From September 19th to 21st 2019

8th

EUROPEAN CONFERENCE ON INFECTIONS IN LEUKAEMIA

CARVS Recommendation Update 2019

FINAL SLIDE SET CONFIDENTIAL

Mercure Sophia Antipolis
Sophia Antipolis France

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

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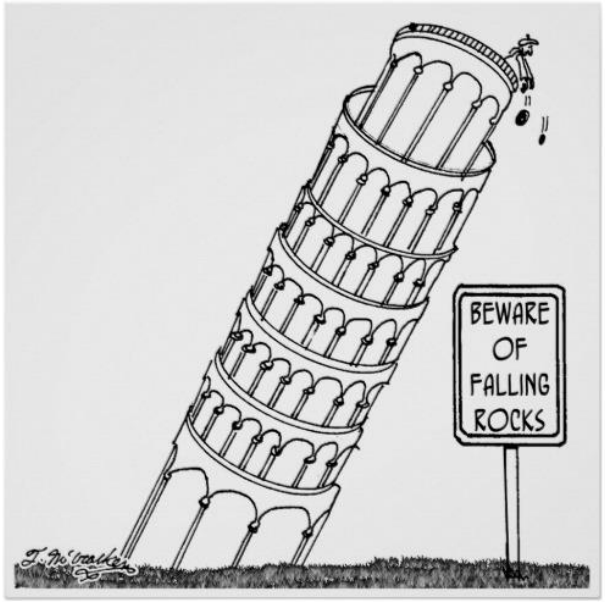

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Update of ECIL- 4 Guidelines

Transplant Infectious Disease, ISSN 1398-2273

Review

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

D. Engelhard, B. Mohty, R. de la Camara, C. Cordonnier, P. Ljungman. 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.
Transpl Infect Dis 2013: **15**: 219–232. All rights reserved

Abstract: Influenza may cause severe disease and mortality in leukemia patients and in hematopoietic stem cell transplantation recipients. The 4th European Conference of Infections in Leukemia (ECIL-4) has developed evidence-based guidelines for prevention and management of influenza infections in these patients. Real-time reverse-transcription polymerase chain reaction is the diagnostic test of choice, as it is the most sensitive and specific test for influenza. The risks for severe influenza and fatal outcome include lymphopenia, older age, influenza soon after transplantation or chemotherapy, steroid treatment, and lack of early antiviral therapy. Neuraminidase inhibitors (oral oseltamivir or inhalation of zanamivir) are currently the most effective therapeutic agents for influenza. Main preventive measures include annual vaccination of patients, household contacts, and hospital staff. This review summarizes ECIL-4's main recommendations.

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Key words: influenza; hematopoietic stem cell transplantation; HSCT; leukemia; The European Conference on Infections in Leukemia; ECIL-4; guidelines; recommendations

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Received 16 July 2012, revised 16 October 2012, 19 November 2012, accepted for publication 23 November 2012

DOI: 10.1111/tid.12054
Transpl Infect Dis 2013: **15**: 219–232

Each year, immunocompromised patients may contract one or more of the A/H1N1, A/H3N2, or B influenza viruses, while the specific strains change by so-called antigenic drift (minor changes in the existing strains) or shift (new strains). The 2009 influenza pandemic raised awareness of the importance of influenza viruses among both the general and immunocompromised populations, including leukemic and post-hematopoietic stem cell transplantation (HSCT) patients, in whom severe disease and mortality were reported (1). These patients are recognized to be at increased risk for complicated and even fatal influenza A and B.

https://onlinelibrary.wiley.com/doi/full/10.1111/tid.12054

REVIEW ARTICLE

Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for Diagnosis and Treatment of Human Respiratory Syncytial Virus, Parainfluenza Virus, Metapneumovirus, Rhinovirus, and Coronavirus

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Community-acquired respiratory virus (CARV) infections have been recognized as a significant cause of morbidity and mortality in patients with leukemia and those undergoing hematopoietic stem cell transplantation (HSCT). Progression to lower respiratory tract infection with clinical and radiological signs of pneumonia and respiratory failure appears to depend on the intrinsic virulence of the specific CARV as well as factors specific to the patient, the underlying disease, and its treatment. To better define the current state of knowledge of CARVs in leukemia and HSCT patients, and to improve CARV diagnosis and management, a working group of the Fourth European Conference on Infections in Leukaemia (ECIL-4) 2011 reviewed the literature on CARVs, graded the available quality of evidence, and made recommendations according to the Infectious Diseases Society of America grading system. Owing to differences in screening, clinical presentation, and therapy for influenza and adenovirus, ECIL-4 recommendations are summarized for CARVs other than influenza and adenovirus.

Keywords. respiratory virus; transplantation; leukemia; bone marrow transplantation; hematopoietic.

Community-acquired respiratory virus (CARV) infections include a variety of RNA viruses such as human orthymyxo-, paramyxo-, picorna-, and coronaviruses, and DNA viruses such as adeno-, boca-, and polyomaviruses [1, 2]. CARVs are detectable in the general population throughout the year, but some CARVs show a pronounced seasonality in temperate climates that can exceed epidemic thresholds [1, 3]. CARV respiratory tract infections (RTIs) range from asymptomatic replication to significant disease that typically affects the very young and the very old populations, patients with chronic medical conditions, and those with inherited, acquired, or drug-induced immune dysfunction [1, 4]. In the past 2 decades, CARV RTIs have been recognized as a significant cause of morbidity and mortality in patients with leukemia and those undergoing hematopoietic stem cell transplantation (HSCT) [5–9]. These patients are at increased risk for progression to lower RTI (LRTI) with clinical and radiological signs of pneumonia, respiratory failure, and fatal outcome. The risk

Received 6 August 2012; accepted 18 September 2012; electronically published 28 September 2012.

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Clinical Infectious Diseases 2013;56(2):258–66

DOI: 10.1093/cid/cis844

https://academic.oup.com/cid/article/56/2/258/316667

Transplant Infectious Disease, ISSN 1398-2273

Review article

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

S. Matthes-Martin, T. Feuchtinger, P.J. Shaw, D. Engelhard, H.H. Hirsch, C. Cordonnier, P. Ljungman, on behalf of the fourth European Conference on Infections in Leukemia. European guidelines for diagnosis and treatment of adenovirus infection in leukemia and stem cell transplantation: summary of ECIL-4 (2011).
Transpl Infect Dis 2012: **14**: 555–563. All rights reserved

Abstract: Human adenovirus (HAdV) infections are increasingly recognized as important pathogens in immunocompromised hosts, especially in patients with severely suppressed T-cell function. The 4th European Conference of Infections in Leukemia (ECIL-4) has developed evidence-based guidelines for diagnosis and management of HAdV infections. The risk for HAdV-associated disease is increased in children, and risk factors for HAdV disease are T-cell depletion, unrelated and cord blood hematopoietic stem cell transplantation, graft-versus-host disease grades III–IV, and lymphopenia. The recommended technique for monitoring of high-risk patients is quantitative polymerase chain reaction. Cidofovir is the most used antiviral therapy, although no controlled study has been performed. HAdV-specific T-cell therapy is in development.

S. Matthes-Martin[1], T. Feuchtinger[2], P.J. Shaw[3], D. Engelhard[4], H.H. Hirsch[5], C. Cordonnier[5], P. Ljungman[7], on behalf of the fourth European Conference on Infections in Leukemia

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Key words: human adenovirus; leukemia; stem cell; guidelines

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Received 6 June 2012, revised 4 August 2012, 15 August 2012, accepted for publication 15 August 2012

DOI: 10.1111/tid.12022
Transpl Infect Dis 2012: **14**: 555–563

Human adenovirus (HAdV) infections are increasingly recognized as important pathogens in immunocompromised hosts, especially in patients with severely suppressed T-cell function such as after allogeneic hematopoietic stem cell transplantation (HSCT), resulting in significant morbidity and also mortality. Children seem to be more frequently affected than adults. In humans, more than 50 different HAdV types have been identified, divided into 7 species denoted A to G, according to their DNA homologies, hemagglutination properties, and oncogenic potential in rodents (1–5).

The clinical manifestations of AdV infections in immunocompetent hosts include upper respiratory disease, gastroenteritis, or (kerato-)conjunctivitis, and are self-limited in most cases, although severe manifestations including encephalitis, myocarditis, and pneumonia have

https://onlinelibrary.wiley.com/doi/abs/10.1111/tid.12022

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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 tranplantation
- 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

Working Definitions (adapted ECDC)

Definitions of Respiratory Tract Infectious Disease

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

- Fever, cough, headache, myalgia, nausea, vomiting, weakness, fatigue, …
- 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.

	CARV-attributable Pneumonia			
	possible	probable	presumptive	proven
Clinical symptoms and signs of LRTID	+	+	+	+
CARV detected in NPS *	+	+		
New/progressive infiltrates on imaging		+	+ / -	+
New/progressive hypoxemia **		+	- / +	- / +
CARV detected in BAL ***			+	
CARV pneumonia in tissue ******				+

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

CARV Infection Control

CARV	TRANSMISSION	OUTBREAKS	ASBMT Control Recommendation	MD Anderson Cancer Center Control Recommendation	ECIL-8 2019 Control Recommendation
IV-A/B	Largedroplets, small droplets, fomites	Pediatric hematology and pediatric oncology	Droplet	Droplet and contact	Droplet and contact precautions
HRSV	Large droplets, small droplets, fomites	Stem cell transplant units	Contact	Droplet and contact	
HMPV	Small droplets, close contacts, fomites	Hematology unit	No recommendation	Droplet and contact	
HPIV	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	Large droplets, fomites	No reports in patients with cancer	Contact	Droplet and contact	
HRV/EV	Large droplets, small droplets, fomites	Hemato-oncology wards	Contact	Droplet and contact	

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

Patient presenting with laboratory-confirmed RTID	Deferral of chemotherapy/conditioning allogeneic HCT *if possible*	Deferral of chemotherapy /conditioning for HM or autologous HCT *if possible*	REFERENCE
IV-A/B URTID or LRTID	AII*	BIII*	
HRSV URTID or LRTID	AII	BIII	allo-HCT: Peck AJ *et al* (2004) CID 39: 673 ped allo-HCT: Ottaviano et al (2018) BJH (doi: 10.1111/bjh.16216) auto-HCT: Aslan et al (1999) BMT 24: 505
HMPV URTID or LRTID	AII	BIII	
HPIV URITD or LRTID	AII	BIII	
HAdV URTID or LRTID	AII	BIII	Campbell AP et al (2015) CID 61: 192 Waghmare A 2019, IDWeek Presentation **
HCoV LRTID	CIII	CIII	
HRV/EV LRTID	AII	CIII	Campbell AP et al (2015) CID 61: 192 Waghmare A 2019, IDWeek Presentation ** ped allo-HCT: Ottaviano et al (2018) BJH (doi: 10.1111/bjh.16216)
HBoV	No recommendation	No recommendation	

* in addition to immediate antiviral treatment

** A Waghmare et al submitted (IDWeek 2019 (#926 - Pre-Transplant Resp Viral Infection Impacts Post-Transplant Outcomes Infection; https://www.eventscribe.com/2019/IDWeek/searchGlobal.asp)

Specific Recommendations for Influenzavirus 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. ***AII 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*

Refs. Cordonnier *et al* (2019) *Vaccination of haemopoietic stem cell transplant recipients: guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7)* Lancet ID 19: e200-212 (doi: 10.1016/S1473-3099(18)30600-5) https://www.sciencedirect.com/science/article/abs/pii/S1473309918306005
Mikulska *et al* (2019) *Vaccination of patients with haematological malignancies who did not have transplantations: Guidelines from the 2017 European Conference on Infections in Leukaemia (ECIL 7)* Lancet ID 19: e188–99 (doi: 10.1016/ S1473-3099(18)30601-7) https://www.sciencedirect.com/science/article/abs/pii/S1473309918306017

Vaccination against Influenza Virus-A and -B

- In children ≥9 y and in adults, a 2nd 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. ***BII***
- Children 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. ***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 2nd dose after 4 weeks should be considered. ***BII r***

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. ***AII 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. ***AII 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. ***AII***

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 insufficent 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***

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)

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/B[a]

University Hospital Basel immunodeficiency grading system		MD Anderson Cancer Center immunodeficiency scoring index	
Criterion or parameter	Score	Criterion or parameter	Score
Neutropenia, $<0.5 \times 10^9$/liter	1	Neutropenia, $<0.5 \times 10^9$/liter	3
Lymphopenia, $<0.1 \times 10^9$/liter	1	Lymphopenia, $<0.2 \times 10^9$/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.

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

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)
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. ***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 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 t***
- For autologous HCT- and HM-patients with RSV-LRTID or at high risk for RSV-LRTID, and 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). ***CIII t***

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. ***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 for allogeneic HCT-patients with LRTID, or with HMPV-URTID at high-risk for progression to LRTID, oral ribavirin could be considered. ***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-γ-globulinemia (<4.5 g/L). ***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. ***CIII***
- In allogeneic HCT patients, spirometry at least 6 weeks after laboratory-confirmed HMPV-RTID diagnosis could be considered to identify chronic lung dysfunction. ***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. ***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***
- 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

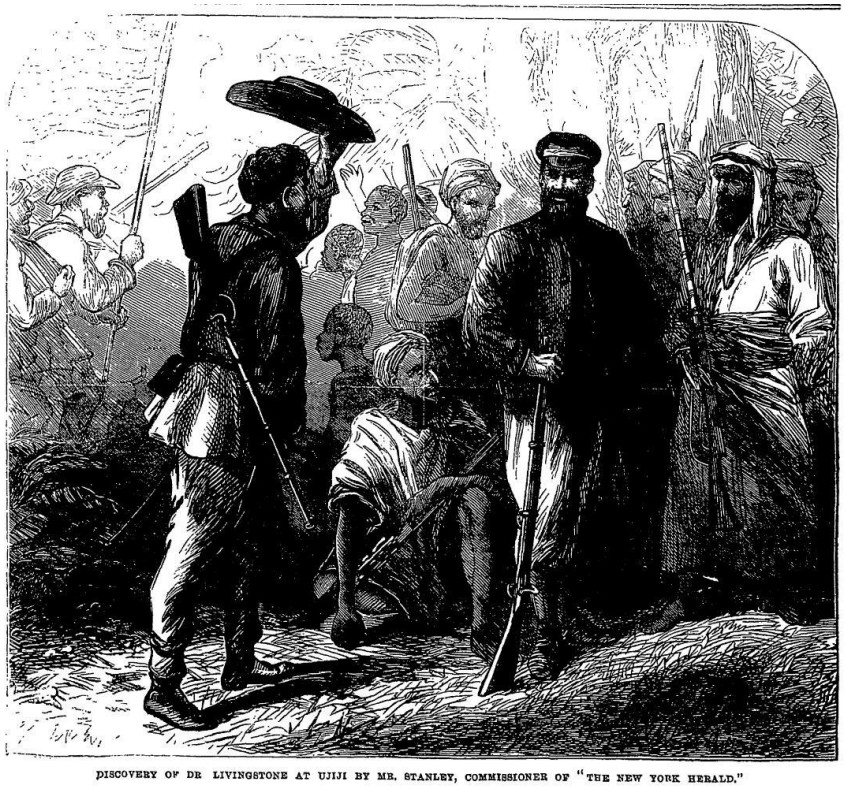
- Deferral of conditioning therapy should be considered for patients with HAdV-RTID planned for allogeneic HCT, if possible. ***AII***
- Deferral of conditioning/chemotherapy could be considered for autologous HCT- and HM-patients with HAdV-RTID scheduled for chemotherapy of hemato-oncological diseases, 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



DISCOVERY OF DR LIVINGSTONE AT UJIJI BY MR. STANLEY, COMMISSIONER OF "THE NEW YORK HERALD."

Terminology

"Doctor Livingstone,
I presume…."

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.

The action-oriented character of presumption comes into its own in the context of an inquiry into an emerging infectious disease. Diseases such as BSE and, more recently, SARS have posed a potentially serious, but at the time of their emergence largely unquantifiable, risk to humans. Scientists charged with responding to this risk have had the dual tasks of developing theoretical knowledge of the disease agents involved and of undertaking practical measures to contain the spread of an outbreak. The implementation of disease containment measures cannot await the outcome of inquiry, but must be initiated in advance of the attainment of complete or even partial knowledge of the disease processes that are responsible for an epidemic. Presumption warrants these actions in the practical sphere, actions that must proceed out of necessity and before the process of inquiry has terminated (and, in some cases, even started).

Thank you