Pitfalls in definitions on respiratory viruses and particularities of Adenovirus infection in hematopoietic cell transplantation patients : Recommendations from the EBMT practice harmonization and guidelines committee

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General review

Pitfalls in definitions on respiratory viruses and particularities of Adenovirus infection in hematopoietic cell transplantation patients: Recommendations from the EBMT practice harmonization and guidelines committee

José Luis Piñana [a], Simone Cesaro [b], Malgorzata Mikulska [c,d], Paul E. Verweij [e], Anne Bergeron [f], Dionysios Neofytos [g], Jan Styczynski [h], Isabel Sánchez-Ortega [i], Raffaella Greco [j], Francesco Onida [k], Ibrahim Yakoub-Agha [l], Dina Averbuch [m], Rafael de la Cámara [n], Per Ljungman [o,p,*]

[a] Department of Hematology. Hospital Clínico Universitario of Valencia, INCLIVA, Biomedical Research Institute, Valencia, Spain
[b] Pediatric Hematology Oncology, Department of Mother and Child, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
[c] Division of Infectious Diseases, Department of Health Sciences (DISSAL), University of Genova, Genova, Italy
[d] IRCCS Ospedale Policlinico San Martino, Genova, Italy
[e] Department of Medical Microbiology and Radboudumc-CWZ Center of Expertise for Mycology, Radboud University Medical Center, Nijmegen, the Netherlands
[f] Division of Pulmonology, University Hospitals of Geneva, Geneva, Switzerland
[g] Transplant Infectious Diseases Unit, Division of Infectious Diseases, University Hospitals Geneva, Geneva, Switzerland
[h] Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University Torun UMK, University Hospital, Bydgoszcz, Poland
[i] EBMT Medical Officer, Executive Office, Barcelona, Spain
[j] Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy
[k] Hematology and BMT Unit ASST Fatebenefratelli, Sacco University of Milan, Italy
[l] CHU de Lille, Univ Lille, INSERM U1286, Infinite, 59000, Lille, France
[m] Faculty of Medicine, Hebrew University of Jerusalem, Hadassah Medical Center, Jerusalem, Israel
[n] Department of Hematology, Hospital de la Princesa, Madrid, Spain
[o] Dept. of Cellular Therapy and Allogeneic Stem Cell Transplantation, Karolinska Comprehensive Cancer Center, Karolinska University Hospital Huddinge, Stockholm, Sweden
[p] Dept. of Medicine Huddinge, Karolinska Institutet (KI), Stockholm, Sweden

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ABSTRACT

In 2023, the EBMT Practice harmonization and Guidelines Committee partnered with the EBMT Infection Diseases Working Party (IDWP) to undertake the task of delivering best practice recommendations, aiming to harmonize by expert consensus, the already existing definitions and future epidemiological and clinical studies among centers of the EBMT network. To attain this objective, a group of experts in the field was convened. The workgroup identified and discussed some critical aspects in definitions of community-acquired respiratory viruses (CARV) and adenovirus (ADV) infections in recipient of hematopoietic cell transplant (HCT). The methodology involved literature review and expert consensus. For CARV, expert consensus focused on defining infection severity, infection duration, and establishing criteria for lower respiratory tract disease (LRTD). For ADV, the expert consensus focused on surveillance methods and the definitions of ADV infection, certainty levels of disease, response to treatment, and attributable mortality. This consensus workshop provided indications to EBMT community aimed at facilitating data collection and consistency in the EBMT registry for respiratory viral infectious complications.

* Corresponding author at: Karolinska University Hospital Huddinge, SE-14186, Stockholm, Sweden.
E-mail address: per.ljungman@ki.se (P. Ljungman).

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Introduction - current state of the art

More than a decade ago, the European Conference on Infections in Leukemia (ECIL-4) proposed the definitions for infections related to Community-Acquired Respiratory Viruses (CARV) such as influenza virus, respiratory syncytial virus, common seasonal human coronavirus, enterovirus/rhinovirus, human metapneumovirus, human parainfluenza virus, human bocavirus and adenovirus (ADV), in the setting of hematopoietic cell transplantation (HCT) [1]. An update of definitions and guidelines for CARV has been issued at ECIL-8, in 2019 (available at https://www.ecil-leukaemia.com/en/resources/resources-ecil), Both ECIL-4 and ECIL-8 differentiated between asymptomatic infections and symptomatic diseases and distinguished between upper respiratory tract (URT) (above the larynx) and/or lower respiratory tract (LRT) (below the larynx) involvement. Additionally, ECIL definitions assessed the likelihood of a *bona fide* CARV infection by considering the presence or absence of an epidemiological link [1]. Nevertheless, certain critical features such as the severity of CARV infection, its duration, the likelihood of recurrences, and the presence of concurrent or overlapping co-infections or the determination of CARV as primary cause of LRT disease, have not been comprehensively established yet [2]. These points are further complicated by the fact that various CARV studies have utilized disparate definitions for these parameters which render comparisons between studies challenging [2].

While most of CARV infections are caused by RNA viruses, *Adenovirus* (ADV) is a DNA virus that may cause respiratory clinical manifestations similar to CARV; for instance, ADV of group B, C, and E may cause URT and LRT while ADV of group A, F, and G can cause pneumonia, [3,4]. The definition of ADV infection and disease in HCT recipients were addressed by ECIL 4 [5].

Community acquired respiratory viruses (CARV)

CARV infection/disease severity

In the literature, assessment of the severity of CARV infections has primarily relied on two factors: the anatomical site of infection [7] (upper or lower respiratory tract disease) and the need for oxygen support (severity) [8]. Although some severity scoring systems have emerged for CARV infections in non-immunocompromised pediatric patients [9–11], their practical application is limited because they solely rely on clinical symptoms (e.g., cough, rales, wheezing, apnea, tachypnea, shortness of breath) and oxygenation/ventilation-related parameters (e.g., pH <7.35, PCO2 >45, arterial saturation <87%, oxygen or mechanical ventilation requirements) in hospitalized patients. The World Health Organization (WHO) Operational Guidelines for Sentinel Severe Acute Respiratory Infection (SARI) surveillance, updated in September 2014 [12], defined severe cases as patients (adults or children) meeting all of the specific criteria: fever (≥38 °C), cough, symptom onset within the last ten days, and the need for hospitalization. However, these guidelines lack radiological data and specific oxygen support requirements. Recently, the WHO introduced a severity classification for SARS-CoV-2 infection [7], which comprises five categories: asymptomatic or pre-symptomatic infection (positive for SARS-CoV-2 but without COVID-19 symptoms), mild (fever, cough, sore throat, without shortness of breath or abnormal chest imaging), moderate (evidence of LRT disease with SpO2 ≥94% on room air at sea level), severe (SpO2 <94%, PaO2/FiO2 <300 mm Hg, respiratory rate >30 breaths/min, or significant lung infiltrates >50%), and critical (respiratory failure, septic shock, and/or multiple organ dysfunction). The limitation lies in the reliance on dynamic parameters such as SpO2 (oxygen saturation) and respiratory rate, as well as the quantitative assessment of lung infiltrates. These measurements can fluctuate over time or often go unreported, placing significant emphasis on physician interpretation when determining and reporting severity classifications.

Defining CARV infection duration and infectivity

The detection of viral mRNA by the standard method of RT-PCR does not necessarily mean that the virus is viable, and subsequently, capable to shed and be transmitted, although alternative PCR techniques like genomic RT-PCR have shown reasonable correlation with viral cultures [13]. Unfortunately, viral culture is often impractical or not performed in many healthcare settings, while RT-PCR and, to a lesser extent, antigen test for some CARVs look more practical, although not 100% specific for decision-making. Furthermore, immunocompromised patients and in particular cellular therapy recipients commonly have prolonged infections (either clinical or microbiological) as compared to the general population [14–18]. Moreover, the host immune response makes the duration of an infectious episode a dynamic process, where clinical signs/symptoms and/or microbiological tests could fluctuate/evolve from short time to a chronic state and/or recurrences.

Clinical, radiological and/or microbiological criteria to define CARV LRT disease according to the certainty that a CARV is causing the disease

In clinical practice, healthcare providers use a combination of clinical judgment, radiological findings, laboratory testing, and epidemiological factors to determine the likelihood of a viral cause for LRT symptoms. These determinations are crucial for guiding treatment decisions, implementing infection control measures, and understanding the epidemiology of CARV. Specific definitions and criteria for these categories may be outlined in clinical practice guidelines or research studies for individual respiratory viruses.

LRT diseases caused by CARV can vary in terms of certainty of viral causation and may be categorized based on diagnostic criteria and clinical judgment. A classification of possible, probable, or proven CARV LRTD has been developed by investigators from Seattle that showed valuable prognostic information in terms of mortality [19] validated in several CARV types and transplant centers [20,21]. However, there is an obvious limitation with this classification regarding the probable category since in very rare instance bronchoalveolar lavage is performed in recipients without radiological proof of pulmonary involvement. Thus, only two categories were available for comparisons.

Adenovirus

The clinical manifestations of ADV infection are variable because they are determined by the different affinity for organs or anatomic sites of the ADV species involved [22,23]. However, in the severely immunocompromised host, ADV infection presents some features, such as a) the higher incidence of infection and disease in children, b) the high replication rate in the lymphoid tissue of the gut in the early phase of infection in children (not adults) making stool a reliable sample allowing early diagnostic and therapeutic intervention, c) the predictive value of ADV viremia for disseminated disease and mortality in children after high-risk allogeneic HCT, d) the infection usually occurring in the first months after allogeneic HCT similar to the herpes viruses (CMV, EBV, HHV-6) and polyoma virus BK [24,25].

The ECIL-4 recommendations for ADV infection in HCT patients [5] were published more than a decade ago and they still represent a key reference for clinicians regarding prevention, diagnosis and treatment and are valuable for clinical research and data reporting, providing the definition of ADV infection, ADV disease, and identification of risk factors.

The quantitation of ADV-DNAemia in blood on at least a weekly basis is recommended both for adult and pediatric patients, who are considered at high-risk of ADV infection. In addition to the monitoring of blood, it has been demonstrated in the recent years that, in pediatric patients, weekly testing of the stool is indicated during the HCT period at risk of ADV infection. In fact, high ADV load in this compartment can precede the positivity in blood with up to 11 days [26–28]. Moreover, an increased risk of viral reactivations, such as CMV, HHV6 and ADV, has been recently reported in the adult setting with the use of

post-transplant cyclophosphamide as GvHD prophylaxis.

In this workshop, the expert consensus focused on updating and addressing previously undefined topics for both CARV infections (infection severity, infection duration, and CARV LRTD criteria) and ADV infections (ADV disease, defining response criteria and outcome). The CARV section is also applicable to the emergent SARS-CoV-2 as a new CARV.

Ensuring consensus on the intricacies of CARV and ADV infections holds paramount importance due to the diverse spectrum and complexity of diseases linked with these viruses in HCT patients. Establishing consensus on reporting data is essential for fostering consistent and comprehensive data for both research endeavors and clinical reliability. We summarize herein the outcome of the consensus achieved.

Methodology

This workshop was conducted according to the methodology outlined by the EBMT pH&G Committee, as detailed in their published guidelines, with the aim of harmonizing clinical practices and standardizing procedures in critical, undefined areas within EBMT and HCT [6]. At the 2023 Workshop, a panel of experts from the EBMT IDWP was invited to define best practice recommendations about CARV and ADV infections. The workshop entailed thorough preparatory work, including comprehensive literature reviews to address pertinent, unanswered clinical questions. Literature review encompassed PubMed, Google Scholar, and Cochrane searches utilizing keywords relevant to the selected topic. A two-day face-to-face meeting was dedicated to drafting the foundational document, which underwent the several round of reviews. Once consensus was reached, a summary of results was presented during a plenary session, leading to the final approval by participants (Table 1).

Table 1
These highlights summarize key points from the workshop, addressing important aspects of CARV infection and ADV peculiarities in the context of hematopoietic cell transplantation.

Topic	Summary
CARV Infection/Disease Severity	- Importance of classifying severity for reliable EBMT data registration and clinical decision-making. - Current reliance on anatomical site and oxygen support for severity assessment - Workshop suggests a comprehensive approach, including clinical, radiological, and virological factors for severity classification - Proposed severity categories: Asymptomatic, Upper, Lower (Moderate, Severe, Very Severe).
CARV Detection Duration	- Discussion on the clinical significance of defining CARV detection duration - Recommendations for three categories based on duration: Standard, Prolonged, Very Prolonged - Emphasis on the dynamic nature of duration and the need for further research.
CARV LRTD Criteria	- Proposal for three categories: Possible, Probable, Proven CARV LRTD - Challenges in the current classification, especially in the probable category. - Call for further research to evaluate the prognostic significance of this classification.
Adenovirus (ADV) Surveillance	- ADV-DNAemia in blood (quantitative PCR) for surveillance and early intervention - Stool testing in pediatric patients for surveillance and early intervention. - Various methods for diagnostic purposes: viral culture, PCR in biopsy tissue, immunohistochemistry.
Clinical Extension of ADV Infection	- Classification into Local ADV, Systemic ADV, and Disseminated ADV - Importance of ADV viremia for systemic and disseminated disease. - Definition of each category based on clinical signs, symptoms, and viremia.
Response to ADV Treatment	- Three types of response: Virological (major and minor), Clinical (complete and partial), and Failure - Criteria for each response type to evaluate treatment effectiveness.
Attributable Mortality of ADV Disease	- Definition of death caused by organ failure due to ADV disease in the absence of response to therapy. - Emphasis on a common frame of interpretation for attributing mortality to a specific infectious etiology.

Workshop recommendations

Community acquired respiratory viruses (CARV)

CARV infection/disease severity

A consensus definition of the severity of a CARV is important for providing reliable criteria for EBMT data registration but it is also valuable for design of clinical trials, prognostic information, and for decision-making in daily clinical practice regarding different levels of intervention.

For the purposes to homogenize data collection among the hundreds of EBMT centers, the expert consensus proposed the following five easy-to-use category classification of the severity of CARV, also associating the level of clinical management:

- *Asymptomatic:* no sign/symptoms of CARV infection (level of intervention: preventive transmission measures and clinical monitoring)
- *Upper:* sign/symptoms limited to the URT (level of intervention: preventive transmission measures, clinical monitoring in the outpatient setting, with/out antiviral therapy).
- *Lower:*
  - Moderate: lower respiratory symptoms such as tracheitis, bronchitis, bronchiolitis with or without subtle radiological image of pulmonary parenchyma involvement without oxygen support needed (level of intervention: preventive transmission measures, antiviral therapy if available, rule out co-infections, need for hospital admission assessment, clinical monitoring in the outpatient setting, pulmonary function test after recovery).
  - Severe: radiological proof of pulmonary involvement (presence of infiltrates or interstitial pattern) with need of non-intensive oxygen support (<15 liters/min), with or without hemodynamic support (hypotension requiring fluid resuscitation). (Level of intervention: preventive transmission measures, antiviral therapy, co-infections workup, hospital admission, clinical/virological monitoring, and pulmonary function test after recovery)
  - Very severe: respiratory failure requiring high-flow oxygen (≥15 l/min) or mechanical ventilation or requiring progressive increase of oxygen support in the last 24 h with or without hemodynamic support (Level of intervention: preventive transmission measures, antiviral therapy, co-infections workup, ICU admission requirement, clinical/virological monitoring, and pulmonary function test after recovery)

Defining CARV infection duration and infectivity

To clearly define the duration of a CARV infection, identification of the same CARV in repeated detection with the same test type is necessary. However, certainty that a new infection has not occurred can only be obtained by RNA sequencing. The definition of microbiological duration of CARV (infectivity) is a relevant point in deciding the risk of contagiousness and eventually the duration of antiviral therapy. While clinical and microbiological duration of CARV infection is often closely linked to each other, CARV detection could persist several weeks/months after clinical resolution in a proportion of cases.

Based on the median CARV shedding of 10 days in immunocompetent patients and of 4 weeks in immunocompromised patients, the expert consensus defined three categories:

1. Standard: < 15 days from the first detection until negativity.
2. Prolonged: 15–60 days from the first detection until negativity.
3. Very prolonged: > 60 days from the first detection until negativity.

Clinical, radiological and/or microbiological criteria to define CARV LRT disease according to the certainty that a CARV is causing the disease

The expert consensus proposes three categories.

- ➢ Possible CARV-LRTD: When clinical signs/symptoms (cough, productive sputum, dyspnea, short of breath, pulmonary wheezing, crackles or rales) epidemiological link, seasonality, radiological findings (preferably by chest CT-scan in particular when chest X-ray did not show abnormalities), with detection of CARV in URT strongly suggesting a viral etiology, but specific laboratory tests (such as bronchoalveolar lavage, tracheal aspirates or induced sputum) are not available/performed or negative for any other microbiological agent potentially associated with LRTD.
- ➢ Probable CARV-LRTD: When a CARV episode meet criteria of possible, but the CARV has been detected in lower respiratory samples at high risk of URT contamination (e.g., induced sputum, tracheal aspirates) with consistent radiological images suggesting LRT involvement.
- ➢ Proven CARV-LRTD: In cases where laboratory tests, such as RT-PCR, antigen detection or viral culture, conclusively identify the presence of a specific CARV in lower respiratory samples (e.g., BAL or lung biopsy), the infection is considered a proven CARV-LRTD. Although the performance of lung biopsies is extremely rare and risky in allogeneic HCT recipients, this represents the highest level of certainty.

Adenovirus

Considering some advances in the knowledge of ADV infection and therapy [29–31], the expert panel identify other points to integrate previous ECIL-4 definitions and recommended practices.

Clinical definition of ADV infection and disease

Three types of ADV infection and disease, according to the presence or ADV replication without (infection) or with (disease) clinical signs and symptoms, were proposed: local, systemic, and disseminated.

- ➢ Local infection/disease is ADV detection without (infection) or with (disease) clinical signs and symptoms confined to an organ, without ADV DNAemia in blood, i.e. conjunctivitis, cystitis, enteritis.
- ➢ Systemic infection/disease is ADV infection detected in blood, i.e. ADV DNAemia confirmed in at least 2 consecutive blood samples; without (infection) or with (disease) fever not attributable to other causes.
- ➢ Disseminated disease is defined as ADV infection involving blood (ADV viremia) and one or more organs, i.e. lungs, gut, bladder, central nervous system, or colitis. Organ involvement, clinically asymptomatic or symptomatic, is defined by the presence of biochemical, virological or histological signs of infection.

Definition of response to treatment

The response to treatment for systemic infection/disease or disseminated disease was classified as virologic response, clinical response, and failure.

- ➢ Virologic response was divided into major and minor response. A major response is defined as the reduction of the viral load of ≥ 2 $\log_{10}$ while a minor response is defined as the reduction ≥ 1 $\log_{10}$ but < 2 $\log_{10}$ after two weeks of treatment. This definition is applicable for quantitative PCR assessment performed in blood, while it is not applied for other biological samples (for example respiratory secretions) where there is no sufficient experience with quantitative PCR.
- ➢ Clinical response was defined as complete or partial. Complete response is the disappearance of all clinical signs or symptoms of ADV disease, while partial response is an objective improvement of clinical signs or symptoms of disease (having as reference for example, the reduction of at least one grade in the score of organ common toxicity criteria of adverse events (CTCAE).
- ➢ Failure was defined as the progression from ADV infection (with or without increasing ADV viremia) to ADV disease while the patient is on treatment or worsening of ADV disease after two weeks of treatment.

Definition of attributable mortality of ADV disease

The contribution of an infectious episode relatedness to death is often decided on a clinical basis because an autopsy is rarely performed, except for single cases that deserve specific investigations. Considering the multifactorial pathogenesis of transplant-related outcomes, the adjudication of death to a specific infectious etiology requires a common frame of interpretation of the events. Attributable mortality is death caused by the failure of one or more organs affected by ADV disease within 28 days of diagnosis in the absence of clinical and/or virological signs of response to therapy, for example death of respiratory failure in a patient with adenovirus pneumonia or death of hepatic failure in a patient with ADV proven hepatitis [32,33].

Summary and unanswered questions/need for further research

A summary of the recommendations is shown in Table 1. The expert panel believes that these consensus definitions could mitigate the heterogeneity in reporting data stemming from the highly variable and complex viral infections observed in HCT recipients. This could enhance the quality and reliability of future research in these domains. Moreover, in clinical practice, these classifications/definitions may assist practitioners in decision-making regarding different levels of intervention. The expert panel suggests assessing the clinical significance of these classifications/definitions and evaluating the benefits of antiviral therapy for both CARV infections and ADV. Additionally, the panel recommends conducting studies to identify immunocompromised phenotypes capable of predicting various durations of CARV detection. Furthermore, exploring the impact of prior vaccination and antiviral drugs on CARV duration is advisable.

Contributions

DA, AB, SC, RdC, PL, MM, DN, JLP, PV, ISO and JS: conceptualized the subject for this workshop; participated in the face to face meeting and wrote the original manuscript draft; RG, FO, ISO and IYA developed the methodology and edited the manuscript. All co-authors: played an important role in interpreting results, revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. They also accepted final responsibility for the decision to submit for publication.

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AB: No conflict of interest to declare.

SC: No conflict of interest to declare.

RdC: Participation in advisory boards for Astra-Zeneca, Astella, Moderna and MSD. Speaker for MSD, Gilead. None of these conflicts were related to this manuscript.

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PL: Participation in advisory boards for Astra-Zeneca and Moderna. Speaker for MSD. None of these conflicts were related to this manuscript.

MM: No conflict of interest to declare.

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ISO: Declares no conflict of interest related to this work. For non-profit organization, she is the current secretary of the EBMT PH & G committee.

JS: Declares no conflict of interest related to this work.

IYA: Declares no conflict of interest related to this work. For non-profit organization, he is the current chair of the EBMT PH & G committee.

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