratory Syncytial Virus (RSV) on adult haematology oncology patients

Dear Editor,

respiratory syncytial virus (RSV) is primarily associated with severe respiratory infections in children and newborns; however, it also poses a significant risk in elderly and immunocompromised patients,[1] especially those who have undergone hematopoietic stem cell transplantation (HSCT) or CAR-T cell therapy. Of note, RSV is a frequent community-acquired respiratory virus (CARV), accounting for 5% to 30% of CARV infections after HSCT.[2] Currently, no standardized treatment strategies neither approved virus-specific therapies for this specific patient population are available. Moreover, the clinical manifestations of RSV infection differ significantly between pediatric patients and the elderly or immunocompromised individuals. In the latter group, respiratory failure is more prevalent than bronchiolitis, possibly due to the presence of comorbidities, delayed diagnoses, and an ineffective immune response.[3]

During the COVID-19 pandemic, RSV infections decreased significantly in children age < 5 years, likely due to social distancing and universal masking, with reduced community transmission worldwide.[4] Conversely, in the late autumn of 2022, at the end of the COVID-19 pandemic crisis, the European Centre for Disease Prevention and Control (ECDC) reported an early-onset intensified circulation of RSV in European countries, including viral peaks outside of the typical season and resulting in increased pressure on the healthcare system.[5] Several reports revealed a strong resurgence of RSV in the autumn of 2022 after the lifting of anti-COVID-19 measures, both in United States and in Europe with a role as a causative agent of serious respiratory illnesses.[6–8]

Here, we present our data on the high prevalence of RSV infection among hematological patients in a large tertiary HSCT center in north of Italy from November 2022 to March 2023. Despite the withdrawn community protections against COVID-19 and other respiratory tract infections, individual protective measures such as respirator masks, gloves, and HEPA filtration system were maintained in both the ward and outpatient clinic of our Hematology and Stem Cell Transplant Unit. Compared with the pre-COVID-19 pandemic, screening policy and patient care management have not been changed. Indeed, all immunocompromised and neutropenic hematological patients who presented with respiratory symptoms underwent active testing using a nasal-specimen multi-virus polymerase chain reaction (PCR) test which detects common agents of CARV. The test results were available within a median of 48–72 h, although a rapid 1-hour PCR test was additionally available specifically for RSV and Influenza A and B viruses. In a median of 75 daily outpatient access and 35 inpatient patients, a total of 243 nasal swabs were analyzed in a time period of 5 months: RSV was detected in 54 cases (22%), either as a single infection (81%) or in co-infection with other pathogens (19%) – Table 1. Specifically, RSV B was detected in 48 cases (89%), while RSV A in 6 cases (11%). The median age of patients at the time of diagnosis was 59 years (range 17–78 years). Among these, 31 (58%) had undergone allogenic HSCT, 11 (19%) autologous HSCT, 2 (4%) had received CAR-T cell therapy, and 10 (19%) were undergoing chemotherapy. The most common hematological diagnoses were acute myeloid leukemia (30%), multiple myeloma (26%), lymphoma (12%), myelodysplastic/myeloproliferative diseases (11%), severe aplastic anemia (8%), and acute lymphoblastic leukemia (8%). It is noteworthy that 25 out of 54 patients (46%) were receiving systemic immunosuppressive therapy, including high-dose steroids, sirolimus, cyclosporine, and ruxolitinib,

Table 1
Patients' characteristics.

	RSV cases n 54
Median Age years, (range)	59 (17–78)
Comorbidities, (%)	39 (72)
Cardiovascular	13 (24)
Respiratory	4 (7)
Diabetes	2 (4)
Metabolic syndrome	8 (15)
Others	12 (22)
Disease, (%)	
AML	16 (30)
MM	14 (26)
ALL	4 (8)
Lymphomas	6 (12)
Others (MDS, MPD, SAA)	14 (26)
HSCT, (%)	
Autologous HSCT	11 (19)
Allogenic HSCT	31 (58)
CAR-T	2 (4)
Chemoimmunotherapy	10 (19)
Ongoing immunosoppression, (%)	25 (46)
Type of RSV, (%)	
RSV-A	6 (11)
RSV-B	48 (89)
Coinfections, (%)	10 (19)
GvHD (acute/chronic)	11 (20)
ISI risk, (%)	
Low	16 (30)
Moderate	25 (47)
High	13 (23)
LRTI progression	24 (44)
Outpatient, (%)	30 (56)
Inpatient, (%)	24 (44)
Treatments, (%)	
No therapy	26 (48)
Immunoglobulin only	1 (2)
Immunoglobuline + ribavirin	18 (34)
Immunoglobulin + ribavirin + palivizumab	9 (16)

ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; GvHD, graft-versus-host disease; LRTI, lower-tract respiratory infection; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN (myeloproliferative disease); RSV, respiratory syncytial virus; SAA, severe aplastic anemia.

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	URTI	LRTI
ISI low	Immunoglobulines	Immunoglobulines + Ribavirine
ISI moderate	Immunoglobulines + Ribavirine	Immunoglobulines + Ribavirine + Palivizumab
ISI high	Immunoglobulines + Ribavirine + Palivizumab	Immunoglobulines + Ribavirine + Palivizumab

Fig. 1. Local approach in case of RSV infection in immunocompromised patients.

while 11 out of 54 (20%) were suffering from active acute or chronic graft-versus-host disease (GvHD). The median time for symptoms resolution was 12 days (range 1–59 days). Upper respiratory tract infections (URTI) progressed to lower respiratory tract infections (LTRI) in 24 out of 54 cases (44%), requiring low-flow oxygen support in 15 out of 24 cases (63%), High-Flow Nasal Cannula (HFNC) in 1 case (2%), non-invasive ventilation (NIV) in 2 cases, and 2 patients required admission to the Intensive Care Unit (ICU) for tracheal intubation. All patients received pulmonary imaging with both X-Ray and CT-scan of the chest to assess the extent of infection and to detect early signs of acute respiratory distress syndrome (ARDS). We have not identified a specific radiologic pattern predictable of progression. Instead, all patients were evaluated using the MD Anderson Immunodeficiency Scoring Index (ISI-score),[9] which categorizes patients into three risk levels: low, moderate, and high, on a scale from 0 to 12. The median ISI score was 3 (range 0–11), with the majority of patients falling into the moderate risk category. Of note, only one patient with ISI score low (overall 16 patients scored low) progressed from URTI to LRTI, while all patients with ISI score high (13 patients) developed LRTI.

Since urgent treatment was necessary and no approved drugs were available for this condition, internal guidelines were established through discussions among hematologists, infectious disease specialists, and hospital infection control unit (Fig. 1). Twenty-eight patients received intravenous immunoglobulins (0.5 mg/kg for 4 days if hospitalized or 20 g if outpatient), 9 out of 28 (32%) were also administered oral off-label ribavirin (30 mg/kg every 8 h), and 9 out of 28 (32%) received both ribavirin and off-label palivizumab (15 mg/kg once). Bacterial or fungal superinfections were documented in 8/54 patients (15%), but empiric antibiotic regimens were started in 29 cases (51%). After a median follow-up of 161 days (range 100–239 days), our analysis revealed an overall case fatality rate (CFR) of 11% (6 out of 54 patients) while the infection-related CFR was 5.5% (3 out of 54 patients). Death occurred within a median of 12 days from the positive RSV test result (range 4–43 days). Three patients died for ARDS caused by RSV infection within the first month after undergoing allo-HSCT, while the remaining three patients died due to disease progression or GvHD. No cases of reinfection were documented in our study population.

Our single-center experience emphasizes not only the severity of RSV infection in immunocompromised hematological patients but also the high rate of RSV transmission despite high level of care and preventive measures. Although the ISI score has been shown to predict the progression from URTI to LRTI in recipients of allo-HSCT, we still lack a validated risk score and an approved drug for this patients' subgroup.[10] However, ISI score has not been validated for use in other hematological diseases, such as multiple myeloma, which may have severe immunoparesis, thus potentially underestimating their risk. In addition to risk assessment, urgent environmental measures, including patient cohorting, contact isolation, and rigorous cleaning protocols, have proven effective in preventing further transmission of RSV, as previously reported.[11] Close collaboration with other specialists has been essential in developing specific treatment strategies such as the combination of immunoglobulins, oral ribavirin, and palivizumab that has demonstrated effectiveness in preventing severe pneumonia. We report a higher CFR associated with RSV infection in hematological patients compared to that reported for SARS-CoV-2 infection in the same group.[12] This underscores the critical importance of maintaining a high level of clinical suspicion, widespread testing, implementing preventive measures, and initiating early treatment. Furthermore, we have a positive outlook on the development of new promising vaccines, as we believe they will be the most effective way to prevent severe complications related to RSV infection.[13,14]

Data availability

The datasets generated for this study are available on request to the corresponding author.

Ethics approval and consent to treatment

All patients were treated according to current Institutional programs upon written informed consent for pharmacological treatment and/or cellular therapy procedures, use of medical records and immunological studies for patients undergoing allogeneic HSCT within the non-interventional ALMON study, approved by San Raffaele Institutional Ethical Committee in date 19/10/2007. Treatment with ribavirin and/or palivizumab was given off-label after the provision of an informed signed consent.

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Author contributions

All authors substantially contributed to: (1) the conception and design of the study [FF, SD, LSMT], (2) acquisition of data [all authors], or analysis and interpretation of data [FF, SD, CF, LSMT], (3) drafting the article [FF, SD, CF, LSMT], or revising it critically for important intellectual content [all authors], (4) final approval of the version to be submitted [all authors].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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