10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

Community-acquired respiratory virus (CARV) infections in HM and HCT patients 2024 (Update of 2019 recommendations)

Final slide set
Post meeting

CONFERENCE
From September 19th to 21st, 2024

2024 Update of 2019 ECIL 8 recommendations

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Abbreviations

- aIIV3 - adjuvanted inactivated influenza vaccine in trivalent formulation
- BAL – bronchoalveolar lavage
- BALOXAVIR
- DAD – direct antigen detection
- HAdV – Human adenovirus
- HBoV – human bocavirus
- HCT – hematopoietic cell transplantation
- HCoV – Human coronavirus
- HCP – health care provider
- 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 (picornavirus)
- IV-A/B – influenzavirus A and B
- 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
- SCoV2 – SARS-Coronavirus-2
- URTID – upper RTID
- VIC – virus isolation by cell culture

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***
- Because of the higher risk of CARV exposure, prolonged shedding, and ease of transmission, the contact of HM- and HCT patients with children should be regulated by a local policy for outpatient and inpatient services. ***BIIt***
- All visitors and HCPs with CARV-RTI or 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 RTI or RTID, including isolation rooms and application of strict protection measures (droplet and contact isolation measures incl. gloves, gowning, masks, eye protection) for HCPs and visitors. ***AIIt***
- Outpatients with RTI 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***
- Theses consideration should also be applied also to patients before and after the administration of CAR T cells or bispecific antibodies. ***BIIt***

Working Definitions (adapted from ECDC Influenza-like illness - ILI)

Definitions of CARV Respiratory Tract Infectious Disease

Clinical Criteria

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

AND

- One of 4 *new* respiratory symptoms/signs
  - ✓ Cough
  - ✓ Sore throat
  - ✓ Shortness of breath
  - ✓ Coryza

AND

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

Epidemiological Criteria

- Epidemiological link by human-to-human transmission
- CARV activity in the community

AND

- Unprotected contact out of hospital
- Unprotected contact in hospital with visitor, other patient, or health care provider (HCP)

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 testing (NAT)
  - Direct virus antigen detection (DAD)
  - Virus isolation by cell culture (VIC)

Evidence-based Classification (Strength of diagnosis)

- Possible case
  - Person meeting the clinical criteria (RTID)
- Probable case
  - Person meeting the clinical criteria (RTID) *and* having an epidemiological link
- Laboratory-confirmed case (presumptive*)
  - Person meeting the clinical (RTID) *and* the laboratory criteria
- Proven case
  - Person having histological evidence of CARV pathology in tissue

*best evidence to account for symtoms and signs, if other (co-existing) etiologies unlikely/ruled out, without more invasive diagnostic procedures

Overview

CARV Infection control: evidence and recommendation

CARV diagnosis	TRANSMISSION	OUTBREAK REPORTS	ASBMT Control Recommendation	MD Anderson Cancer Center Control Recommendation	ECIL-10 2024 Control Recommendation
IV-A/B	small droplets, large droplets, fomites	Pediatric hematology and pediatric oncology	Droplet and	Droplet and contact	Apply droplet and contact isolation measures (***All u***) (There are differences in center-specific preferences for HCP to use surgical masks or to use N95 mask when a patient is diagnosed with CARV)
SCoV2*	small droplets, large droplets, fomites, aerosols	Pediatric hematology and pediatric oncology	Aerosol, droplet and contact	Aerosol and contact	
HRSV	small droplets, large droplets, fomites	Stem cell transplant units	Contact	Droplet and contact	
HMPV	small droplets, large droplets, fomites	Hematology unit	No recommendation	Droplet and contact	
HPIV	small droplets, large droplets, fomites	Pediatric and adult hematology	Contact	Droplet and contact	
HAdV	Large and small droplets, fomites, urine, feces	Stem cell transplant units	Droplet and contact	Droplet and contact	
HCoV	small droplets, large droplets, fomites,	No reports in patients with cancer	Contact	Droplet and contact	
HRV/EV	small droplets, large droplets, fomites,	Hemato-oncology wards	Contact	Droplet and contact	

*SARS-CoV-2 see separte ECIL-10 update document

CARV Laboratory Testing

- *Nucleic acid testing* (NAT) detecting CARV genomes are the preferred method for a laboratory-confirmed respiratory tract infection (RTI). ***AII***
- Rapid tests with *turn-round time* (TAT) of less than *2 hours* 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***
- *Direct antigen detection* (DAD) has lower sensitivity compared to CARV-NAT and reduced specificity in low prevalence setting, but if used for *rapid* (self-)testing, the result should be discussed with HCP to evaluate the consequences for care including the need of early antivirals or for confirmation by NAT. ***AII***
- (Semi-)quantitative QNAT can be considered to follow the course of viral replication in HCT and HM patients based on local expertise, but lack of standardisation and commutability currently precludes providing general thresholds and recommendations regarding clinical decisions including infection control measures. ***CIII***
- *Virus isolation by cell culture* (VIC) is less sensitive than NAT and more time and resource consuming, and should *not* be used for routine laboratory confirmation in HCT- and HM-patients. ***DII***
- Testing for CARV-specific antibody titers should *not* be used for the laboratory diagnosis of CARV-RTID in HCT- and HM-patients. ***DII***
- Testing for CARV-specific antibody titers should *not* be used for decisions regarding the need (re-) vaccination. ***DII***

CARV Respiratory Tract Infection and Disease

- 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 (see *deferral*). ***AII***
- In health care centres not providing CARV-multiplex NAT, *first-line* diagnostic testing should be performed for IV-A/B, SCoV2 and HRSV, and, if negative, followed by HMPV and HPIV1-4, and other specific CARVs as epidemiologically indicated (→*Diagnostics*). ***AII t***
- For all RTID-patients to be hospitalized or already hospitalized, comprehensive diagnostic NAT (CARV multiplex-NAT) is recommended covering IV-A/B, HRSV, HPIV, HMPV, HRV/EV, HCoV, HAdV. ***BIII***
- HBoV detection cannot be recommended for adults as recent studies suggest no clinical impact of, and question the pathogenic role of HBoV in HCT- or HM-patients. ***DIII***
- For pediatric patients, no recommendations for HBoV detection can be made due little/inconclusive data. ***CIII***
- Specimens should be taken from the site of clinical involvement, preferably nasopharyngeal specimens or pooled naso-pharyngeal swabs (NPS) or naso-oropharyngeal swabs (NOPS) for upper RTID, or BAL for LRTID, (or tracheal aspirate or sputum, if BAL is not feasible) ***AII***
- Patients with LRTID should be considered for BAL and broader diagnostic testing. ***AII***
- Lung biopsy (transbronchial, thoracoscopic, open) remains an extreme diagnostic measure which can be considered to evaluate clinical failure and other concomitant pulmonary conditions. ***CIII***

Working Definitions

CARV-attributable Pneumonia

- To capture the strength of the diagnosis "*CARV-attributable pneumonia*" for treatment and outcome of CARV-RTID for HCT- and HM-patients, the following criteria are considered by some experts. (***statement***)

	CARV-attributable Pneumonia			
	possible	**probable**	**laboratory-confirmed**	**proven**
Clinical symptoms of LRTID	+	(+ / -)	(+ / -)	(+ / -)
CARV detected in NPS *	+	+	(+/ND/-)	(+/ND/-)
New/progressive infiltrates on imaging		+ or - or +	+ or - or +	(+) or (-) or (+)
New/progressive hypoxemia **		- + +	- + +	(-) (+) (+)
CARV detected in BALF ***			+	(+/ND/-)
CARV histopathology in lung tissue ****				+

* Detection of HRV, HCoV, HBoV, HAdV in NPS is *not* sufficient for a probable diagnosis of pneumonia, needs sampling from lower respiratory tract

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

*** Contamination from upper RTI is unlikely if QNAT loads/Ct values in BALF are significantly higher (e.g., >10-fold, 1 log10 or >3.3 Ct-values)

**** Rarely performed or indicated (e.g. non-responsive course; broadened differential diagnosis for other [co]-existing infectious and non-infectious pathologies)

- , negative
+, positive
(+/ND/-), ND, not done

Clinical Approach to Patients

General considerations of CARV-RTID for HCT and HM Patients

- For patients planned for **allogeneic HCT** and diagnosed with **CARV-LRTID**, deferral ***AII*** or reduced intensity conditioning , if feasible, should be considered. ***BIII***
- For patients planned for **allogeneic HCT** and diagnosed with **CARV-URTID**, deferral ***AII*** or reduced intensity conditioning, if feasible, should be considered for CARVs with **high propensity** for LRTID such as IV-A/B, HRSV, HMPV, HPIV. ***BIII***
- For patients planned for **autologous HCT** and diagnosed with CARV-LRTID, deferral, should be considered. ***AII***
- For patients planned for **autologous 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. ***BIII***
- For **HM** patients planned for chemotherapy, and diagnosed with **CARV-LRTID**, deferral, should be considered. ***AII***
- For **HM** patients planned for chemotherapy and diagnosed with **CARV-URTID**, deferral, should be considered for CARVs with **high propensity** for LRTID such as IV-A/B, HRSV, HMPV, HPIV. ***BIII***

Deferral Strategies for Patients with CARV-RTID (overview)

Patient with lab-confirmed CARV	Location / Anatomic site	Allogeneic HCT Deferral of conditioning (if possible)	Allogeneic HCT Use of less toxic conditioning (if possible)	Deferral of HM chemotherapy or conditioning for autologous HCT (if possible)	References
IV-A/B*	URTID	*AII*	*BIII*	*BIII*	
	LRTID	*AII*	*BIII*	*BIII*	
SCoV2*	Depending on severity of COVID-19 and vaccination status, after assessment of the clinical risk/benefit ratio, deferral until clinical and virological				
	recovery is appropriate before proceeding with hematological treatment				(see ECIL-10 CoVID)
RSV**	URTID	*AII*	*BIII*	*BIII*	
	LRTID	*AII*	*AII*	*AII*	
HMPV	URTID	*AII*	*BIII*	*BIII*	
	LRTID	*AII*	*AII*	*BIII*	
HPIV	URTID	*AII*	*BIII*	*BIII*	
	LRTID	*AII*	*AII*	*BIII*	
HADV**	URTID	*AII*	*AII*	*BIII*	
	LRTID	*AII*	*AII*	*BIII*	
HCoV	URTID	*No*	*No*	*No*	
	LRTID	*CIII*	*CIII*	*CIII*	
HRh/EV	URTID	*No*	*No*	*No*	
	LRTID	*AII*	*AII*	*CIII*	
HBoV	*not required (local management may defer for paediatric patients in some centers)*				

* in addition to antiviral treatment,
** consider antiviral treatment

SPECIFIC RECOMMENDATIONS

Influenzavirus A (IV-A) and Influenzavirus B (IV-B)

- Prevention options
  - Vaccination
  - Antiviral prophylaxis, infection control, deferral
- Antiviral Treatment
  - Neuraminidase inhibitors and other drugs
  - Deferral considerations
  - Treatment recommendations
  - Clinical failure

Prevention

Vaccination against Influenza Virus-A and -B

- Live-attenuated influenza vaccine (LAIV) should *not* be used in immunocompromised patients. ***DII $_t$***

For allogeneic HCT:

- Annual seasonal inactivated influenza vaccination (IIV) is recommended to be given at the beginning of influenza season for all patients at 3 - 6 months post-transplant. ***All u***
- Vaccination should be continued on a yearly basis. ***All t***

For autologous HCT:

- Annual seasonal IIV is recommended to be given at the beginning of Influenza season for all patients 3 - 6 months post-transplant. ***All t u***
- Vaccination should be continued on a yearly basis. ***All t***

For patients with HM:

- Annual seasonal IIV is recommended to be given at the beginning of flu season to all patients ***AIIt*** Vaccination should be continued on a yearly basis. ***All t***

For patients treated with CD20/CD19/BCMA/CPRG5D/CD22-targeting antibodies:

- Unlikely to respond for at least 6 months - similar effects expected for newer anti-B cell antibodies, but only limited data. (***Statement***)

Prevention

Influenza Virus-A and –B vaccination – for Adults

- There is insufficient data supporting an increased *clinical efficacy* of adjuvanted inactivated (aIIV-A/B) or non-adjuvanted inactivated influenza vaccine (IIV-A/B).
- There is data supporting an *increased immunogenicity* of high-dosed non-adjuvanted inactivated influenza vaccine (IIV-A/B)
- High-dose trivalent IIV-A/B is recommended for allogeneic HCT-patients. ***BI***
- A 2nd dose after 4 weeks may have a benefit ***BIII*** and should be considered in patients with severe GVHD, low lymphocyte counts, or during a prolonged community outbreak.

Prevention

Influenza Virus-A and –B vaccination – for Children

- Inactivated Influenza Vaccines (IIVs) should be given to both, allo- and auto-HCT-recipients, as early as 3 months after transplant. ***AII***
- As early vaccination increases risk of insufficient generation and/or early waning of immunity, a 2nd dose after 4 weeks should be considered. ***BII r***

- There is data supporting an increased immunogenicity of high-dosed non-adjuvanted inactivated influenza vaccine (IIV-A/B) in children. (***statement***)
- High-dose trivalent IIV-A/B could be considered pediatric allogeneic HCT-patients. ***BIII***

- Children from 6 months to 8 years of age, receiving influenza vaccination for the first time after transplant should receive a 2nd dose at 4 weeks after the first dose. ***BIIt***
- For children >9 years of age, a 2nd dose can be considered during a prolonged outbreak ***BII***

Prevention

IV-A/B Vaccination of health care providers and contact persons

- Health care providers 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. ***All t***
  - Annually as long as the patient is judged to be immunosuppressed. ***BIII***
- 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. ***DII***

Prevention

Influenza-A/B: Antiviral prophylaxis, infection control, deferral

- Routine antiviral pre-exposure prophylaxis of immunocompromised patients during the influenza season is discouraged. ***DIII***
- Post-exposure prophylaxis with *oseltamivir* 75mg BID to all severely immuno-compromised (regardless of vaccination) is recommended. ***AII t***
- 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 tested negative, or in therapeutic dosing, if tested positive. ***BIII***

- Infection control – *see table in general slides*
- Deferral – *see table general slides*

Antiviral treatment

Antiviral 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-48h after clinical onset. ***AII***

- If rapid NAT or DAD is not available, HCT- and HM-patients 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*. ***BII***
- The recommended adult dose of *oseltamivir* 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 *oseltamivir* treatment until undetectable. ***CIII***

Pediatric dosing of oseltamivir

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

Weight (kg) §	Treatment and post-exposure prophylaxis dosing #	Pre-exposure prophylaxis dosing #
15 kg or less	30 mg twice daily	30 mg once daily
15.1 – 23 kg	45 mg twice daily	45 mg once daily
23.1 – 40 kg	60 mg twice daily	60 mg once daily
40.1 or more	75 mg twice daily	75 mg once daily
§ 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
2. Adapted from: Uyeki et al (2019) *Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza* Clin Inf Dis 68: e1-47 (DOI: 10.1093/cid/ciy866)

Antiviral treatment

Management of severe or prolonged case of Influenza-RTID

- Patients with IV-A/B pneumonia, who fail to clinically improve/worsen despite adequate treatment with neuraminidase inhibitors (NAI) for at least 5 days, should be re-evaluated for complications including super-/co-infections using microbiological testing of samples from the lower respiratory tract. ***BIII***

- In case of continued IV-A/B detection, antiviral treatment could be extended for at least 10 days ***BIII***
- In severe or prolonged influenza disease, combining NAI with *baloxavir* could be considered. ***BIII***

- For patients with severe influenza and suspicion of impaired gastrointestinal absorption, iv *peramivir* or iv *zanamivir* (if available) could be considered. ***CIII***
- When IV-A/B persists (especially at high levels if QNAT is available) despite adequate therapy, genotypic resistance testing could be considered. ***CIII***
- For severely immunocompromised patients presenting with severe disease, some clinical experts consider double-dose of *oseltamivir* 150 mg BID. ***CIII***

SPECIFIC RECOMMENDATIONS

Respiratory syncytial virus (RSV) -A and -B

- Prevention options
  - Infection control
  - Deferral
  - Antiviral prophylaxis
  - Vaccination

Prevention

RSV Infection control, deferral, antiviral prophylaxis

- Infection control – *see table in general slides*
- Deferral – *see table general slides*
- In the absence of data evaluating the efficacy or risk/benefit ratio, *ribavirin* should *not* be used as pre- or post-exposure prophylaxis in adults or in children. ***DII***
- There are currently no other antivirals with documented clinical efficacy or protocols available for pre- or post-exposure prophylaxis. (***statement***)

Prevention

RSV Passive immunisation of adults

- In the absence of data evaluating the efficacy or risk/benefit ratio, *palivizumab* should *not* be used as pre- or post-exposure prophylaxis for adults. ***DII***
- Palivizumab could be considered as post-exposure prophylaxis in severely immunodeficient adults when nosocomial outbreak is occurring. ***CIII***
- Insufficient data to recommend *nirsevimab* seasonal prophylaxis for adults. ***CIII***
- Insufficient data to recommend *nirsevimab* post-exposure prophylaxis for adults. ***CIII***
- Insufficient data to recommend *nirsevimab* for RSV treatment for adults. ***CIII***

No recommendations, but the following that will be mentioned in the manuscript text

- Nirsevimab, motavizumab, motavizumab-YTE, nirsevimab, ALX-0171, suptavumab, clesrovimab LN-RSV01, RSV604, presatovir, MDT-637, lumicitabine, IFN-α1b, rilematovir, enzaplatovir, AK0529, sisunatovir, PC786, and EDP-93
- *https://onlinelibrary.wiley.com/doi/epdf/10.1002/rmv.2576*
- *https://link.springer.com/article/10.1007/s40121-020-00383-6*
- *https://jamanetwork.com/journals/jamanetworkopen/article-abstract/2801583*

Prevention

RSV Passive immunisation of children

- Seasonal pre-exposure prophylaxis with *palivizumab* for children of <2 years of age who have undergone HCT could be considered. ***BIII***
- Post-exposure prophylaxis with *palivizumab* could be considered for imunocompromised children of <2 years of age when a nosocomial outbreak is occurring. ***BIII***

- *RSV s*easonal pre-exposure prophylaxis with *nirvesimab* can be considered for severely imunocompromised children <2 years. ***BII ut***

  (Pediatrics Volume 154, number 4, October 2024:e2024066508)

- There is insufficient data to recommend post-exposure prophylaxis with *nirsevimab* for children. ***CIII***
- There is insufficient data to recommend treatment with *nirvesimab* for children with RSV URTID or LRTID. ***CIII***

Prevention

RSV Active immunisation of adults

- RSV Vaccination is available for patients older than 60 years of age having an increased risk of RSV-LRTID. (***statement***)
- This includes patients with chronic medical conditions that a health care provider determines to increase the risk of severe RSV disease such as hematological disorders. (***statement***).
- In the absence of specific data for HM- and HCT-patients, one single dose of a licensed RSV vaccine is being considered by some experts and some national health authorities in Europe. (***statement***)
- To obtain specific data on the clinical and immunologic efficacy, HCT and HM patients can be considered to be enrolled in respective clinical trials. (***statement***)

https://www.cdc.gov/vaccines/vpd/rsv/hcp/older-adults.html
https://search.cdc.gov/search/?query=rsv%20vaccine&dpage=1

Treatment of RSV-RTID in allogeneic HCT Patients (1)

- Allogeneic HCT recipients at high risk for progression to, or with diagnosis of, RSV-LRTID should be considered for treatment with *ribavirin*. ***BII u***
- For guidance on defining high-risk for poor outcome, the MD Anderson Immunodeficiency Score Index (ISI) or the Basel Severe Immunodeficiency (SID) grading can be considered. ***BIII***
- In allogeneic HCT 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 body weight in 3 divided doses (maximum dose 600 mg/8 h or 1800 mg per day). ***BII u***
- Patients receiving systemic *ribavirin* should be monitored and managed for adverse events (e.g., hemolysis, abnormal liver function tests, drug to drug interactions, declining renal function). ***BII t***
- 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 paediatric setting, but some experts recommend similar per weight dosing as for adults. (***statement***)

Immunodeficiency 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/B[a]

University Hospital Basel immunodeficiency grading system		MD Anderson Cancer Center immunodeficiency scoring index	
Criterion or parameter	Score	Criterion or parameter	Score
Neutropenia, <0.5 × 10^9/liter	1	Neutropenia, <0.5 × 10^9/liter	3
Lymphopenia, <0.1 × 10^9/liter	1	Lymphopenia, <0.2 × 10^9/liter	3
Allo-HCT <6 months ago	1	Preengraftment or allo-HCT <1 months	1
GVHD of ≥2 or requiring treatment	1	GVHD (acute/chronic)	1
T-cell depletion <3 months prior to CARV Dx	1	Corticosteroids	1
B-cell depletion <3 months prior to CARV Dx	1	Myeloablative conditioning	1
Hypo-γ-globulinemia, <4.5 g/liter	1	Age, >40 yr	2
Maximal	7	Maximal	12
Moderate (MID)	0	Low risk	0–2
Severe (SID)	1	Moderate risk	3–6
Very severe (verySID)	2–7	High risk	7–12

[a]Allo-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.

Table from: Ison MG, Hirsch HH (2019) *Community-acquired respiratory viruses in transplant patients: Diversity, impact, unmet clinical needs* Clin Microbiol Rev 32:e00042-19. (doi.org/10.1128/CMR.00042-19)

Vakil E, *et al* (2018) *Risk factors for mortality after respiratory syncytial virus lower respiratory tract infection in adults with hematologic malignancies* Transpl Infect Dis 20: e12994 (doi: 10.1111/tid.12994)

Spahr J, *et al* (2018) *Community-Acquired Respiratory Paramyxovirus Infection After Allogeneic Hematopoietic Cell Transplantation: A Single-Center Experience* Open Forum Infect Dis 5: 10.1093/ofid/ofy077

See special considerations for hyperglycemia, albumin levels, repeat transplantation: Ogimi et al. (2022) BMT 57, 649 https://doi.org/10.1038/s41409-022-01575-z

Treatment of RSV-RTID in allogeneic HCT Patients (2)

- For allogeneic HCT patients with, or at high risk of, RSV-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 1 -2 weeks). ***BIII***
- Corticosteroids of > 1mg/kg/day used at diagnosis of RSV-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***

Treatment of RSV-RTID in allogeneic HCT Patients (3)

- Aerosolized ribavirin is hardly ever used in clinical practice today for reasons of poor availability, administration times, cumbersome infrastructure, required HCP safety measures and poor patient tolerability. (***statement***)
- Aerosolized *ribavirin* for HRSV can be administered as 2 g for 2 h every 8 h for 7–10 days. ***BII***
- Aerosolized *ribavirin* therapy should be accompanied by measures avoiding environmental exposure and thereby potentially teratogenic effects in pregnant HCP and visitors. ***AII***
- 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 RSV-RTID in autologous HCT or in HM Patients

- Treatment of autologous HCT- and HM-patients with diagnosis of RSV-LRTID with *ribavirin* should be considered. ***BIII***
- 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) having *hypo-γ-globulinemia (<4.5 g/L),* adjunct treatment could be considered with intravenous immunoglobulin (IVIG) (e.g. 0.5 g/kg bodyweight at least 3 doses within 1 - 2 weeks). ***CIII***

SPECIFIC RECOMMENDATIONS

Human Metapneumovirus (HMPV)

- Prevention options
  - Infection control, deferral
  - No antiviral prophylaxis available
  - No passive or active immunization available
- Antiviral Treatment
  - Limited evidence for ribavirin
  - Limited evidence for IVIG

Prevention

HMPV Infection control, deferral, antiviral prophylaxis

- Infection control – *see table in general slides*
- Deferral – *see table general slides*
- In the absence of data evaluating the efficacy or risk/benefit ratio, *ribavirin* should *not* be used as pre- or post-exposure prophylaxis in adults or in children. ***DII***
- There are currently no other antivirals with documented clinical efficacy or protocols available for pre- or post-exposure prophylaxis. (***statement***)

Treatment of HMPV-RTID in allogeneic HCT Patients

- Available data are too limited to support specific doses, administration of IVIG (e.g. 0.5 g/kg bodyweight at least 3 doses within 1-2 weeks) can be considered for HCT- or HM-patients with *hypo-γ-globulinemia (<4.5 g/L).* ***BIII***
- Available data are too limited to support the general use of oral *ribavirin*, some expert consider its use for HMPV in allogeneic HCT-patients with HMPV-URTID at high-risk for progression to LRTID or with LRTID. ***CIII***
- Available data are too limited to support the general use of *IVIG*, some expert consider its use for HMPV in allogeneic HCT-patients with HMPV-URTID at high-risk for progression to LRTID or with LRTID. ***CIII***
- Corticosteroids of > 1mg/kg/day at diagnosis of HMPV-LRTID has been associated with progression of disease and mortality, thus reducing corticosteroid administration to less than 1 mg/kg body weight should be considered if possible. ***BIII***

Treatment of HMPV-RTID in autologous HCT or in HM Patients

- Although available data are too limited to support specific doses, administration of *IVIG* (e.g. 0.5 g/kg bodyweight at least 3 doses within 1-2 weeks) can be considered for HPMV-LRTID in autologous HCT-patients or HM patients with *hypo-γ-globulinemia (<4.5 g/L).* ***BIII***
- Available data are too limited to support the general use of *ribavirin* for HPMV, some expert consider its use for HPMV-LRTID in autologous HCT-patients or HM patients. ***CIII***
- Available data are too limited to support the general use of *IVIG* for HPMV, some expert consider its use for HPMV-LRTID in autologous HCT-patients or HM patients. ***CIII***
- Corticosteroids of > 1mg/kg/day at diagnosis of HPMV-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 possible. ***CIII***

SPECIFIC RECOMMENDATIONS

Human Parainfluenzavirus (HPIV)

- Prevention options
  - Infection control, deferral
  - No antiviral prophylaxis available
  - No passive or active immunization available
- Antiviral Treatment
  - Limited evidence for ribavirin
  - Limited evidence for IVIG

Prevention

HPIV Infection control, deferral, antiviral prophylaxis

- Infection control – *see table in general slides*
- Deferral – *see table general slides*
- In the absence of data evaluating the efficacy or risk/benefit ratio, *ribavirin* should *not* be used as pre- or post-exposure prophylaxis in adults or in children. ***DII***
- There are currently no other antivirals with documented clinical efficacy or protocols available for pre- or post-exposure prophylaxis. (***statement***)

Treatment of HPIV-RTID in allogeneic HCT Patients

- Available data are too limited to support the general use of *ribavirin* for HPIV, some expert consider its use for allogeneic HCT-patients with HPIV-LRTID or at high-risk for progression to LRTID. ***CIII***
- Available data are too limited to support the general use of *IVIG* for HPIV, some expert consider its use for allogeneic HCT-patients with HPIV-LRTID or at high-risk for progression to LRTID. ***CIII***
- Although available data are too limited to support specific doses, administration of *IVIG* (e.g. 0.5 g/kg bodyweight at least 3 doses within 1-2 weeks) can be considered for patients with *hypo-γ-globulinemia (<4.5 g/L).* ***BIII***
- Corticosteroids of >1mg/kg/day 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 possible. ***CIII***

Treatment of HPIV-RTID in autologous HCT or in HM Patients

- Although available data are too limited to support specific doses, administration of *IVIG* (e.g. 0.5 g/kg bodyweight at least 3 doses within 1-2 weeks) can be considered for HPIV-LRTID in autologous HCT-patients or HM patients with *hypo-γ-globulinemia (<4.5 g/L).* ***BIII***
- Available data are too limited to support the general use of *ribavirin* for HPIV, some expert consider its use for HPIV-LRTID in autologous HCT-patients or HM patients. ***CIII***
- Available data are too limited to support the general use of *IVIG* for HPIV, some expert consider its use for HPIV-LRTID in autologous HCT-patients or HM patients. ***CIII***
- Corticosteroids of > 1mg/kg/day 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 possible. ***CIII***

SPECIFIC RECOMMENDATIONS

Human Coronaviruses (HCoV)

- Prevention options
  - Infection control, deferral
  - No antiviral prophylaxis available
  - No passive or active immunization available
  - SARS-CoV-2 is not included (see ECIL-10 CoVID19)
- Antiviral Treatment
  - No evidence for ribavirin and other drugs used for SCoV2
  - Limited evidence for IVIG

HCoV Infection control, deferral, antivirals

- Infection control – *see table in general slides*
- Deferral – *see table general slides*
- In the absence of data evaluating the efficacy or risk/benefit ratio, *ribavirin* should *not* be used as pre- or post-exposure prophylaxis in adults or in children. ***DII***
- Although available data are too limited to support use or specific doses, administration of *IVIG* (e.g. 0.5 g/kg bodyweight at least 3 doses within 1-2 weeks) can be considered for HCoV-LRTID in HCT or HM patients with *hypo-γ-globulinemia (<4.5 g/L).* ***BIII***
- There are currently no other antivirals (e.g., with activity for SCoV2) with documented clinical efficacy or protocols available for pre- or post-exposure prophylaxis. (***statement***)
- There are insufficient data for specific treatment of HCoV-RTID with currently available antiviral drugs. (***statement***)

SPECIFIC RECOMMENDATIONS

Human Rhinoviruses/Enteroviruses (HRhV/EV)

- Prevention options
  - Infection control, deferral
  - No antiviral prophylaxis available
  - No passive or active immunization available
- Antiviral Treatment
  - No evidence for ribavirin and other drugs used for SCoV2
  - Limited evidence for IVIG

Management of HRV/EV-RTID in HCT- and HM-Patients

- Infection control – *see table in general slides*
- Deferral – *see table general slides*
- Deferral of conditioning should be considered for patients with laboratory-confirmed HRV/EV-LRTID scheduled for allogeneic HCT. ***AII***
- 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***
- In the absence of data evaluating the efficacy or risk/benefit ratio, *ribavirin* should *not* be used as pre- or post-exposure prophylaxis in adults or in children. ***DII***.
- Although available data are too limited to support use or specific doses, administration of *IVIG* (e.g. 0.5 g/kg bodyweight at least 3 doses within 1-2 weeks) can be considered for HRV/EV-LRTID in HCT or HM patients with *hypo-γ-globulinemia (<4.5 g/L).* ***BIII***

SPECIFIC RECOMMENDATIONS

Human Adenoviruses (HAdV)

- Prevention options
  - Infection control, deferral
  - No antiviral prophylaxis available
  - No passive or active immunization available
- Antiviral Treatment
  - Limited evidence for intravenous cidofovir
  - Limited evidence for IVIG

Management of HAdV-RTID in HCT- and HM-Patients (1)

- Infection control – *see table in general slides*
- Deferral – *see table general slides*
- 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***

Management of HAdV-RTID in HCT- and HM-Patients (2)

- 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 <200/uL), treatment with intravenous cidofovir should be considered. ***BIII***
- Although no efficacious dosing has been established, intravenous cidofovir can be considered for HAdV DNAemia (e.g. 1 mg/kg body weight three times weekly, *without* probenicid) or for LRTID/pneumonia (e.g. 5 mg/kg bodyweight once weekly; *with* probenecid), together with hyper-hydration, and monitoring of renal function. ***B III***
- Although available data are too limited to support use or specific doses, administration of *IVIG* (e.g. 0.5 g/kg bodyweight at least 3 doses within 1-2 weeks) can be considered for HAdV-LRTID in HCT or HM patients with *hypo-γ-globulinemia (<4.5 g/L).* ***BIII***

SPECIFIC RECOMMENDATIONS

Human Bocaviruses (HBoV)

- Prevention options
  - No recommendations for diagnostics, infection control, or deferral
  - No antiviral prophylaxis available
  - No passive or active immunization available
- Antiviral Treatment
  - No specific recommendations for adults
  - Center-dependent selective approach for *paediatric* high-risk allo- and autologous HCT or HM patients?