Community-acquired respiratory virus (CARV) including Influenza, RSV, MPV, PIV, Rhino, Corona, Adeno-, Boca

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Update of ECIL-4 Guidelines

European guidelines for prevention and management of influenza in hematopoietic stem cell transplantation and leukemia patients: summary of ECIL-4 (2011), on behalf of ECIL, a joint venture of EBMT, EORTC, ICHS, and ELN

European guidelines for diagnosis and treatment of adenovirus infection in leukemia and stem cell transplantation: summary of ECIL-4 (2011)


https://academic.oup.com/cid/article/56/2/258/316867

CARV Working Group

- **Chairs:** Catherine Cordonnier and Petr Hubacek
- **Group leader:** Hans
- **Per and Dan for FLU:** LJU and ENG (EIN, NAV, ROB)
- **Roy and Hans for HRSV/MPV:** CHE and HIR (BER, COM, NAV)
- **Christine and Hermann for HPIV:** ROB and EIN (CHE, OE, HIR)
- **Michael and David for HCoV/Rhino:** NAV and BOE (CHE, VON, HIR)
- **Marie and Francesca for HAdV/ Boca:** VON and COM (LJU, DAN, EIN)
Outline

• Abbreviations
• Working Definitions
• Modified ECDC Criteria
• Diagnostic Considerations
• Infection Control
• Specific Recommendations Update 2019 (literature, current practice, consensus)
  • Influenzavirus (IV-) A and B
  • Human Respiratory Syncytial Virus (HRSV)
  • Human Metapneumovirus (HMPV)
  • Human Parainfluenzavirus (HPIV)
  • Human Coronavirus (HCoV)
  • Human Rhinovirus/Enterovirus (HRV/EV)
  • Human Adenovirus (HAdV)
  • Human Bocavirus (HBoV)

• All recommendations apply to adults and children unless otherwise specified
Abbreviations

- aIIV3 – Adjuvanted inactivated influenza vaccine in trivalent formulation
- BAL – Bronchoalveolar lavage
- DAD – Direct antigen detection
- HAdV – Human adenovirus
- HBoV – Human bocavirus
- HCT – Hematopoietic cell transplantation
- HCW – Health care worker
- HD-IIV3 – High-dose inactivated influenza vaccine
- HM – Hematological malignancy (leukaemia, myeloma, myelodysplastic syndrome, ..)
- HMPV – Human metapneumovirus
- HPIV – Human parainfluenzavirus
- HRSV – Human respiratory syncytial virus
- HRV/EV – Human rhino/enterovirus (picorna)
- IV – Influenzavirus
- IIV – Inactivated influenza vaccine
- IIV3 – Inactivated influenza vaccines in trivalent formulation
- IIV4 – Inactivated influenza vaccines in quadrivalent formulation
- IVIg – Intravenous immunoglobulin
- LAIV – Live attenuated influenza vaccine
- LRTID – Lower RTID
- NAI – Neuraminidase inhibitor
- NAT – Nucleic acid testing
- NPS – Nasopharyngeal sampling
- OTV – Oseltamivir
- QNAT – Quantitative nucleic acid testing
- RBV – Ribavirin
- RIV – Recombinant influenza vaccine
- RIV4 – Recombinant influenza vaccine in quadrivalent formulations
- RTI – Respiratory tract infection
- RTID – Respiratory tract infectious disease
- TAT – Turn-around time
- URTID – Upper RTID
- VIC – Virus isolation in cell culture
**Clinical criteria**
- One of 4 new respiratory symptoms/signs
  - Cough
  - Sore throat
  - Shortness of breath
  - Coryza

AND

- One of 4 new systemic symptom/signs
  - Fever
  - Feverishness
  - Myalgia
  - Nausea

AND

- A clinician’s judgement that the illness is due to infectious agent

**Epidemiological Criteria**
- An epidemiological link by human-to-human transmission
  - CARV activity in the community
  - Unprotected contact with visitor, other patient, or healthcare worker

**Laboratory Criteria**
- Detection of CARV in a clinical specimen, preferably from the site of clinical involvement, by at least 1 of the following
  - Nucleic acid amplification testing (NAT)
  - Virus isolation by cell culture (VIC)
  - Direct virus antigen detection (DAD)

**Case Classification**
- **Possible case**
  - Person meeting the clinical criteria (RTID)

- **Probable case**
  - Person meeting the clinical criteria (RTID) and having an epidemiological link

- **Laboratory-confirmed case**
  - Person meeting the clinical (RTID) and the laboratory criteria

- **Proven case**
  - Person having histological evidence of CARV pathology
Working Definitions

CARV upper RTID, lower RTID, and Pneumonia

- Upper RTID
  - Runny nose, nasal congestion
  - Burning eye sensation
  - Watery eyes
  - Clogged hearing
  - Sinus congestion
  - Painful sinus
  - Coryza
  - Sore throat
  - Cough
  - Imaging (CT-scan, MRI)
  - Endoscopy
  - Symptoms and signs of RTID not fulfilling the criteria of lower RTID

- Lower RTID
  - Tracheitis
    - Sore breathing, inspiratory stridor, painful chest when coughing, barking cough, productive sputum
  - Bronchitis
    - Wheezing, cough, productive sputum, shortness of breath, chest pain
  - Pneumonia
    - Wheezing, cough, productive sputum, chest pain, rales, shortness of breath
    - Airflow obstruction
    - Hypoxemia
    - Compatible new infiltrates on imaging (X-ray, CT-scan)
    - …
Working Definitions

CARV Pneumonia

- To reflect the strength of the diagnosis “CARV-attributable pneumonia” for treatment and outcome of CARV-RTID, the minimal criteria can be considered in HCT- and HM-patients.

<table>
<thead>
<tr>
<th>CARV-attributable Pneumonia</th>
<th>possible</th>
<th>probable</th>
<th>presumptive</th>
<th>proven</th>
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<tbody>
<tr>
<td>Clinical symptoms and signs of LRTID</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CARV detected in NPS *</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New/progressive infiltrates on imaging</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>New/progressive hypoxemia **</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CARV detected in BAL ***</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* HRV, HCoV, HBoV, HAdV in NPS is not sufficient for a probable diagnosis of pneumonia, needs BAL

** If X-ray and CT-scan is negative, or not informative, or not available, consider airflow obstruction (other [non]- pulmonary causes excluded)

*** Contamination from upper RTI to be excluded

**** Rarely indicated (e.g. non-responsive course; broadened differential diagnosis for other [co ]-existing pathologies)
CARV Diagnostic Laboratory Considerations

- **Nucleic acid testing** (NAT) detecting CARV genomes are the preferred method for a laboratory-confirmed respiratory tract infection (RTI). *All*

- Rapid tests with TAT of less than 60 min are preferred for a laboratory-confirmed diagnosis and the decisions regarding infection control measures, admission to hospital, antiviral and/or antibiotic treatment, deferral of chemotherapy or HCT. *BII t*

- Semi-quantitative CARV-NAT could be considered to follow the course of viral replication in HCT- and HM-patients, but lack of standardisation and commutability currently precludes general recommendations regarding clinical decisions other than infection control in case of CARV detection. *CIII*

- **Direct antigen detection** (DAD) have inferior specificity and sensitivity compared to NAT and should *not* be used for laboratory confirmation in HCT- and HM-patients.

- **Virus isolation by cell culture** (VIC) is less sensitive than NAT and resource consuming, with long TAT of 2 to 5 days and should *not* be used for laboratory confirmation of RTID in HCT- and HM-patients.

- Testing for CARV-specific antibody titers should *not* be used for laboratory confirmation of CARV-RTID in HCT- and HM-patients.
Recommendations on Prevention of CARV Infections

- Patients and contact persons should adhere to good personal hygiene, including frequent hand washing, covering the mouth when coughing and sneezing, and disposing safely of oral and nasal secretions. *All*

- HCT- and HM-patients should avoid contact with individuals with RTI or RTID in the hospital and in the community. *All*

- Young children should be restricted from visiting patients and wards because of the higher risk of CARV exposure, prolonged shedding, and ease of transmission. *BII*

- All visitors and HCWs with CARV-RTID should be restricted from access to patients and wards. *All*

- Inside care facilities, infection control measures should be applied to HCT- and HM-patients with RTID, including isolation rooms and application of strict precautions measures (droplet and contact isolation incl. gloves, gowning, masks, eye protection) for HCWs and visitors. *All t*

- Outpatients with RTID should be seen and treated in accordance with infection control measures, i.e. in facilities and rooms separated from other HCT- and HM-patients. *All*
## CARV Infection Control

<table>
<thead>
<tr>
<th>CARV</th>
<th>TRANSMISSION</th>
<th>OUTBREAKS</th>
<th>ASBMT Control Recommendation</th>
<th>MD Anderson Cancer Center Control Recommendation</th>
<th>ECIL-8 2019 Control Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV-A/B</td>
<td>Largedroplets, small droplets, fomites</td>
<td>Pediatric hematology and pediatric oncology</td>
<td>Droplet</td>
<td>Droplet and contact</td>
<td></td>
</tr>
<tr>
<td>HRSV</td>
<td>Large droplets, small droplets, fomites</td>
<td>Stem cell transplant units</td>
<td>Contact</td>
<td>Droplet and contact</td>
<td></td>
</tr>
<tr>
<td>HMPV</td>
<td>Small droplets, close contacts, fomites</td>
<td>Hematology unit</td>
<td>No recommendation</td>
<td>Droplet and contact</td>
<td></td>
</tr>
<tr>
<td>HPIV</td>
<td>Large droplets, fomites</td>
<td>Pediatric and adult hematology</td>
<td>Contact</td>
<td>Droplet and contact</td>
<td></td>
</tr>
<tr>
<td>HAdV</td>
<td>Large and small droplets, fomites, urine, feces</td>
<td>Stem cell transplant units</td>
<td>Droplet and contact</td>
<td>Droplet and contact</td>
<td></td>
</tr>
<tr>
<td>HCoV</td>
<td>Large droplets, fomites</td>
<td>No reports in patients with cancer</td>
<td>Contact</td>
<td>Droplet and contact</td>
<td></td>
</tr>
<tr>
<td>HRV/EV</td>
<td>Large droplets, small droplets, fomites</td>
<td>Hemato-oncology wards</td>
<td>Contact</td>
<td>Droplet and contact</td>
<td></td>
</tr>
</tbody>
</table>
**Diagnostic Testing**

**CARV Respiratory Infection and Disease**

- HCT-candidates or -recipients presenting with URTID or LRTID should be tested for CARVs to guide infection control measures, treatment, and decisions regarding deferral of chemotherapy or HCT (see Deferral Strategy Table). *AII*

- Specimens should be taken from the site of clinical involvement, preferably nasopharyngeal specimens or pooled nasal/oropharyngeal swabs (NPS) for URTID, or BAL for LRTID, (or tracheal aspirate or sputum, if BAL is not available). *AII*

- Patients with LRTID should be considered for BAL and broader diagnostic testing. *AII*

- Lung biopsy (transbronchial, thoracoscopic, open) can be considered as clinically indicated including evaluation for concomitant pulmonary conditions. *BIII*

- In health care centres not providing rapid CARV-multiplex NAT, first-line diagnostic testing should be performed for IV-A/B and HRSV, HMPV and HPIV1-4, or specific CARVs as epidemiologically indicated. *AII*

- For all RTID-patients to be hospitalized or already hospitalized, comprehensive diagnostic NAT is recommended covering IV-A/B, HRSV, HPIV, HMPV, HAdV, HRV/EV, HCoV. *BIII*

- No recommendations regarding HBoV detection can be made due no/inconclusive data.
General considerations of CARV-RTID for HCT and HM Patients

• For patients planned for allogeneic HCT and diagnosed with CARV-URTID, deferral of conditioning therapy should be considered for CARVs with high propensity for LRTID such as IV-A/B, HRSV, HMPV, HPIV. *AII*

• Deferral of conditioning therapy for allogeneic HCT should also be considered in case of CARV-LRTID caused by any CARV including HCoV, HRV, HAdV. *BIII*

• Deferral of conditioning/chemotherapy could be considered for autologous HCT and HM-patients with CARV-LRTID, or having a CARV-URTID with a high propensity for LRTID such as IV-A/B, HRSV, HMPV, HPIV. *BIII*

• Deferral of conditioning/chemotherapy could be considered for autologous HCT and HM-patients with CARV-LRTID. *CIII*
## Deferral Strategies for Patients with CARV-LRTID

<table>
<thead>
<tr>
<th>Patient presenting with laboratory-confirmed RTID</th>
<th>Deferral of chemotherapy/conditioning allogeneic HCT <em>if possible</em></th>
<th>Deferral of chemotherapy/conditioning for HM or autologous HCT <em>if possible</em></th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV-A/B URTID or LRTID</td>
<td>All*</td>
<td>BIII*</td>
<td></td>
</tr>
<tr>
<td>HMPV URTID or LRTID</td>
<td>All</td>
<td>BIII</td>
<td></td>
</tr>
<tr>
<td>HPIV URTID or LRTID</td>
<td>All</td>
<td>BIII</td>
<td></td>
</tr>
<tr>
<td>HAdV URTID or LRTID</td>
<td>All</td>
<td>BIII</td>
<td>Campbell AP et al (2015) CID 61: 192 Waghmare A 2019, IDWeek Presentation **</td>
</tr>
<tr>
<td>HCoV LRTID</td>
<td>CIII</td>
<td>CIII</td>
<td></td>
</tr>
<tr>
<td>HBoV</td>
<td>No recommendation</td>
<td>No recommendation</td>
<td></td>
</tr>
</tbody>
</table>

* in addition to immediate antiviral treatment

Specific Recommendations for Influenza Virus A (IV-A) and B (IV-B)
Influenza Virus A and B Overview

• Prevention options
  • Vaccination
  • Antiviral prophylaxis
  • Post-exposure prophylaxis
  • Deferral
  • Infection control

• Antiviral Treatment
  • Neuraminidase inhibitors and other drugs
  • Deferral considerations
  • Treatment recommendations
  • Clinical failure
PREVENTION
Vaccination against Influenza Virus-A and -B

• There are insufficient data to support an increased clinical efficacy of adjuvanted (aIIV) or non-adjuvanted inactivated influenza vaccine (IIV).

• There are insufficient data to support an increased clinical efficacy of double-dose trivalent influenza vaccine (IIV3).

• It is recommended to use an inactivated influenza quadrivalent vaccine (IIV4), if available, although no comparative clinical data exist in HCT- or HM-patients. BIII

• Live-attenuated influenza vaccine (LAIV) should not be used in immunocompromised patients.
**PREVENTION**

**Vaccination against Influenza Virus-A and -B**

- **For allogeneic HCT**: Annual seasonal IIV, 1 dose, at the beginning of influenza season in all patients >6 months post-transplant and pursued during the first years following transplant, at least until 6 months after discontinuing immunosuppression and:
  - Option 1: As long as the patient is judged to be immunosuppressed. *All r*
  - Option 2: Life-long. *BII r*

- **In autologous HCT**: Annual seasonal inactivated influenza vaccination, 1 dose, at the beginning of flu season in all patients >6 months post-transplant, at least as long as the patient is judged to be immunosuppressed. *BII r*

- **In patients with HM**: Annual seasonal inactivated influenza vaccination, 1 dose, at the beginning of flu season in all patients as long as the patient is judged to be immunosuppressed*, **.

  * Patients treated recently with CD20/CD19/BCMA/CPRG5D/CD22-targeting antibodies are unlikely to respond for at least 6 months.

  ** Although no data are available, similar effects can be expected from newer anti-B cell antibodies

PREVENTION

Vaccination against Influenza Virus-A and -B

• In children >9 y and in adults, a 2\textsuperscript{nd} dose of IIV after 4 weeks may have a marginal benefit and should be considered in patients with severe GVHD, low lymphocyte counts, or during a prolonged community outbreak. \textit{BII}

• Children 6 months to 8 years of age, receiving influenza vaccination for the first time after transplant should receive a 2\textsuperscript{nd} dose at 4 weeks after the first dose. \textit{BII}

• During a community outbreak: IIV can be given to both, allo- and auto-HCT-recipients, from 3 months after transplant. As this increases risk of insufficient generation and/or early waning of immunity, a 2\textsuperscript{nd} dose after 4 weeks should be considered. \textit{BII r}
PREVENTION
IV-A/B Vaccination of health care and contact persons

• Hospital staff working with immunocompromised patients should receive inactivated influenza vaccine (IIV3 or IIV4) annually. **All t**

• Individuals in close contact with, or household members of HCT recipients should receive inactivated influenza vaccine (IIV3 or IIV4):
  - Beginning season before transplant and first season after transplant. **AIII**
  - Annually as long as the patient is judged to be immunosuppressed. **CIII**

• The live-attenuated influenza vaccine (LAIV) should **not** be used in individuals in close contact with, or household members of, a HCT recipient in the first 12 months of transplant or those treated for GVHD.
PREVENTION
Antiviral prophylaxis and deferral

• Routine antiviral prophylaxis with NAI to immunocompromised patients during the influenza season is discouraged. BIII

• Post-exposure prophylaxis with oseltamivir 75mg BID to all severely immuno-compromised (regardless of vaccination) is recommended. All t

• Targeted prophylaxis with oseltamivir to severely immuno-compromised patients (regardless of vaccination) can be considered e.g. during a suspected nosocomial outbreak for at least 7 days in prophylactic dosing if testing of potentially exposed is negative, or in therapeutic dosing if positive. BIII

• Deferral of conditioning therapy should be considered for patients with IV-A/B-RTID planned for allogeneic HCT, if possible. All

Ref. CDC recommendation https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
Treatment of Influenza-RTID

- Allogeneic and autologous HCT recipients and HM-patients during chemotherapy and in the following 6 months with laboratory-confirmed IV-A/B-RTID should be treated as soon as possible, preferably within less than 24h to 48h after clinical onset. **AII**

- If rapid NAT is not available, HCT- and HM-patients with probable IV-A/B-RTID (with compatible symptoms/signs and epidemiological link e.g. during influenza season), should be treated promptly while awaiting laboratory confirmation. **BIII**

- First line treatment is oseltamivir (OTV). **BII**
  - The recommended adult dose of OTV is 75 mg BID until significant clinical improvement, usually 5 – 10 days. **BII**

- For patients with continuing symptoms, it is advised to confirm a role of IV-A/B replication by repeating NAT on clinically relevant respiratory specimens after 5-7 days as rationale for continued treatment until undetectable. **CIII**

- In allogeneic HCT patients, spirometry at least 6 weeks after laboratory-confirmed IV-A/B RTID diagnosis could be considered to identify chronic lung dysfunction. **CIII**
Treatment of severe or prolonged cases of Influenza RTID

- Patients with pneumonia due to IV-A/B, who worsen or fail to improve despite adequate treatment with neuraminidase inhibitors (NAI) for at least 5 days, should be re-evaluated for complications (superinfections) and repeat NAT from the lower respiratory tract for IV-A/B. BIII

- For severe or prolonged influenza disease some clinical experts administer double-dose of OTV 150 mg BID. CIII

- In severe influenza when gastrointestinal absorption might be impaired, iv peramivir or iv zanamivir (if available) might be an option. CIII

- In case of continued IV-A/B detection, extended antiviral treatment should be considered for at least 10 days BIII

- In symptomatic patients with persisting IV-A/B loads despite adequate therapy, genotypic resistance testing could be considered. CIII

- In severe or prolonged influenza disease, combination therapy of NAI with baloxavir or with ribavirin or adamantanes could be considered (“compassionate use”). CIII

- There are insufficient data supporting an increased clinical efficacy of oseltamivir/zanamivir combinations.
Pediatric dosing of oseltamivir

- Oseltamivir treatment of IV-A/B-RTID in children should be dosed according to body weight as detailed in Table. *All t*

<table>
<thead>
<tr>
<th>Weight (kg) §</th>
<th>Treatment and post-exposure prophylaxis dosing #</th>
<th>Pre-exposure prophylaxis dosing #</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 kg or less</td>
<td>30 mg twice daily</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td>15.1 – 23 kg</td>
<td>45 mg twice daily</td>
<td>45 mg once daily</td>
</tr>
<tr>
<td>23.1 – 40 kg</td>
<td>60 mg twice daily</td>
<td>60 mg once daily</td>
</tr>
<tr>
<td>40.1 or more</td>
<td>75 mg twice daily</td>
<td>75 mg once daily</td>
</tr>
</tbody>
</table>

§ Patients 1 to 12 years of age based on body weight

* An oral dosing dispensing device that measures the appropriate volume in mL should be utilized with oral suspension

# Oral suspension is the preferred formulation who cannot swallow capsules

Refs:
1. Adapted from the oseltamivir package insert
HRSV

• Prevention options
  • Deferral
  • Infection control
  • No vaccine available
  • No antiviral available
  • Monoclonal antibody post-exposure prophylaxis

• Antiviral Treatment
  • Oral ribavirin, aerosolized ribavirin,
  • Intravenous immunoglobulin (IVIg)
  • Treatment recommendations
PREVENTION
Vaccination, antivirals and deferral for HRSV-A and -B

- Currently, no active vaccination is available for clinical use.
- In the absence of data evaluating the efficacy or risk/benefit ratio, oral ribavirin should not be used as prophylaxis (primary or post-exposure).

- In the absence of data evaluating the efficacy or risk/benefit ratio, palivizumab is discouraged as primary or post-exposure prophylaxis for adults of children >2 years. BIII
- Palivizumab could be considered as post-exposure prophylaxis in severely immunosuppressed patients when nosocomial outbreak is occurring. CIII
- Children of <2 years of age who have undergone HCT may benefit from immunoprophylaxis with palivizumab during the HRSV season. CIII

- Deferral of conditioning therapy should be considered for patients with HRSV-RTID planned for allogeneic HCT, if possible. AII
Treatment of HRSV-RTID in allogeneic HCT Patients (1)

- Allogeneic HCT recipients at high risk for progression to, or with diagnosis of RSV-LRTID should be treated with systemic or aerosolized ribavirin. **BII**
- For guidance on ribavirin administration, the MD Anderson Immunodeficiency Score Index (ISI) or the Basel Severe Immunodeficiency (SID) can be considered. **BIII**
- In allogeneic HCT recipients at low risk for progression to RSV-LRTID, systemic or aerosolized ribavirin treatment can be withheld. **BIII**
- Systemic ribavirin can be administered orally at 10–30 mg/kg body weight in 3 divided doses (maximum dose 600 mg/8 h or 1800 mg per day). **BII**
- Patients on systemic ribavirin should be monitored and treated for adverse events including hemolysis, abnormal liver function tests, and declining renal function. **BII**
- In case of failing renal clearance, systemic (oral or intravenous) ribavirin should be lowered to 200 mg / 8h for clearance of 30–50 mL/min (no recommendation for less than 30mL/ min. **BIII**

- **There are insufficient data defining the dosing of systemic ribavirin in the pediatric setting.**
### Immunodeficiency Grading and Scoring Index Criteria

**TABLE 2** Clinical criteria proposed to identify patients undergoing allo-HCT at risk for complicated CARV lower RTID caused by HRSV, HPIV, or IV-A/B²

<table>
<thead>
<tr>
<th>University Hospital Basel immunodeficiency grading system</th>
<th>MD Anderson Cancer Center immunodeficiency scoring index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criterion or parameter</strong></td>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>Neutropenia, &lt;0.5 × 10⁹/liter</td>
<td>1</td>
</tr>
<tr>
<td>Lymphopenia, &lt;0.1 × 10⁹/liter</td>
<td>1</td>
</tr>
<tr>
<td>Allo-HCT &lt;6 months ago</td>
<td>1</td>
</tr>
<tr>
<td>GVHD of ≥2 or requiring treatment</td>
<td>1</td>
</tr>
<tr>
<td>T-cell depletion &lt;3 months prior to CARV Dx</td>
<td>1</td>
</tr>
<tr>
<td>B-cell depletion &lt;3 months prior to CARV Dx</td>
<td>1</td>
</tr>
<tr>
<td>Hypo-γ-globulinemia, &lt;4.5 g/liter</td>
<td>1</td>
</tr>
<tr>
<td>Maximal</td>
<td>7</td>
</tr>
<tr>
<td>Moderate (MID)</td>
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<tr>
<td>Severe (SID)</td>
<td>1</td>
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<tr>
<td>Very severe (verySID)</td>
<td>2–7</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Score</strong></th>
<th><strong>Criterion or parameter</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Neutropenia, &lt;0.5 × 10⁹/liter</td>
</tr>
<tr>
<td>3</td>
<td>Lymphopenia, &lt;0.2 × 10⁹/liter</td>
</tr>
<tr>
<td>1</td>
<td>Preengraftment or allo-HCT &lt;1 months</td>
</tr>
<tr>
<td>1</td>
<td>GVHD (acute/chronic)</td>
</tr>
<tr>
<td>1</td>
<td>Corticosteroids</td>
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<tr>
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<td>Myeloablative conditioning</td>
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<tr>
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<td>Age, &gt;40 yr</td>
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<td>2</td>
<td>Maximal</td>
</tr>
<tr>
<td>12</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>3–6</td>
<td>High risk</td>
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</tbody>
</table>

²Allo-HCT, allogeneic hematopoietic cell transplantation; CARV, community-acquired respiratory virus; Dx, diagnosis; GVHD, graft-versus-host disease; HRSV, human respiratory syncytial virus; HPIV, human parainfluenzavirus; IV-A/B, influenza virus A or B; RTID, respiratory tract infectious disease.


https://cmr.asm.org/content/32/4/e00042-19.abstract
Treatment of HRSV-RTID in allogeneic HCT Patients (2)

• Aerosolized ribavirin for HRSV can be administered as 2 g for 2 h every 8 h or as 6 g over 18 h/d for 7–10 days. BII

• Aerosolized ribavirin therapy should be accompanied by measures avoiding environmental exposure and thereby potentially teratogenic effects in pregnant HCW and visitors. All

• Patients on aerosolized ribavirin should be monitored and treated for adverse events including claustrophobia, bronchospasm, nausea, conjunctivitis, and declining pulmonary function. BII t
Treatment of HRSV-RTID in allogeneic HCT Patients (3)

• For allogeneic HCT patients with, or at high risk for, HRSV-LRTID, especially with hypo-γ-globulinemia (<4.5 g/L), adjunct treatment with intravenous immunoglobulin (IVIg) (e.g. 0.5 g/kg bodyweight, at least 3 doses within 2 weeks). BIII

• Corticosteroids of > 1mg/kg/day used at diagnosis of HRSV-LRTID, has been associated with progression of disease and mortality, thus reducing corticosteroid administration to less than 1 mg/kg bodyweight could be considered if feasible. CIII

• In allogeneic HCT patients, spirometry at least 6 weeks after laboratory-confirmed HRSV-RTID diagnosis could be considered to identify chronic lung dysfunction. CIII
Treatment of RSV-RTID in autologous HCT and HM Patients

- Treatment of autologous HCT- and HM-patients at high risk for progression to RSV-LRTID or with diagnosis of RSV-LRTID with systemic or aerosolized ribavirin could be considered. \( CIII \)

- Systemic or aerosolized ribavirin administration and monitoring should follow the recommendations outlined for allogeneic HCT-recipients. \( BIII \)

- For autologous HCT- and HM-patients with RSV-LRTID or at high risk for RSV-LRTID, and hypo-\( \gamma \)-globulinemia (<4.5 g/L), adjunct treatment with intravenous immunoglobulin (IVIg) (e.g. 0.5 g/kg bodyweight at least 3 doses within 2 weeks). \( CIII \)
HMPV

• Prevention options
  • Deferral
  • No specific antivirals available

• Antiviral Treatment
  • Limited evidence for systemic ribavirin
  • Limited evidence for IVIg
Treatment of HMPV-RTID in allogeneic HCT Patients

- Deferral of conditioning therapy should be considered for patients with HMPV-RTID planned for allogeneic HCT, if possible. \textit{All}

- Deferral of conditioning/chemotherapy can be considered for HCT- and HM-patients with HMPV-RTID scheduled for chemotherapy, if possible. \textit{BIII}

- Although available data are too limited to support the general use for allogeneic HCT-patients with LRTID, or with HMPV-URTID at high-risk for progression to LRTID, oral ribavirin could be considered. \textit{CIII}

- Although available data are too limited to support the general use of IVIg for HCT or HM-patients with HMPV-LRTID, administration of IVIg (e.g. 0.5 g/kg bodyweight at least 3 doses within 2 weeks) can be considered, especially for patients with hypo-$\gamma$-globulinemia ($<4.5$ g/L). \textit{BIII}

- Corticosteroids of > 1mg/kg/day used at diagnosis of HMPV-LRTID, has been associated with progression of disease and mortality, thus reducing corticosteroid administration to less than 1 mg/kg bodyweight could be considered if feasible. \textit{CIII}

- In allogeneic HCT patients, spirometry at least 6 weeks after laboratory-confirmed HMPV-RTID diagnosis could be considered to identify chronic lung dysfunction. \textit{CIII}
HPIV

• Prevention
  • Deferral for LRTID
  • No specific antivirals available

• Antiviral Treatment
  • Limited evidence for systemic ribavirin
  • Limited evidence for aerosolized ribavirin
  • Limited evidence for IVIg
Treatment of HPIV-RTID in HCT- and HM-Patients

• Deferral of conditioning therapy should be considered for patients with HPIV-RTID planned for allogeneic HCT, if possible. *AII*

• Deferral of conditioning/chemotherapy can be considered for HCT- and HM-patients with HMPV-RTID scheduled for chemotherapy, if possible. *BIII*

• Although available data are too limited to support the general use of systemic ribavirin for allogeneic HCT-patients with HPIV-URTID and at high-risk for progression to LRTID, or with diagnosed LRTID, oral ribavirin might be considered. *CIII*

• Although available data are too limited to support the general use of IVIg for allogeneic HCT-, autologous HCT, or HM-patients with HPIV-LRTID, IVIg administration (e.g. 0.5 g/kg bodyweight at least 3 doses within 3 weeks) could be considered, especially in patients with hypo-γ-globulinemia (<4.5 g/L). *CIII*

• Corticosteroids of > 1mg/kg/day used at diagnosis of HPIV-LRTID, has been associated with progression of disease and mortality, thus reducing corticosteroid administration to less than 1 mg/kg bodyweight could be considered if feasible. *CIII*

• In allogeneic HCT patients, spirometry at least 6 weeks after laboratory-confirmed HPIV-RTID diagnosis could be considered to identify chronic lung dysfunction. *CIII*
HCoV

• Prevention
  • Deferral for LRTID
  • No specific recommendations available
  • SARS-CoV and MERS-CoV are not included

• Antiviral Treatment
  • Limited evidence
Treatment of HCoV-RTID in HCT- and HM-Patients

• There are insufficient data to support the deferral of conditioning of patients with HCoV RTID scheduled for allogeneic HCT, but might be considered for patients with laboratory-confirmed HCoV-LRTID by some experts. CIII

• No data exist for deferral of conditioning/chemotherapy for autologous HCT or HM-patients with HCoV infection scheduled for chemotherapy, but might be considered for patients with laboratory-confirmed HCoV-LRTID by some experts, if possible. CIII

• There are insufficient data to support the specific treatment of HCoV-RTID with currently available antiviral drugs.
HRV/EV

• Prevention
  • Deferral for LRTID
  • No specific recommendations available

• Antiviral Treatment
  • Limited evidence
Treatment of HRV/EV-RTID in HCT- and HM-Patients

• Deferral of conditioning should be considered for patients with laboratory-confirmed HRV/EV-LRTID scheduled for allogeneic HCT. *All*

• No data exist for deferral of conditioning/chemotherapy for HM-patients with HRV/EV infection scheduled for chemotherapy, but might be considered for patients with laboratory-confirmed LRTID by some experts. *CIII*

• No data exist to support the treatment with ribavirin.
HAdV

• Prevention
  • Deferral for LRTID
  • No specific recommendations available

• Antiviral Treatment
  • Limited evidence
Treatment of HAdV-RTID in HCT- and HM-Patients

- Deferral of conditioning therapy should be considered for patients with HAdV-RTID planned for allogeneic HCT, if possible. AII

- Deferral of conditioning/chemotherapy could be considered for autologous HCT- and HM-patients with HAdV-RTID scheduled for chemotherapy of hemato-oncological diseases, if possible. BIII

- In HCT- and HM-patients with HAdV-URTID with or without risk factors for dissemination and undetectable plasma HAdV loads, reducing immunosuppression, if possible, and close observation are recommended. BIII

- Because of the propensity to disseminate to multiple organs with poor outcome, HCT- and HM-patients having HAdV detected in respiratory specimen should be tested for HAdV DNA in blood using quantitative NAT assays. BIII

- If blood HAdV load of >1000 c/mL in a lymphopenic host with RTID (lymphocytes <100/uL), treatment with intravenous cidofovir should be considered. BIII

- Although no efficacious dosing has been established, intravenous cidofovir should be considered for HAdV DNAemia (e.g. 1 mg/kg bodyweight three times weekly) or for LRTID/pneumonia (e.g. 5 mg/kg bodyweight once weekly) together with probenecid, hyper-hydration, and monitoring of renal function. B III

- Brincidofovir has been used for treatment of patients HAdV viremia/disease, but direction of future clinical development is currently unclear (limited availability).
HBoV

• Prevention
  • No specific recommendations available

• Antiviral Treatment
  • No specific recommendations available
CARVs in HCT and HM patients: Outlook & Research Agenda

• Prospective multicenter cohort studies determining the risk factors of progression to LRTID and attributable mortality of HCT- or HM-patients
• Validation of risk scores for HRSV, HMPV and HPIV for progression to LRTID, morbidity, mortality of HCT- or HM-patients
• Prospective multicenter cohort studies determining the role reducing corticosteroids in the treatment of CARV progression to LRTID and -attributable mortality of HCT- or HM-patients
• Prospective randomized controlled trials comparing HRSV treatment with RBV plus IVIG in high-risk patients versus low-risk of (high-risk) HCT- or HM-patients
• Prospective randomized controlled trials determining the use of intravenous monoclonal antibody preparations for pre-, post-exposure prophylaxis or treatment of (high-risk) HCT- or HM-patients
• Prospective randomized controlled trials determining the use of specific antivirals for treatment of (high-risk) HCT- or HM-patients
• Development of CARV-specific vaccines (especially HRSV, HMPV, HPIV)
• (Prospective) multicenter cohort studies determining the impact on progression and/or vaccine protection by different conditioning regimens (i.e. reduced intensity protocols) or with newer cell depleting antibodies
The Difference Between Assume and Presume

*Assume* and *presume* both mean "to take something for granted" or "to take something as true," but the words differ in the degree of confidence the person assuming or presuming has. *Presume* is used when someone is making an informed guess based on reasonable evidence. *Assume* is used when the guess is based on little or no evidence.

"Doctor Livingstone, I presume...."
Thank you