# Community-acquired respiratory virus infections in patients with haematological malignancies or undergoing haematopoietic cell transplantation: updated recommendations from the 10th European Conference on Infections in Leukaemia

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**To update recommendations of the 4th European Conference on Infections in Leukaemia (ECIL-4) on community-acquired respiratory virus (CARV) infections published in 2013, we reviewed publications from between Jan 1, 2014, and June 30, 2024 on adenovirus, bocavirus, coronavirus, influenzavirus, metapneumovirus, parainfluenzavirus, respiratory syncytial virus (RSV), and rhinovirus in patients with haematological malignancies or undergoing haematopoietic cell transplantation (HCT), or both. In the current ECIL recommendations (ECIL-10), we outline a common approach to infection control, laboratory testing, and diagnosis for all CARVs (including SARS-CoV-2) and specific management and deferral strategies for CARVs other than SARS-CoV-2. For influenzavirus, seasonal inactivated-vaccines and early antivirals are recommended, whereas routine antiviral prophylaxis is discouraged for immunocompromised patients. For RSV, licensed vaccines can be considered according to local approval, despite scarce evidence for patients with haematological malignancies and those undergoing HCT. Passive immunisation with palivizumab or nirsevimab is recommended for children younger than 2 years, but data are insufficient for pre-exposure or post-exposure prophylaxis, or treatment of older children and adults. Oral ribavirin or intravenous immunoglobulins, or a combination of the two, are recommended for patients undergoing HCT with severe immunodeficiency scores. For other CARVs, recommendations include only supportive care, improving immune functions, correcting hypogammaglobulinaemia, and judicious lowering of corticosteroids. We highlight unmet needs in immunisation and antivirals for reducing CARV-associated morbidity and mortality in patients with haematological malignancies and those undergoing HCT.**

## Introduction

Community-acquired respiratory viruses (CARVs) are major causes of morbidity and mortality in the general population. Children, older adults, and immunocompromised people are at the highest risk for severe manifestations and poor outcomes.[1,2] CARVs particularly affect patients with haematological malignancies, patients undergoing autologous or allogeneic haematopoietic cell transplantation (HCT), and patients receiving other treatments such as B-cell targeting small molecule drugs, monoclonal or bispecific antibodies, or chimeric antigen receptor (CAR) T-cell therapy.[3–5] Risk factors for severity and poor outcomes include the underlying disease, short-term and long-term effects of chemotherapy and conditioning regimens, persistent hypogammaglobulinaemia, and immunosuppressive effects of medications administered for treating the underlying disease or adverse immune responses such as graft-versus-host disease (GVHD).[1,4–7]

The pathophysiology of respiratory tract infectious disease (RTID) caused by CARVs (CARV-RTID) has been reviewed previously.[1] RTID is caused by absent or suppressed humoral and cellular immunity specific to CARVs that is needed to neutralise and terminate infections early following viral exposure. Extensive and prolonged CARV replication drives cytopathic damage in the respiratory mucosal and epithelial lining. Excessive activation of the innate immune response aggravates symptoms and signs of local and systemic inflammation, which results in diffuse alveolar damage, reduced oxygen saturation, life-threatening capillary leakage, and increased pulmonary fibrosis. Moreover, impaired mucociliary clearance increases the risk of bacterial and fungal co-infections, all of which can contribute to acute and long-term morbidity and mortality of CARV-RTID.[1] Lower RTID (LRTID) is particularly critical and can result from primary viral pneumonia caused by agents such as influenzavirus A or B or SARS-CoV-2. However, most cases arise after upper RTID (URTID).[8] The leading causes of LRTID in patients undergoing HCT and those with haematological malignancies are influenzavirus A and B, RSV, human metapneumovirus (HMPV), human parainfluenzaviruses (HPIVs), SARS-CoV-2, and human adenoviruses (HAdVs). Cases attributed to human rhinoviruses (HRhVs) or human coronaviruses (HCoVs) have been described, whereas information is scarce on human bocaviruses (HBoVs) and human polyomaviruses. Notably, the progression to LRTID has been correlated with clinical and laboratory surrogates of impaired immune functions.[9,10] Thus, immunodeficiency scoring has been helpful in identifying patients undergoing allogeneic HCT at high risk for progression to LRTID,

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See Online for appendix

hospital admission, intensive care, and death.[3,10–13] Vaccination, infection control, prompt diagnostic testing, early interventions aimed at improving immune effector cell functions, and initiation of antiviral treatment, if available, can mitigate otherwise adverse CARV outcomes in patients with haematological malignancies, patients undergoing HCT, or patients receiving CAR T-cell and other therapies.

## What is the epidemiology of CARVS in patients with haemotological malignancies or patients undergoing HCT?

CARV infections in patients with haematological malignancies and patients undergoing HCT show a seasonality similar to the general population.[1] Although CARVs can be detected all year round, HRhVs predominate during the warmer seasons, whereas rates for influenzaviruses, RSVs, HMPVs, HPIVs, and HCoVs increase during the colder seasons and can reach epidemic thresholds in both the northern and southern hemispheres. However, a dramatic decrease in the incidence of CARVs in the general population and in patients with haematological malignancies and those undergoing HCT were noted during the first phase of the 2009 influenza pandemic and during the 2020 COVID-19 pandemic.[14,15] Although the number of patients undergoing autologous and allogeneic HCT briefly declined in Europe during the early phase of the COVID-19 pandemic (mostly due to the deferral of indications for non-malignant disorders),[16] the relative rates of bacterial and fungal superinfections remained similar or even increased. These rates reflect the common pathophysiology following extensive viral cytopathic damage caused by SARS-CoV-2 and established CARVs, as well as the need for intensive care, invasive oxygenation, and the use of anti-inflammatory therapies.[17] Following the post-pandemic resurgence of CARVs other than SARS-CoV-2 in the general population, CARV-RTID rates also increased among patients with haematological malignancies and patients undergoing HCT.[18] Notably, the clinical impact of CARV infections remains highest among patients receiving high-dose chemotherapy, HCT conditioning, or high-dose corticosteroids, with pronounced morbidity and mortality for influenzavirus A and B, SARS-CoV-2, RSVs, HMPVs, and HPIVs.[3,10,12,13,19–23]

In this Review, we provide evidence-based updates of the 4th European Conference on Infections in Leukaemia recommendations on the management of CARV infections[24] (panel) in patients with haematological malignancies or patients undergoing HCT, published in 2013, and highlight unmet needs in immunisation and antivirals for reducing CARV-associated morbidity and mortality in these patients.

### Development of recommendations

The methodology for European Conference on Infections in Leukaemia guidelines has been previously published (appendix p 1). Relevant studies identified through the literature search were reviewed by the working group, who proposed grading recommendations on the basis of the quality of evidence according to the European Society of Clinical Microbiology and Infectious Diseases grading system (appendix p 1). The suggested recommendations were discussed and presented in two plenary sessions of the tenth ECIL meeting, held between Sept 19 and 21, 2024 in Sophia Antipolis, France.

## What virological tests are recommended for patients with haemotological malignancies or patients undergoing HCT?

Nucleic acid testing (NAT) is the preferred method for a laboratory-confirmed diagnosis of CARV infection in patients with haematological malignancies and patients undergoing HCT (appendix p 2). Rapid NAT with turnaround times of less than 2 h are preferred to support timely decisions on hospital admission, infection control, modification or deferral of chemotherapy or conditioning procedures, and antiviral treatment (if available).[10,25–29] Most commercially available assays, including multiplex NAT, report qualitative results by default.[14] However, some licensed assays can obtain relative CARV loads by cycle threshold values or number of copies per mL of total nucleic acid extract.[15,28,30–32] Quantitative NAT is used in some centres to determine CARV loads, allowing clinicians to track the specific virological course in affected patients and avoid costly repeats of multiplex NAT that provides solely qualitative results.[30,32,33] Notably, sampling and assay variability and the absence of commutable standards currently preclude general recommendations regarding CARV loads or cycle threshold values. NAT also serves as a reference method for CARVs not routinely tested in local laboratories, such as avian influenzavirus A variants. Given the rising numbers of avian influenza cases in North America and elsewhere, NAT specific to avian influenzavirus A are provided by reference laboratories for a laboratory-confirmed diagnosis.[34]

Direct antigen testing for CARVs can provide rapid results including by self-testing, independent of health-care providers or institutions. Nevertheless, health-care providers should interpret the results in the clinical context to decide whether confirmatory testing by NAT is needed, considering the potential consequences for medical care. Although positive antigen tests are considered to be reliable, negative results cannot rule out influenzavirus A or B, RSV, or SARS-CoV-2 because they are less sensitive than NATs[33] (appendix p 2). Virus isolation by cell culture technique has been largely abandoned because of long turnaround times and the need for expert laboratory resources. CARV-specific serology is not recommended for diagnosis or management of CARV-RTID, since antibody responses are particularly unreliable in immunocompromised

patients with haematological malignancies and those undergoing HCT (appendix p 2).

## How can CARV infections be prevented in patients with haemotological malignancies and patients undergoing HCT?

Infection control measures are key to preventing CARV exposure of patients with haematological malignancies and patients undergoing HCT, both inside and outside of health-care facilities (table 1). Measures include avoiding crowding in public places and adhering to personal protection measures according to the epidemiological risk. Hospital access should be restricted for visitors or health-care providers with symptoms or signs of RTID. Contact between patients with haematological malignancies or those undergoing HCT and children should be regulated by an institutional policy in hospitals and facilities caring for such patients. CARVs differ in transmission efficacy and modality and in their inactivation-sensitivity to disinfection and hand-hygiene procedures.[1] Notwithstanding, we recommend uniform droplet and contact precautions for all patients with haematological malignancies or patients undergoing HCT with respiratory symptoms, or patients who test positive for CARVs (appendix p 3). For patients receiving in-patient care who test positive for CARVs, we recommend private rooms (and negative pressure rooms are preferred, if available). For patients in high-efficiency, particulate air-filtered hospital rooms because of profound and prolonged neutropenia, a local policy is needed to prevent nosocomial spread due to contaminated filters or positive pressure. We recommend the universal use of personal protective equipment for health-care providers and visitors.[5,35] Prolonged CARV shedding in asymptomatic patients with haematological malignancies or undergoing HCT frequently exceeds 1–2 months after initial diagnosis[8,20,28,32,36] and can be an important source of nosocomial spread,[36,37] intrahost and interhost viral evolution, immune escape, and antiviral resistance.[38,39] Immunosuppressive drugs and severe immunodeficiency scores have been correlated with prolonged shedding.[30,32,38]

| | ESCMID grade* |
|---|---|
| Patients and contacts should adhere to good personal hygiene such as frequent hand washing, covering the mouth when coughing and sneezing, and disposing safely of oral and nasal secretions | AII |
| Patients should avoid contact with individuals with RTIDs in the hospital and in the community | AII |
| Outside of care facilities, patients should avoid crowding in public places and adhere to personal protection measures according to the local epidemiological risk | AIII |
| Inside care facilities, infection control measures should be applied to patients with RTIDs, which include private rooms and strict personal protection measures (droplet and contact precautions, including gloves, gowning, and masks) for health-care providers and visitors | AIIt |
| All visitors and health-care providers with RTIDs caused by CARVs should be restricted from access to patients and wards | AII |
| Because of the high risk of CARV exposure, prolonged shedding, and ease of transmission, contact between patients and children should be regulated by an institutional policy for outpatient and inpatient services | BIIt |
| Outpatients with RTIDs should be seen and treated in accordance with infection control measures—ie, in facilities and rooms separated from other patients undergoing HCT or with haematological malignancies | AII |
| All of these recommendations should be applied to patients before and after the administration of CAR T cells or B-cell targeting antibody and drug therapy | BIIt |

CAR=chimeric antigen receptor. CARV=community-acquired respiratory virus. ESCMID=European Society for Clinical Microbiology and Infectious Diseases. HCT=haematopoietic cell transplantation. RTID=respiratory tract infectious disease. *Recommendations graded according to the ESCMID grading system (appendix p 1). Further guidance on prevention is provided in the appendix (p 3).

***Table 1:*** **Recommendations for prevention of CARV infections in patients with haematological malignancies and patients undergoing HCT**

## What are clinical considerations relevant to patients with haematological malignancies and those undergoing HCT?

Patients with haematological malignancies and patients undergoing HCT who are symptomatic are diagnosed as recommended previously,[1,24] whereby confidence in diagnosis is based on clinical criteria supported by epidemiology, virological testing, imaging, and a clinician's judgement that the illness is due to an infectious agent (appendix p 4). However, patients receiving CAR T-cell therapies might show symptoms and signs mimicking infection, due to therapy-associated immune dysregulation.[40] For virological testing, samples should be obtained from the major site of clinical involvement (table 2). Nasal swabs, nasopharyngeal swabs, or combined naso-oropharyngeal swabs are typically submitted for URTID. Saliva, buccal, nasal, or mid-turbinate swabbing (by patients themselves or health-care professionals) have been combined with nasopharyngeal swabbing, but might have lower sensitivity on their own.[41] For LRTID, diagnostic considerations are detailed later in this section and include testing of bronchoalveolar lavage fluid.

Asymptomatic patients with haematological malignancies and patients undergoing HCT present a challenge for management as they could be: post-symptomatic (the period after clinical recovery from RTID is often associated with prolonged and high amounts of CARV shedding in this group); pre-symptomatic (if recently exposed), and therefore at risk of worsening; or truly asymptomatic and remain so during the entire follow-up.[42,43] Importantly, chemotherapy, conditioning, or immunosuppressive medication are known to abruptly induce an adverse clinical course. Nevertheless, universal screening of asymptomatic patients on admission is controversial because of the financial and diagnostic

| | ESCMID grade* |
|---|---|
| **Diagnostic testing recommendations†** | |
| HCT candidates or recipients presenting with URTID or LRTID should be tested for CARVs by multiplex NAT to guide infection control measures, treatment, and decisions regarding deferral of chemotherapy or HCT | AII |
| For all patients with RTID due to be admitted to hospital or already admitted, comprehensive diagnostic NAT (CARV multiplex NAT) is recommended, covering influenzavirus A and B, SARS-CoV-2, RSV, HPIV, HMPV, HRhV, HCoV, and HAdV | BIII |
| In health-care centres not providing CARV multiplex NAT, first-line diagnostic testing should be done for influenzavirus A and B, SARS-CoV-2, and RSV, and if negative, followed by second-line diagnostic testing for HMPV and HPIV 1–4 or other specific CARVs (eg, HRhV and HAdV) as epidemiologically indicated | AIIt |
| Specimens should be taken from the site of clinical involvement, preferably nasal, nasopharyngeal, or naso-oropharyngeal swabs for URTID, or by bronchoalveolar lavage fluids for LRTID (or tracheal aspirate if bronchoalveolar lavage is not feasible) | AII |
| Patients with LRTID caused by CARV should be considered for bronchoalveolar lavage and broader diagnostic testing | AII |
| Lung biopsy (transbronchial, thoracoscopic, or open surgery techniques) remains an extreme diagnostic measure that could be considered to evaluate clinical failure and other concomitant pulmonary conditions | CIII |
| HBoV testing is not recommended for adults as studies suggest no clinical impact and question a pathogenic role of HBoV in patients undergoing HCT or patients with haematological malignancies | DIII |
| For paediatric patients, HBoV testing is not recommended because of insufficient or inconclusive data | CIII |
| **Deferral recommendations‡** | |
| For patients planned for allogeneic HCT and diagnosed with LRTID caused by CARV, deferral or reduced-intensity conditioning, if feasible, should be considered | AII (deferral) or BIII (conditioning) |
| For patients planned for allogeneic HCT and diagnosed with URTID caused by CARV, deferral or reduced intensity conditioning, if feasible, should be considered for CARVs with high propensity for LRTID such as influenzavirus A or B, RSV, HMPV, or HPIV | AII (deferral) or BIII (conditioning) |
| For patients planned for autologous HCT and diagnosed with LRTID caused by CARV, deferral should be considered | AII |
| For patients planned for autologous HCT and diagnosed with URTID caused by CARV, deferral of conditioning therapy should be considered for CARVs with high propensity for LRTID such as influenzavirus A or B, RSV, HMPV, or HPIV | BIII |
| For patients with haematological malignancies planned for chemotherapy and diagnosed with LRTID caused by CARV, deferral should be considered | AII |
| For patients with haematological malignancies planned for chemotherapy and diagnosed with URTID caused by CARV, deferral should be considered for CARVs with high propensity for LRTID such as influenzavirus A or B, RSV, HMPV, or HPIV | BIII |

CARV=community-acquired respiratory virus. ESCMID=European Society for Clinical Microbiology and Infectious Diseases. HAdV=human adenovirus. HBoV=human bocavirus. HCT=haematopoietic cell transplantation. HCoV=human coronavirus. HMPV=human metapneumovirus. HPIV=human parainfluenzavirus. HRhV=human rhinovirus (including enteroviruses or picornaviruses). LRTID=lower respiratory tract infectious disease. NAT=nucleic acid testing. RSV=respiratory syncytial virus. RTID=respiratory tract infectious disease. URTID=upper respiratory tract infectious disease. *Recommendations graded according to the ESCMID grading system (appendix p 1). †Further considerations on diagnosis are provided in the appendix (pp 2, 5). ‡Further guidance on deferral is provided in the appendix (p 6).

***Table 2:*** **Diagnostic and deferral recommendations for patients with haematological malignancies and those undergoing HCT presenting with CARV-RTID**

burden. Although no general recommendations can be given, when planning therapies that substantially impair immune functions, CARV testing of asymptomatic patients with haematological malignancies and patients undergoing HCT is considered in some institutions at times of increased epidemiological risk.

URTID (eg, runny nose, coryza, postnasal drip, coughing, and nasal and sinus congestion) in patients with haematological malignancies and patients undergoing HCT often presents as a continuum to LRTID (eg, tracheitis, bronchitis, and pneumonia; appendix p 5). Early in the clinical course of RTID, most cases will be managed as probable CARV-attributable pneumonia when CARVs are detected in upper respiratory samples from patients who have clinical symptoms and signs and hypoxaemia, diagnostic imaging showing new or progressive abnormalities, or a combination of these factors (appendix p 5). Clinical worsening and severe cases of RTID require broadening of the differential diagnosis for coexisting pathologies, especially in the context of multimorbidity in patients with haematological malignancies and patients undergoing HCT. Chest CT scans have a higher predictive value for ruling in and ruling out CARV-attributable pneumonia compared with conventional chest x-rays. Chest CT scans also allow health-care providers to evaluate the clinical course and guide bronchoscopy, bronchoalveolar lavage, or biopsy acquisition.[44] However, detecting particular CARVs (such as HRhV, HCoV, HAdV, and HBoV) in nasopharyngeal swabs might not be sufficient for a probable diagnosis of CARV-attributable pneumonia because different CARVs might be present in the lower respiratory tract.[45,46] The detection of CARVs in bronchoalveolar lavage fluid supports the diagnosis of laboratory-confirmed CARV-attributable pneumonia. Bronchoscopy bears some risk of detecting contaminating CARVs from the upper respiratory tract by sensitive NAT of bronchoalveolar lavage fluid. Although no generalised guidance can be given, some experts request CARV loads that are 10–100-times higher in bronchoalveolar lavage fluid than in matched nasopharyngeal swabs for a diagnosis of CARV-LRTID.[45,46] Showing CARV pathology in lung tissue is the ultimate proof, but is rarely done early in the clinical course for patients with haematological malignancies and those undergoing HCT, due to the invasiveness and associated risk of complications for transbronchial forceps biopsy, cryobiopsy, open lung biopsy, or video-assisted thoracoscopic surgery.[47] However, improved transbronchial cryobiopsy techniques might provide higher diagnostic yields than forceps procedures at similarly low complication rates for lesions presenting as interstitial lung disease.[48,49] Besides chronic lung allograft disease, bronchiolitis obliterans syndrome, or pulmonary GVHD, the differential diagnosis in patients with haematological malignancies and those undergoing HCT includes leukaemic or infectious infiltrates.[50,51] In a meta-analysis of 95 studies published between 1980 and 2014, an infectious diagnosis was made more frequently by bronchoalveolar lavage, whereas a non-infectious diagnosis was made more frequently by lung biopsy and more likely to change management.[47] Unlike for bacterial, fungal, and some viral causes such as adenoviruses or herpes viruses, CARV-specific diagnostic investigations of lung biopsies are currently limited by the lack of standardised tools, and therefore depend on local expertise for CARV-specific immunohistochemistry or on novel molecular and

metagenomic approaches. In many studies, laboratory-confirmed and biopsy-proven CARV-LRTIDs are combined as proven CARV-pneumonia.

## When does clinical management change for CARV-positive patients?

Deferral or modification of the clinical management of patients with haematological malignancies and patients undergoing HCT with laboratory-confirmed CARVs should only be attempted if delaying treatment for the underlying disease is justifiable (table 2). Patient characteristics such as frailty and comorbidities, the choice of treatment (specifically immunosuppressive or myelosuppressive drugs), and the specific CARV detected and its treatment options are key factors for determining the CARV-RTID prognosis (appendix p 6).[6,43,52] Increasingly, lymphoid malignancies are treated with small molecule drugs; CAR T cells; and depleting

| | ESCMID grade* |
|---|---|
| **General aspects** | |
| Live-attenuated influenzavirus vaccines should not be used in patients who are immunocompromised | DIIt |
| **Patients undergoing allogeneic HCT** | |
| Annual seasonal IIV is recommended at the beginning of influenza season for all patients at 6 months post-transplant | AII |
| Annual seasonal IIV should be considered at the beginning of the influenza season for all patients at 3 months post-transplant, despite a likely lower efficacy than when given at 6 months | AIIIu |
| Vaccination should be repeated annually | AIIt |
| **Patients undergoing autologous HCT** | |
| Annual seasonal IIV administration is recommended at the beginning of the influenza season for all patients at 3 months post-transplant | AIItu |
| Vaccination should be repeated annually | AIIt |
| **Patients with haematological malignancies** | |
| Annual seasonal IIV administration is recommended at the beginning of the influenza season to all patients | AIIt |
| Vaccination should be repeated annually | AIIt |
| **Patients treated with B-cell-targeting therapies by depleting antibodies, CAR T cells, bispecific antibodies, or small molecule inhibitors** | |
| Data are currently insufficient, but since vaccine responses are expected to be low or absent for the time of treatment and several months thereafter, seasonal IIV could be considered, as defined by national regulations, or by a local protocol that adapts the recommendations for patients undergoing allogeneic HCT with respect to dose, timing, and repetition | CIII |
| **Adult patients** | |
| High-dose trivalent IIV targeting influenzavirus A and B is recommended for patients undergoing allogeneic HCT | AII |
| There are data supporting an increased immunogenicity of high-dose non-adjuvanted IIV | Statement |
| There are insufficient data supporting an increased clinical efficacy of adjuvanted over non-adjuvanted IIV | Statement |
| **Paediatric patients** | |
| IIV should be given to paediatric allogeneic and autologous HCT recipients as early as 3 months post-transplant | AII |
| Annual high-dose trivalent IIV is recommended for paediatric patients undergoing allogeneic HCT | BII |
| A second standard-dose of trivalent IIV 4 weeks after the first should be considered for patients undergoing HCT who were vaccinated as early as 3 months post-transplant or who are at risk for low or absent vaccine responses | BIIt |
| For children aged 6 months to 3 years receiving standard-dose influenza vaccination for the first time after transplant, a second standard dose can be recommended at 4 weeks after the first dose | BII |
| For children older than 3 years, a second high-dose trivalent IIV can be recommended during a prolonged outbreak | BII |
| Recommendation updates need to be harmonised with national regulations defining specific IIVs and age ranges for paediatric administration | Statement |
| **Health-care providers and close contacts** | |
| Health-care providers in contact with patients who are immunocompromised should receive IIV annually | AIIt |
| Individuals in close contact with, or household members of, HCT recipients should receive IIV at the beginning of the season before transplant and during the first season after transplant | AIIt |
| Individuals in close contact with, or household members of, HCT recipients should receive IIV annually, for as long as the patient is judged to be immunocompromised | BIII |
| The live-attenuated influenzavirus vaccine should not be used for individuals in close contact with, or household members of, HCT recipients in the first 12 months post-transplant, patients treated for graft-versus-host-disease, or patients with haematological malignancies on active chemotherapy | DII |
| If live-attenuated influenzavirus vaccines were inadvertently used in contacts, masking and contact precautions should be applied for 1 week in the case of asymptomatic individuals or for as long as the contact person is symptomatic | CIII |

CAR=chimeric antigen receptor. CARV=community-acquired respiratory virus. ESCMID=European Society for Clinical Microbiology and Infectious Diseases. HCT=haematopoietic cell transplantation. IIV=inactivated influenza vaccine. RTID=respiratory tract infectious disease. *Recommendations graded according to the ESCMID grading system (appendix p 1).

***Table 3:*** **Vaccination recommendations against influenza A and B**

monoclonal or bispecific T-cell-engaging antibodies targeting CD19, CD20, CD22, B-cell maturation antigen, G-protein-coupled receptor class C group 5 member D, or Fc-receptor homolog-5.[40] These treatments can induce long-lasting B-cell dysfunction, depletion, hypogammaglobulinaemia, and even T-cell dysfunction.[53] Most centres consider delaying such therapies in CARV-positive patients, even those with asymptomatic upper respiratory tract infections. Of note, these recommendations are not based on randomised trials.

## What is recommended for influenzavirus?

Annual active immunisation against influenzavirus A and B with a seasonal inactivated influenza vaccine (IIV) is recommended for all patients with haematological malignancies and patients undergoing HCT (table 3).[54] Live-attenuated influenzavirus vaccine should not be used for these patients and their close contacts, as viral shedding can increase the risk of transmission.[55,56] If live-attenuated virus vaccines were inadvertently used in contact persons, mask-wearing and contact precautions should be applied for at least 1 week, although there is an absence of definitive data supporting this recommendation.

For adult patients undergoing allogenic HCT, active immunisation is strongly recommended at the beginning of the influenza season for those who are at least 6 months post-transplant. However, due to the increasing risk of transmission and severe disease, vaccination can be recommended as early as 3 months post-transplant.[57] Current data do not indicate an increased clinical efficacy of adjuvanted over non-adjuvanted IIV in adult patients undergoing allogenic HCT.[58] Data do indicate that two doses of high-dose trivalent IIV is preferrable over two standard doses because of the better immunogenicity of high-dose IIV in people who are immunocompromised.[59,60] As immune protection is more likely to be compromised following early seasonal vaccination, during prolonged or late influenzavirus A or B circulation, or if the patient is receiving immunosuppression as prophylaxis or therapy (eg, for GVHD), we recommend a second administration of high-dose trivalent IIV in these scenarios.

For adult autologous HCT, one dose of the annual seasonal IIV is recommended at the beginning of the influenza season in all patients, starting at 3 months post-transplantation. For adult patients with haematological malignancies, one dose of the annual IIV at the beginning of the influenza season is recommended.

For paediatric patients undergoing allogeneic and autologous HCT, IIVs are recommended as early as 3 months post-transplant (table 3). Allogeneic HCT recipients aged between 6 months and 3 years who receive influenza vaccination for the first time after their transplant can be given a second standard dose of trivalent IIV 4 weeks after the first dose, based on recent studies.[59,61] However, these updated paediatric recommendations need to be harmonised with national regulations, which might define different specific IIVs and age ranges for paediatric administration. One dose of high-dose trivalent IIV post-HCT might be sufficient after a two-dose schedule in the previous year,[62] but a second dose could be considered for patients at risk of low or absent vaccine responses, or in case of long-lasting influenzavirus A or B circulation.

For patients treated with B-cell targeting drugs,[53,63] monoclonal or bispecific antibodies,[64] or CAR T cells,[40,65–67] vaccine responses are presumably impaired or absent during treatment administration and several months thereafter. Accordingly, seasonal vaccination with IIV targeting influenzavirus A or B can be considered as defined by national regulations (or, if national regulations are unavailable, by a local protocol adapting the dose and timing) and repeated as recommended for patients undergoing allogeneic HCT. Health-care providers and all individuals in close contact with immunocompromised patients should receive IIV annually at the beginning of the influenza season.[68]

Antiviral drugs are available to prevent or treat RTID due to influenzavirus A or B viruses in patients with haematological malignancies and those undergoing HCT (table 4). General seasonal antiviral prophylaxis is discouraged. Post-exposure prophylaxis (within 48 h) with oseltamivir (75 mg given twice per day) is recommended for a duration of 7–10 days for all severely immunocompromised patients with haematological malignancies and patients undergoing HCT regardless of vaccination history[69] (appendix p 7). The rationale for therapeutic dosing in this setting is the high likelihood of treating early infection in immunologically compromised patients at high risk.[70,71] During a nosocomial influenza outbreak, 75 mg oseltamivir once per day could be considered as prophylaxis for non-exposed patients who are severely immunocompromised and on the same wards.[72] HCT recipients and patients with haematological malignancies with laboratory-confirmed influenzavirus A or B should be treated with antivirals as soon as possible (preferably within 24–48 h after symptom onset)[73] for 5–10 days or until clinically significant improvement (table 4). If rapid virological testing is not available, patients undergoing HCT and patients with haematological malignancies with compatible signs and symptoms during the influenza season should be treated promptly while awaiting laboratory confirmation. The recommended adult dose of oseltamivir is 75 mg twice per day. For children, oseltamivir is administered according to bodyweight (appendix p 7).

Although baloxavir marboxil is now recommended by WHO as a first-line antiviral,[74,75] few data are available for patients with haematological malignancies or those undergoing HCT.[76] Given its novel mechanism of action, baloxavir marboxil has been used for treating neuraminidase inhibitor-resistant influenza.[77] One dose of baloxavir marboxil is administered within 48 h of symptom onset according to bodyweight (appendix p 8). Baloxavir

marboxil has been studied in children older than 1 year.[78] Patients can receive multiple doses every 72 h, as clinically indicated.[79] However, drug resistance mutations have been observed in the polymerase acidic protein and might emerge more rapidly in children and immunocompromised people.[80] Zanamivir inhalation is available for out-patient treatment of uncomplicated influenza,[81,82] but data are scarce for first-line treatment of patients with haematological malignancies or patients undergoing HCT.

For adult patients at risk for or presenting with severe or persistent influenza, some experts recommend a double-dose of oseltamivir at 150 mg twice per day,[71] even though late initiation (beyond 48 h after symptom onset) might not change the clinical outcome.[73,83] Clinical data suggest oseltamivir should not be combined with zanamivir, but combining neuraminidase inhibitors with either baloxovir marboxil or ribavirin could be considered. Adamantanes are obsolete because of rapid resistance emergence and near universal resistance among currently cirulating influenzavirus A and B.[1] When gastrointestinal absorption is impaired, intravenous zanamivir or peramivir (if available, as not licensed in Europe) could be considered (appendix p 9). Patients with LRTID due to influenzavirus A or B who do not improve despite adequate treatment with neuraminidase inhibitors for at least 5 days should be re-evaluated for other causes such as bacterial or fungal co-infections, GVHD, or interstitial lung disease. If influenzavirus A or B persist (at high amounts, if quantitative NAT is available) in patients not responding despite adequate therapy for 10 days, genotypic resistance testing could be considered and antiviral treatment adapted as suggested (table 4).

## What is recommended for RSV?

Active immunisation against RSV A or RSV B is currently licensed for adults older than 60 years and those at risk for severe LRTID caused by RSV (RSV-LRTID).[84–86] Patients with haematological malignancies and those undergoing HCT are at considerable risk,[87] but were not included in the licensing trials. Although no recommendations on RSV vaccination can be made presently (appendix p 10), vaccine effectiveness is expected to be reduced by immunosuppression, chemotherapy, or recent HCT. For the available RSV vaccines,[84–86] a single dose provided 70–80% efficacy during the first season after RSV vaccination and the second RSV season in non-immunosuppressed older individuals.[88] However, efficacy and safety in patient populations with haematological malignancies or undergoing HCT have not been defined. Contraindications include a history of severe allergic reactions to any component of the respective vaccines. There is a recent warning about Guillain-Barré syndrome for the protein vaccines Abrysvo (RSVpreF; Pfizer) and Arexvy (RSVPreF3OA; GSK), but rates of the syndrome among immunocompromised populations are unknown (appendix p 10). To obtain clinical and immunological efficacy data, both adult and paediatric patients undergoing HCT and patients with haematological malignancies should be included in prospective clinical trials. Since such results are unlikely to be available for immunocompromised people within the next 2 years, some experts and national authorities support RSV vaccination for patients

| | ESCMID grade* |
|---|---|
| **Antiviral prophylaxis** | |
| Routine antiviral pre-exposure prophylaxis of patients who are immunocompromised during the influenza season is discouraged | DIII |
| Post-exposure prophylaxis (within 48 h) with oseltamivir (75 mg given twice daily for 7–10 days) is recommended for all patients with haematological malignancies and those undergoing HCT regardless of vaccination history | AIIt |
| Pre-exposure prophylaxis with oseltamivir for patients who are severely immunocompromised (regardless of vaccination status) can be considered (eg, during a suspected nosocomial outbreak for at least 7 days in prophylactic dosing if NAT is negative, or in therapeutic dosing, if NAT is positive) | BIII |
| **Antiviral therapy** | |
| Laboratory-confirmed influenzavirus RTID in allogeneic and autologous HCT recipients, or patients with haematological malignancies who test positive during chemotherapy and in the following 6 months, should be treated with antivirals as soon as possible, preferably less than 48 h after symptom onset | AII |
| If rapid NAT or direct antigen testing is not available, patients undergoing HCT and with haematological malignancies with compatible symptoms or signs and an epidemiological risk (eg, during influenza season) should be treated promptly while awaiting laboratory confirmation | BIII |
| The first-line antiviral is oseltamivir | BII |
| The recommended adult dose of oseltamivir is 75 mg twice per day until clinically significant improvement, usually within 5–10 days (appendix p 7) | BII |
| The first-line alternative antiviral is baloxavir marboxil | BIIt |
| The recommended adult dose of baloxavir marboxil is calculated according to bodyweight (appendix p 8) | BIIt |
| If longer treatment is clinically indicated, administration of baloxavir marboxil every 72 h could be considered | CII |
| Zanamivir inhalation is available for outpatient treatment of uncomplicated influenza, but data are insufficient for first-line treatment of patients with haematological malignancies or those undergoing HCT | Statement |
| **Management of severe or prolonged cases of influenza-related RTID** | |
| For patients with severe influenza and suspicion of impaired gastrointestinal absorption, intravenous zanamivir or peramivir (if available) could be considered (appendix p 9) | CIII |
| Patients with influenzavirus A or B pneumonia who do not clinically improve or worsen despite adequate treatment with neuraminidase inhibitors for at least 5 days should be re-evaluated (with microbiological testing of samples from the lower respiratory tract) for complications including co-infections | BIII |
| For patients with continuing symptoms after 5-7 days, a role of influenzavirus A or B replication could be evaluated by repeating NAT of clinically relevant respiratory specimens as rationale for continued oseltamivir treatment until undetectable | CIII |
| In patients continuing to test positive for influenzavirus A or B after 5–7 days, antiviral treatment could be extended for at least 10 days | BIII |
| In patients with severe or prolonged influenzavirus A or B replication, combining neuraminidase inhibitors with baloxavir could be considered | BIII |
| When influenzavirus A or B replication persists for 10 days (at high levels, if quantitative NAT is available) despite adequate therapy, genotypic resistance testing could be considered | CIII |
| For patients who are severely immunocompromised presenting with severe RTID, some experts consider a double dose of oseltamivir (150 mg twice per day) | CIII |

ESCMID=European Society for Clinical Microbiology and Infectious Diseases. HCT=haematopoietic cell transplantation. NAT=nucleic acid testing. RTID=respiratory tract infectious disease. *Recommendations graded according to the ESCMID grading system (appendix p 1).

***Table 4:*** **Recommendations on antiviral prophylaxis and therapy for influenzavirus A and B**

undergoing HCT and those with haematological malignancies in accordance with local approval.

Passive immunisation to prevent RSV infection is recommended for children younger than 2 years (table 5). Currently, two monoclonal antibodies are commercially available, palivizumab (short-acting) and nirsevimab (long-acting). Immunocompromised children younger than 2 years (including those with haematological malignancies or undergoing HCT) might benefit from pre-exposure prophylaxis with palivizumab or nirsevimab for the RSV season. However, use of palivizumab as primary, pre-exposure, or post-exposure prophylaxis is discouraged for children older than 2 years, and for adults. Nevertheless, some experts consider palivizumab as post-exposure prophylaxis for severely immunosuppressed, hospitalised patients during a nosocomial outbreak on the same ward. Because it targets the pre-fusion conformation of the fusion glycoprotein F0 protein and has a longer half-life, most experts expect nirsevimab to be more efficacious than palivizumab. No recommendations can be made regarding nirsevimab or other agents in development (eg, motavizumab, motavizumab-YTE, suptavumab, clesrovimab) in adult patients with haematological malignancies or those undergoing HCT due to the absence of detailed data on dose, timing, efficacy, or adverse events in these groups.[91,92]

Antiviral drugs with potential clinical activity against RSV replication are in different stages of development (eg, LN-RSV01, RSV604, presatovir, MDT-637, lumicitabine, IFN-α1b, rilematovir, enzaplatovir, AK0529, sisunatovir, PC786, and EDP-93) but are currently not available for clinical use.[91,92] Ribavirin has become part of selective management recommendations in adult patients undergoing allogeneic HCT based on uncontrolled observational data (table 5). However, ribavirin should not be used as RSV pre-exposure or post-exposure prophylaxis in adults or in children. For RSV-positive adult allogeneic HCT recipients with a diagnosis of RSV-LRTID (or high risk of progression), treatment with ribavirin should be considered (table 5).[10,28,93,94] Oral or intravenous ribavirin is currently preferred in many institutions.[11,95] Despite the absence of controlled data, prompt initiation of oral ribavirin is viewed by some clinicians as a key to efficacy, preferentially at an early stage of RSV-URTID in allogeneic HCT recipients at high risk for progression to LRTID. Conversely, ribavirin treatment is not supported for allogeneic HCT recipients at low risk for progression to LRTID. Risk factors for progression and poor outcome can be estimated by the MD Anderson Immunodeficiency Score Index[25,26] or the Basel Severe Immunodeficiency grading[3,10,28] (appendix p 11). Immunodeficiency scores have been validated for several other CARVs in allogeneic HCT recipients.[54,96–98] Data validating immunodeficiency scores, efficacy, or dosing of systemic ribavirin in the paediatric setting are insufficient. Nevertheless, some experts suggest using systemic ribavirin together with intravenous immunoglobulin or palivizumab, at similar per weight dosing as for adults.[99,100] Ribavirin is administered orally at 10–30 mg/kg bodyweight in three divided doses up to a maximum dose of 600 mg every 8 h, corresponding to a total dose of 1800 mg/day (table 5). Higher loading doses and more rapid dose escalation have been suggested to improve efficacy.[93,101] Oral and intravenous ribavirin are dosed alike. Patients should be monitored and treated for adverse events as outlined (table 5). In case of declining renal function, the dosage of systemic ribavirin can be reduced to 200 mg every 8 h for creatinine clearance of 30–50 mL/min, but no recommendation can be made for clearance of less than 30 mL/min. Ribavirin use has been questioned because of poor antiviral efficacy and treatment limitations caused by haemolysis, abnormal liver function, renal failure, drug–drug interactions, and teratogenicity in rodent models. Teratogenicity is particularly relevant for aerosolised ribavirin, thus safe handling precautions for health-care providers and contacts are required. The cost of aerosolised ribavirin has substantially increased since 2015. This, together with poor tolerability and safety concerns, has decreased its clinical use.

Intravenous immunoglobulin preparations can be used alone or in combination with oral ribavirin for allogeneic HCT recipients with RSV-LRTID or who are at high risk of developing it.[10,28,93,102,103] At least three doses of intravenous immunoglobulin should be administered at 0·5 g/kg bodyweight within 1–2 weeks of diagnosis, particularly if hypogammaglobulinaemia (<4·5 g/L) is present (table 5). Corticosteroid treatment of more than 1 mg/kg per day at RSV diagnosis has been associated with disease progression and death and should be evaluated for dose reduction, if possible. For RSV-positive autologous HCT recipients or patients with haematological malignancies with a diagnosis of RSV-LRTID (or at high risk for progression), treatment with ribavirin might be considered as outlined for allogeneic HCT recipients (table 5). For cases where hypogammaglobulinaemia is less than 4·5 g/L, adjunct treatment with at least three doses of intravenous immunoglobulin at 0·5 g/kg bodyweight within 1–2 weeks of diagnosis could be considered.

## What is recommended for HMPV?

Active or passive immunisation is not available, and specific antiviral drugs for prophylaxis or treatment are lacking, for HMPV. Current management of adult patients positive for HMPV who are undergoing allogeneic HCT consists of supportive therapy, correction of hypogammaglobulinaemia of less than 4·5 g/L, and judicious evaluation of lowering corticosteroid treatment (appendix p 12). Given the virological relatedness to RSV,[1] some experts administer oral ribavirin alone or in combination with intravenous immunoglobulin to patients with high immunodeficiency scores (appendix p 11).[10,104,105] For adult patients with haematological malignancies or undergoing autologous HCT, with a diagnosis of HMPV-LRTID (or high risk for progression

| | ESCMID grade* |
|---|---|
| **Recommendations on passive immunisation for RSV** | |
| For children | |
| Seasonal pre-exposure prophylaxis with palivizumab for children <2 years who have undergone HCT can be considered | BIII |
| Post-exposure prophylaxis with palivizumab[89] could be considered for immunocompromised children <2 years when a nosocomial outbreak is occurring | BIII |
| RSV seasonal pre-exposure prophylaxis with nirsevimab can be considered for severely immunocompromised children <2 years | BIIut |
| There are insufficient data to recommend post-exposure prophylaxis with nirsevimab[90] for children | CIII |
| There are insufficient data to recommend treatment with nirsevimab for children with URTID or LRTID caused by RSV | CIII |
| For adults | |
| In the absence of data evaluating the efficacy or risk–benefit ratio, palivizumab should not be used for RSV pre-exposure or post-exposure prophylaxis or treatment of adult patients with haematological malignancies or patients undergoing HCT | DII |
| Palivizumab is considered by some experts as post-exposure prophylaxis for severely immunodeficient adults (eg, allogeneic HCT recipients before engraftment) when a nosocomial outbreak is occurring on the same ward | CIII |
| There are currently insufficient data for adult patients with haematological malignancies or patients undergoing HCT to recommend nirsevimab for seasonal or post-exposure prophylaxis or for treatment | Statement |
| **Recommendations on use of antivirals for RSV** | |
| Antiviral prophylaxis for RSV | |
| Due to insufficient data, ribavirin should not be used as pre-exposure or post exposure prophylaxis in adults or in children | DII |
| Systemic ribavirin for RSV in allogeneic HCT recipients | |
| Recipients with high risk for progression to, or diagnosed with, RSV-LRTID should be considered for treatment with ribavirin | BIIu |
| For guidance on defining high risk for poor outcome, the MD Anderson Immunodeficiency Score Index or the Basel Severe Immunodeficiency grading† can be considered | BIIu |
| In recipients at low risk for progression to RSV-LRTID, ribavirin treatment can be withheld | BIII |
| Systemic ribavirin can be administered orally at 10–30 mg/kg of bodyweight in three divided doses (max 600 mg/8 h, up to a maximum dose of 1800 mg/day) | BIIu |
| Patients receiving systemic ribavirin should be monitored and managed for adverse events (eg, haemolysis, abnormal liver function tests, drug–drug interactions, or declining renal function) | BIIt |
| There are insufficient data describing the immunodeficiency scores, efficacy, or dosing of systemic ribavirin in the paediatric setting, but some experts suggest a similar approach and per-weight dosing as for adults | Statement |
| Aerosolised ribavirin for RSV | |
| Although currently rarely used because of high costs and demanding logistics, 2 g aerosolised ribavirin can be administered for 2 h every 8 h for 7–10 days to treat RSV | BII |
| Aerosolised ribavirin therapy should be accompanied by measures avoiding environmental exposure, and thereby potentially teratogenic effects, in pregnant health-care providers and visitors | AII |
| Patients on aerosolised ribavirin should be monitored and treated for adverse events including claustrophobia, bronchospasm, nausea, conjunctivitis, and declining pulmonary function | BIIt |
| **Other management considerations for RSV in patients undergoing allogeneic HCT** | |
| For patients at high risk for progression to, or who have been diagnosed with, RSV-LRTID, adjunct treatment could be considered with at least three doses of intravenous immunoglobulin at 0·5 g/kg bodyweight within 1–2 weeks of diagnosis | BIII |
| For patients testing positive for RSV and hypogammaglobulinaemia (<4·5 g/L), treatment with at least three doses of intravenous immunoglobulin at 0·5 g/kg bodyweight administered within 1–2 weeks of diagnosis could be considered | BIII |
| Use of corticosteroids at more than 1 mg/kg per day at diagnosis of RSV-LRTID has been associated with disease progression and mortality; thus, reducing corticosteroid administration to less than 1 mg/kg of bodyweight can be considered if feasible | CIII |
| **Management considerations for RSV in patients undergoing autologous HCT or in patients with haematological malignancies** | |
| Treatment of patients with a diagnosis of RSV-LRTID with ribavirin should be considered | BIII |
| Systemic or aerosolised ribavirin administration and monitoring should follow the recommendations outlined for allogeneic HCT recipients | BIII |
| For patients with RSV-LRTID (or at high risk for progression to RSV-LRTID) and hypogammaglobulinaemia (<4·5 g/L), adjunct treatment with at least three doses of intravenous immunoglobulin at 0·5 g/kg of bodyweight administered within 1–2 weeks of diagnosis can be considered | CIII |

ESCMID=European Society for Clinical Microbiology and Infectious Diseases. HCT=haematopoietic cell transplantation. LRTID=lower respiratory tract infectious disease. RSV=respiratory syncytial virus. RTID=respiratory tract infectious disease. URTID=upper respiratory tract infectious disease. Considerations on active immunisation for RSV are provided in the appendix (p 10). *Recommendations graded according to the ESCMID grading system (appendix p 1). †Immunodeficiency according to clinical and laboratory parameters is provided in the appendix (p 11).

***Table 5:*** **RSV prevention and treatment recommendations**

to LRTID), treatment with ribavirin remains controversial (appendix p 12). In the case of hypogammaglobulinaemia of less than 4·5 g/L, adjunct treatment with at least three doses of intravenous immunoglobulin at 0·5 g/kg bodyweight within 1–2 weeks of diagnosis could be considered.

## What is recommended for HPIV?

Active or passive immunisation is not available for HPIV, and specific antiviral drugs for prophylaxis or treatment are unavailable. Current management of adult and paediatric patients with haematological malignancies or undergoing HCT who are HPIV-positive relies on supportive therapy, correction of hypogammaglobulinaemia of less than 4·5 g/L, and judicious evaluation of lowering corticosteroid treatment (appendix p 13). Prolonged asymptomatic shedding and nosocomial outbreaks are well documented for HPIV, emphasising the role of infection control measures. More severe manifestations have been observed in allogeneic HCT recipients with HPIV-3 infection, lymphopenia, and higher corticosteroid use (eg, >30 mg/day, often >1 mg/kg bodyweight).[19,23,42,44,97] Effective antivirals and neutralising antibodies are still under development,[1] and use of ribavirin is controversial.[23] Although available data are too limited for a general recommendation, some centres consider intravenous immunoglobulin, sometimes in combination with ribavirin, for HPIV-positive adult recipients of allogeneic HCT with high immunodeficiency scores, as outlined for adult patients positive for RSV undergoing allogeneic HCT (table 5).[10,95,97,101]

## What is recommended for HCoVs (other than SARS-CoV-2)?

HCoVs consist of four species (229E, NL63, OC43, and HKU1)[21,106,107] in addition to SARS-CoV-2. Unlike for SARS-CoV-2, active or passive immunisation is not available for HCoVs. There is no documented clinical efficacy of antivirals for pre-exposure or post-exposure prophylaxis, or for treatment with ribavirin or with antivirals licensed for SARS-CoV-2 (appendix p 14). Although available data are too scarce to support use or specific doses, administration of intravenous immunoglobulin (eg, at least three doses of 0·5 g/kg bodyweight within 1–2 weeks of diagnosis) could be considered for patients undergoing HCT or with haematological malignancies presenting with LRTID attributed to HCoV and hypogammaglobulinaemia of less than 4·5 g/L. Observational studies from the pre-pandemic era provide no support for stringent deferral of chemotherapy or conditioning for patients positive for HCoV with haematological malignancies or undergoing HCT (appendix p 6).

### Search strategy and selection criteria

References for this Review were identified through searches of PubMed and Google Scholar for articles published in English between Jan 1, 2014, and June 30, 2024, with the terms "respiratory", "virus", "haematopoietic cell transplantation", or "haematological malignancy". Specific searches were done for "adenovirus", "bocavirus", "coronavirus", "influenzavirus", "metapneumovirus", "parainfluenzavirus", "respiratory syncytial virus", and "rhinovirus". Articles resulting from these searches and relevant references cited in those articles were reviewed. Selective updates were done during manuscript revision to identify relevant publications in English published up to March 30, 2025.

## What is recommended for HRhV?

Active or passive immunisation is not available, and specific antiviral drugs for prophylaxis or treatment are in clinical development but not available for HRhVs. There are no data supporting the use of ribavirin for HRhVs (appendix p 15). The current management approach is supportive, and may involve administration of at least three doses of intravenous immunoglobulin (eg, 0·5 g/kg bodyweight within 1–2 weeks of diagnosis) for LRTID caused by HRhV (HRhV-LRTID) in patients undergoing HCT or with haematological malignancies having hypogammaglobulinaemia of less than 4·5 g/L. High-dose corticosteroids of more than 2 mg/kg bodyweight have been identified as risk factors for progression to HRhV-LRTID,[22] thus judicious dose reduction should be considered.[19,22,106–108]

## What is recommended for HAdV?

Active or passive immunisation is not available for HAdVs. Approaches have been developed for specific HAdV types to counter institutional outbreaks in military and other facilities, but there are no data for vaccinating patients undergoing HCT or patients with haematological malignancies.[1] There is also no documented clinical efficacy with sufficient specificity and an acceptable adverse event profile for pre-exposure or post-exposure prophylaxis with antivirals such as cidofovir or brincidofovir. For patients undergoing HCT and those with haematological malignancies with URTID caused by HAdV, improving HAdV-specific immune responses (eg, by reducing immunosuppression) should be considered (appendix p 16). Because HAdV might disseminate to multiple organs with subsequent poor outcomes, blood HAdV loads should be determined in patients at risk for dissemination. Although HAdV-load thresholds have not been standardised across assays and analytes (eg, plasma or whole blood), treatment with intravenous cidofovir should be considered if HAdV loads in blood rise above 1000 copies per mL in symptomatic patients at high risk.[109–111] The role of intravenous immunoglobulin for management is unclear and solely based on case reports, but could be considered for patients with hypogammaglobulinaemia of less than 4·5 g/mL. No recommendations can be made for ribavirin, ganciclovir, or combinations with intravenous immunoglobulin.[112–114]

Similarly, intravenous brincidofovir is awaiting clinical development. HAdV-specific T cells are of great interest and have shown promising results in phase 2 trials. However, no recommendations can be made other than trying to enrol patients with HAdV-RTID in clinical trials.

## What is recommended for HBoV and human polyomavirus 3 and 4?

HBoVs are exceptional causes of RTID in adults,[115] although clinical studies on RTID caused by HBoV are scarce. Similarly, the clinical relevance of human polyomavirus 3 (known as Karolinska Institute polyomavirus [KIPyV]) and human polyomavirus 4 (known as Washington University polyomavirus [WUPyV]) is unclear for adult patients undergoing HCT and patients with haematological malignancies.[1] As KIPyV and WUPyV are not present in current multiplex NAT assays, dedicated studies are needed to define their clinical relevance.

## Outlook and research agenda

Overall, the available evidence and strength of recommendations are low for patients undergoing allogeneic HCT and even lower or not available for patients undergoing autologous HCT, patients with haematological malignancies, or patients undergoing other immunological therapies. Randomised controlled trials will need to be designed against the current standard of care for patients undergoing HCT and patients with haematological malignancies. Primary endpoints, feasibility, sample sizes, costs, and safety will be major concerns in such studies.[9] For CARV-specific antivirals, targeting specific patient populations early in the clinical course and preferrably promptly at the stage of URTID, should be considered, based on post-hoc analyses from the presatovir trials.[29] Clinical immunodeficiency scores predicting the risk of progression to LRTID, hospitalisation, and death should be further refined and considered for patient stratification in prospective clinical trials. Validating CARV loads for clinical management during clinical follow-up and novel diagnostic technologies might emerge as relevant cornerstones in the future. The evaluation of active and passive immunisation for RSV, and of CARV-specific antibodies and T cells, represent considerable research opportunities. Thus, enrolling patients undergoing HCT and those with haematological malignancies in clinical trials is an important opportunity to improve medical care for CARVs in this highly vulnerable patient population.

#### Contributors

This Review is based on the European Conference on Infections in Leukaemia (ECIL) Guidelines Working Group's updating of recommendations on community-acquired respiratory virus infections in patients with haematological malignancies or haematopoietic cell transplantation during the tenth meeting (ECIL-10) held between Sept 19 and 21, 2024, in Sophia Antipolis, France. The working group was chaired by HHH (project administration and conceptualisation). All authors participated equally in identifying and reviewing the literature, grading the quality of the evidence, and grading the strength of the recommendations. MvL-T, RFC, and HHH wrote the first draft and revised the prefinal version. All authors reviewed and edited each version of the manuscript. HHH finalised the manuscript.

#### Declaration of interests

FK has received research support paid to his institution from Merck, Eurofins Viracor, and Symbio. CR has received an honorarium for participation on an advisory board from Mundipharma and as a speaker from Gilead and MSD, and support for attending meetings from Pfizer, Mundipharma, Gilead, and Takeda. J-LP has received an honorarium for consulting from Merck Sharp & Dohme and speaker fees and travel support from Kite, and is currently the Vice President of the Spanish Hematopoietic Transplant and Cell Therapy Group. PL has received honoraria for consulting from AstraZeneca, GSK, and Moderna and speaker fees from Pfizer, and has served as Data Safety Monitoring Board Chair for Enanta and Octapharma, and Chair for the European Society for Blood and Marrow Transplantation (EBMT) registry committee. DN has received an honorarium for lectures from Pfizer, Merck Sharp & Dohme, Roche, Abbott, bioMérieux, Gilead, and AstraZeneca, and support for attending meetings from Pfizer and Merck Sharp & Dohme. MB has received honoraria for consulting from AstraZeneca, Merck, Symbio Pharmaceuticals, and Moderna, and research support paid to the Fred Hutchinson Cancer Center (USA), from Ansun Biopharma, Pulmotect, AstraZeneca, Merck, GSK, and Moderna. RFC has received personal fees as a consultant and advisor for ADMA Biologics, Merck/MSD, Takeda, Shionogi, Gilead, AiCuris, Astellas, Tether, Oxford Immunotec, Karius, Moderna, InflaRx, Pfizer, Invivyd, Biotest, Assembly Bio, IntegerBio, Eurofins Viracor, Symbio, and Ansun Biopharma. He also received research grants paid to his institution from Merck, Karius, AiCuris, Ansun Biopharma, Takeda, Genentech, OM1, Symbio, and Eurofins Viracor; speaker fees from Merck/MSD, Eurofins Viracor, and Takeda; and support to attend meetings from Merck/MSD, Takeda, Gilead, Shionogi, Karius, Moderna, Invivyd, InflaRx, and Biotest. He has stock options from Xenex. HHH has received honoraria as a speaker for Eurofins Viracor, Biotest, Gilead, Takeda, and VeraTx; for consulting from AiCuris, AlloVir, Anocca, AstraZeneca, Roche, Moderna, and VeraTx; and research support paid to the University of Basel (Switzerland) from Moderna. All other authors declare no competing interests.

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For the **conference partners** see https://www.ecil-leukaemia.com/en/partners

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