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ORIGINAL ARTICLE

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Approach for defining human adenovirus infection and disease for central review adjudication in clinical studies

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Abstract

Background: Pediatric allogeneic hematopoietic cell transplant (allo-HCT) recipients are at risk for morbidity and mortality from human adenovirus (HAdV). HAdV can be detected in an asymptomatic state, referred to as infection or with signs or symptoms of illness, referred to as disease. Standardized case definitions are needed to distinguish infection from disease and allow for consistent reporting in both observational cohort studies and therapeutic clinical trials.

Methods: A working group of experts in virology, transplant infectious disease, and HCT was assembled to develop HAdV infection and disease definitions with the degree of certainty (i.e., possible, probable, and proven). Definitions were further refined through an iterative process and independently applied by two central review committees (CRCs) to 20 pediatric allo-HCT recipients with at least one HAdV-positive PCR.

Results: Initial HAdV infection and disease definitions were developed and updated through an iterative process after reviewing clinical and virological details for 81 subjects with at least one positive HAdV PCR detected in a clinical specimen. Independent application of final definitions to 20 HAdV positive allo-HCT recipients by two CRCs yielded similar number of HAdV infection or disease events but with variation of degree of certainty for some events.

Conclusions: Application of definitions by a CRC for a study of HAdV infection and disease is feasible and can provide consistency in the assignment of outcomes. Definitions need further refinement to improve reproducibility and to provide

Abbreviations: CMV, cytomegalovirus; CRC, central review committee; HAdV, human adenovirus; HCT, hematopoietic cell transplant; IFD, invasive fungal disease; IRB, Institutional Review Board; PCR, polymerase chain reaction.

For affiliations refer to page 8.

guidance on determining clinical improvement or worsening after initial diagnosis of HAdV infection or disease.

KEYWORDS
hematopoietic cell transplantation, human adenovirus, pediatrics

1 | INTRODUCTION

Human adenoviruses (HAdV) are nonenveloped linear double-stranded DNA viruses. The group currently includes over 110 genotypes and 52 serotypes classified into seven subgroups or species (A-G).[1,2] In immunocompetent individuals, HAdV typically causes mild to moderate community-acquired infections that present as pharyngitis, conjunctivitis, gastroenteritis, cystitis, or respiratory illness.[3,4] Less commonly, they lead to more severe illnesses such as hepatitis, myocarditis, and meningoencephalitis.[5] Regardless of severity, HAdV illness in the immunocompetent host is typically self-limited. However, after resolution of the primary illness, HAdV can persist in lymphoid tissue posing a risk for reactivation during future periods of immunocompromise.[6–9]

Pediatric allogeneic hematopoietic cell transplant (allo-HCT) recipients represent a patient group at highest risk for HAdV infection from primary exposure or reactivation. In this population, HAdV can be detected in any clinical specimen in the absence of symptoms, referred to as HAdV infection, or be detected in conjunction with clinical symptoms or signs such as fever or organ dysfunction, referred to as HAdV disease. Because of the concern of morbidity and mortality related to HAdV in the post-HCT period, many centers employ surveillance HAdV polymerase chain reaction (PCR) testing to allow for pre-emptive management. As such, HAdV is often first detected in the asymptomatic state (i.e., HAdV infection). In a subset of these patients HAdV will be associated with fever alone or progress to cause organ dysfunction (i.e., HAdV febrile syndrome or HAdV disease, respectively). Reports from various retrospective pediatric allo-HCT cohorts have documented HAdV infection rates ranging from 11% to 47%.[10–15] Among those with documented HAdV infection, 31%–72% will progress to HAdV disease.[10,11,13,14,16,17] This broad range in event rates may reflect true differences in disease occurrences but may also reflect a lack of accepted standard definitions.

Currently, there are no approved HAdV-directed therapies for any indication.[18] However, the substantial burden of HAdV infection and the potential for progression to disease with resultant morbidity and mortality have led to significant interest in administering agents that target HAdV. Ideally, an anti-HAdV agent could be administered as prophylaxis to prevent HAdV infection or as pre-emptive therapy to mitigate the risk of progression from infection to HAdV disease. The approval process for any anti-HAdV therapy will require efficacy data from well-designed clinical trials that utilize established definitions for HAdV infection and disease. Prior publications have provided definitions for HAdV infection and disease[10,18,19]; however, these definitions have not recently been updated, do not incorporate levels of confidence for a designation of end-organ disease (i.e., possible, probable, or proven), or do not consider contemporary HAdV monitoring strategies that implement frequent use of highly sensitive molecular tests. This approach of establishing definitions for an illness state has been implemented in studies for other infectious conditions such as invasive fungal disease (IFD), cytomegalovirus (CMV), and BK polyomavirus nephropathy.[20–23] Published definitions for these complex outcomes have served to harmonize infection and disease outcome designations for both observational studies and randomized clinical trials.[24,25] In addition, definitions that distinguish between viral infection and disease can inform eligibility criteria for studies aiming to assess a pre-emptive intervention for infection or definitive intervention for disease. We hypothesized that a similar approach could be developed for HAdV infection and disease.

The overall objective of this study was to describe the approach used to arrive at definitions for HAdV infection and disease and to assess the feasibility and reproducibility of a central review process to apply these definitions.

2 | METHODS

2.1 | Definition working group

A working group consisting of experts in virology, pediatric transplant infectious disease, and HCT was assembled to develop consensus definitions for HAdV infection and disease. Definitions previously used in a retrospective cohort at one of the participating sites (Table S1) served as a starting point for the first draft of the consensus definitions.[13]

2.2 | Application and refinement of consensus definitions

A central review committee (CRC-1) was assembled that included HCT and infectious disease physicians with expertise in supportive care from four pediatric academic children's hospitals. All members of the CRC-1 were also members of the definition working group. The first draft of the consensus definitions was applied by the CRC-1 to allo-HCT recipients with at least one positive HAdV PCR test in the first 180 days post-HCT. Study subjects were enrolled in

a four-center prospective observational study initiated in 2016 to define the incidence and outcomes of HAdV infection and disease in pediatric, adolescent, and young adult allo-HCT recipients (NIH #272201600014C). In this stage of definition application, the CRC-1 members assessed the utility of the first draft of the definitions to capture the clinical experience of these HAdV PCR-positive subjects. The CRC-1 members reviewed a summary of each subject's clinical history provided by the enrolling site investigator alongside laboratory data collected as part of the prospective observational study. CRC-1 members reviewing a subject's data were allowed to ask the enrolling site investigator clarifying questions about the reported information or request additional clinical or laboratory data to reach a consensus designation. Definitions were iteratively refined to capture specific clinical experiences not initially considered in the first round of definition development. Patients who had at least one positive HAdV PCR test from any site but did not meet the criteria for any HAdV disease definition were labeled as having HAdV infection. Once HAdV disease definitions were deemed to be stable without continued change during subsequent subject reviews, they were considered final. A minimum of three CRC-1 members with at least two reviewers from participating sites outside the enrolling site was required to assign a designation.

2.3 | Comparative application of consensus definitions

In September 2020, the aforementioned four-center prospective observational study was expanded to include patients from six additional academic pediatric centers. A second central review committee (CRC-2) was assembled inclusive of pediatric infectious disease specialists at these six institutions with expertise in pediatric transplant supportive care practices. One investigator (B.T.F.) was common to both CRC-1 and CRC-2. Both CRC-1 and CRC-2 utilized the final definitions and established a central review process to determine a designation of HAdV infection or disease for patients enrolled at their respective institutions with at least one HAdV detection by PCR from any clinical specimen (e.g., blood, stool, respiratory, urine, tissue) in the first 180 days post-HCT. Results from this observational study will be published separately.

The existence of the two CRCs presented an opportunity to compare the consistency in application of the definitions and review process between two committees. A random selection of 20 patients initially reviewed by CRC-2 was independently reviewed by CRC-1 to assess for consistency in application of the final definitions. During their review, CRC-1 members reviewed the same data that were available to CRC-2 members. Both committees were allowed to request additional information from the site where the subject was enrolled if they deemed it necessary for final designation. In these circumstances the review was paused and revisited upon receipt of queried information. The outcome designations from CRC-1 and CRC-2 reviews were reported and differences in designations between the two committees were described. A post-hoc kappa statistic was calculated comparing outcome designations from the two CRCs. There were five possible categories of designation considered for this inter-rater assessment: no infection or disease, HAdV infection only, possible HAdV disease, probable HAdV disease, and proven HAdV disease.

This study was performed under a single Institutional Review Board (IRB) approval granted at the Children's Hospital of Philadelphia with reliance agreements in place for most participating institutions. Sites unable to participate in the single IRB submitted the study protocol to their local IRB for independent approval.

3 | RESULTS

3.1 | Draft definition development

The definitions working group initiated monthly virtual meetings in August 2016. The working group started with definitions used for a prior single center retrospective cohort.[13] By October 2018 the committee completed a draft of consensus definitions (Table S2).

3.2 | Application and refinement of consensus definitions

CRC-1 met monthly, starting in March 2019, to assign outcomes of HAdV infection and disease to subjects enrolled in the prospective observational study at the initial four centers. During these initial reviews, CRC-1 members refined study definitions as necessary. After a review of 81 subjects with at least one positive HAdV PCR in the 180-day follow-up period, the updated definitions were deemed stable and considered final on March 12, 2021 (Table 1). Updates to the definitions between March 2019 and March 2021 included clarification of the site of disease, such as the use of the term colitis/enteritis as opposed to colitis alone, and the inclusion of text to capture noninfectious conditions that may downgrade a proven event to a probable event, such as presence of graft-versus-host disease leading to a designation of probable and not proven disease. Finally, conditions not initially included were added such as febrile syndrome to capture events when a patient has fever in the setting of a positive HAdV PCR but without localizing symptoms or isolated upper respiratory infection to identify events where an upper respiratory positive HAdV PCR was associated with only upper respiratory symptoms. HAdV carditis as a site of organ-specific involvement was not included in either the a priori or final versions of the HAdV infection and disease definitions. However, during a CRC-1 review meeting in November 2021, a patient was deemed to have potential cardiac pathology secondary to presence of HAdV. That review was stopped, and CRC-1 members developed definitions for proven, probable, and possible HAdV carditis. These definitions were added to the final version of the definition document and utilized for subsequent reviews although no additional episodes of carditis were identified.

TABLE 1 Final definitions for proven, probable, and possible human adenovirus disease by site of infection after iterative process leading to adjustment of a priori definitions[a].

Disease site	Proven disease	Probable disease	Possible disease
Febrile Syndrome[b]	*No proven designation for febrile syndrome*	*No probable designation for febrile syndrome*	*Fever onset (>38.0°C) occurring within four days of newly positive blood/plasma human adenovirus test or significant increase in blood/plasma human adenovirus viral load (≥1 log increase)*
Isolated upper respiratory infection	*No proven designation for upper respiratory infection*	*Upper respiratory symptoms/pharyngitis/conjunctivitis with human adenovirus as the only pathogen identified from the site of involvement. No lower respiratory tract symptoms*	*Upper respiratory symptoms/pharyngitis/conjunctivitis with human adenovirus with a second pathogen or alternative explanation present (e.g., allergy). No lower respiratory tract symptoms*
Pneumonitis	Specimen from lower respiratory tract (broncho-alveolar lavage, endotracheal aspirate or lung tissue) positive for human adenovirus plus presence of infiltrate(s) on radiographic imaging as well as clinical symptoms of respiratory distress (e.g., hypoxia, tachypnea, change in ventilator settings etc.) WITHOUT microbiologic evidence of another infectious pathogen *and/or evidence of concurrent GVHD at any site that could explain the presentation. If there is histopathological evidence consistent with human adenovirus, then the designation is "Proven" regardless of any other ongoing processes*	Specimen from lower respiratory tract (broncho-alveolar lavage, endotracheal aspirate or lung tissue) positive for human adenovirus plus presence of infiltrate(s) on radiographic imaging as well as clinical symptoms of respiratory distress (e.g., hypoxia, tachypnea, change in ventilator settings etc.) WITH microbiologic evidence of at least one other infectious pathogen *or evidence of concurrent GVHD at any site*	Specimen from upper respiratory tract (e.g., nasopharyngeal swab) positive for human adenovirus plus presence of infiltrate(s) on radiographic imaging as well as clinical symptoms of respiratory distress (e.g., hypoxia, tachypnea, change in ventilator settings etc.) WITH OR WITHOUT microbiologic evidence of another infectious pathogen *or evidence of concurrent GVHD at any site*
Colitis/*enteritis*	Human adenovirus positive gastrointestinal biopsy specimen with histopathology containing viral cytopathic changes and clinical symptoms consistent with colitis/*enteritis*, WITHOUT microbiologic evidence of another infectious pathogen or pathologic evidence of an immune-mediated process (e.g., GVHD)	**(Definition 1):** Human adenovirus positive gastrointestinal biopsy specimen with histopathology containing viral cytopathic changes plus clinical symptoms consistent with colitis/*enteritis*, but WITH microbiologic evidence of another infectious pathogen or immune-mediated process (e.g., GVHD) **(Definition 2):** Human adenovirus positive stool or intestinal biopsy plus clinical symptoms consistent with colitis/*enteritis* but WITHOUT microbiologic or histopathologic evidence of another infectious pathogen or immune-mediated process (e.g, GVHD)	Human adenovirus positive stool, plus clinical symptoms consistent with colitis/*enteritis* but WITH microbiologic evidence of another infectious pathogen or immune-mediated process (e.g., GVHD) *If tissue negative for human adenovirus PCR, then would label as human adenovirus infection and not disease regardless of histopathologic findings*
Hepatitis	*Liver biopsy with viral cytopathic changes (e.g., smudge cells) and human adenovirus-positive tissue With or WITHOUT evidence of another infectious pathogen or immune-mediated process (e.g., GVHD)*	*Increase in ALT or AST consistent with hepatitis (change to above ULN if at baseline normal, or if baseline value already above ULN than 50% increase from that baseline) evident within four days of newly positive blood/plasma human adenovirus test or significant increase in blood/plasma human adenovirus load (≥1 log increase) WITHOUT evidence of another infectious pathogen or immune-mediated process (e.g., GVHD) or hepatotoxic agents started within 1 week of laboratory changes*	*Increase in ALT or AST consistent with hepatitis (change to above ULN if at baseline normal, or if baseline value already above ULN than 50% increase from that baseline) evident within four or days of newly positive blood/plasma human adenovirus test or significant increase in blood/plasma adenovirus load (≥1 log increase) but WITH evidence of another infectious pathogen or immune-mediated process (e.g., GVHD) or hepatotoxic agents started within 1 week of laboratory changes*

TABLE 1 (Continued)

Disease site	Proven disease	Probable disease	Possible disease
Cystitis	*Bladder biopsy with viral cytopathic changes and human adenovirus-positive tissue, plus presence of gross blood in the urine WITH or WITHOUT presence of other potential causes such as BK virus viruria*	*Human adenovirus-positive urine plus the presence of gross blood in the urine WITHOUT presence of other potential causes such as BK virus viruria*	Human adenovirus-positive urine plus the presence of gross blood in the urine but WITH presence of other potential causes such as BK virus viruria
Carditis[c]	*Specimen from cardiac source (e.g., cardiac tissue biopsy, pericardial fluid) positive for human adenovirus plus evidence of carditis, myocarditis, or pericarditis (e.g., ECHO findings or drained fluid reveals evidence of inflammation) WITHOUT microbiologic evidence of another infectious pathogen or evidence of concurrent GVHD at any site that could explain the presentation. If there is histopathological evidence consistent with human adenovirus, then the designation is "Proven" regardless of any other ongoing processes*	*Specimen from cardiac source (e.g., cardiac tissue biopsy, pericardial fluid) positive for human adenovirus plus evidence of carditis, myocarditis, or pericarditis (e.g., ECHO findings or drained fluid reveals evidence of inflammation) WITH microbiologic evidence of at least one other infectious pathogen or evidence of concurrent process (e.g., GVHD, TMA) at any site that could result in this clinical presentation*	*Specimen from blood positive for human adenovirus plus evidence of carditis, myocarditis, or pericarditis (e.g., ECHO findings) WITH OR WITHOUT microbiologic evidence of another infectious pathogen or evidence of concurrent GVHD at any site*
CNS Disease	CSF *specimen* or central nervous tissue biopsy that is human adenovirus-positive plus presence of pleocytosis, and clinical symptoms or radiographic findings of meningitis or encephalitis WITHOUT microbiologic evidence of another infectious pathogen	CSF specimen or central nervous tissue biopsy that is human adenovirus-positive plus presence of pleocytosis, and clinical symptoms or radiographic findings of meningitis or encephalitis but WITH microbiologic evidence of another infectious pathogen	*CSF specimen that is human adenovirus-positive, WITHOUT pleocytosis or clinical symptoms or radiographic findings of meningitis or encephalitis*
Death designation			
	Proven adenovirus-related death	**Probable adenovirus-related death**	**Possible adenovirus-related death**
Human Adenovirus-related death	*Autopsy with histopathologic evidence for human adenovirus presence associated with tissue destruction regardless of other etiologies for death*	*Previously met criteria for probable or proven human adenovirus-related disease within the preceding 8 weeks without resolution of symptoms consistent with adenovirus-associated disease and without other clear etiology for death and with no autopsy available*	*Previously met criteria for possible, probable, or proven human adenovirus-related disease within the preceding 8 weeks without resolution of symptoms consistent with human adenovirus-associated disease but with other documented etiologies for death*

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, Central nervous system; CSF, cerebral spinal fluid; GVHD, Graft versus host disease; TMA, thrombotic microangiopathy.

[a]Updates to Definitions from a priori definitions (Table S2) are shown in *italics*.

[b]Febrile syndrome can only be assigned in the absence of any other HAdV disease type.

[c]Carditis was added in November of 2021. This was not part of the initial definitions and only was added when a patient review suggested this as a potential entity. The central review committee deemed it important to capture carditis as a possible site of HAdV disease.

3.3 | Comparative application of consensus definitions

Of the randomly selected 20 subjects with at least one positive HAdV PCR, the CRC-1 and CRC-2 reviews yielded 28 and 27 distinct HAdV events, respectively (Table 2). CRC-1 designated 12 of their 28 events as probable disease while CRC-2 identified 15 probable disease events. There were no proven disease designations for either committee. There were seven events that were discordant between the two committees because of differences in certainty of the designation; four HAdV infection events identified by CRC-1 were labeled as colitis/enteritis (two possible and two probable) by CRC-2, one possible colitis/enteritis for CRC-1was deemed probable colitis/enteritis for CRC-2, and one possible pneumonitis for CRC-1was reported as probable upper respiratory infection by CRC-2. There was only one HAdV event (probable hepatitis) identified by CRC-2 that did not have a concomitant event identified by CRC-1. A post-hoc analysis comparing inter-committee outcome designation results yielded a kappa statistic of 0.65 (95% CI: 0.44 to 0.85).

The two committees had similar (within 7 days) assignments for the onset day after HCT for 18 of 19 HAdV disease events that were common to both committees. For the two disease events where degree of designation differed (i.e., possible versus probable) the assigned onset days were within 7 days for both events.

TABLE 2 Application of adenovirus infection and disease definitions by two central review committees for 20 randomly selected allogeneic HCT recipients with at least one positive adenovirus PCR result.

Subject ID (Site ID-Study ID)	HAdV Episode	Central Review Committee #1		Central Review Committee #2		Event concordance	Onset date concordance
			Disease onset day[a]	Disease designation	Disease onset day		
AT005	1	Probable colitis/enteritis	D+11	Probable colitis/enteritis	D+11	Yes	Yes
AT009	1	Probable colitis/enteritis	D+3	Probable colitis/enteritis	D+3	Yes	Yes
AT013	1	Probable colitis/enteritis	D-3	Probable colitis/enteritis	D-3	Yes	Yes
AT021	1	Possible upper respiratory disease	D+65	Possible upper respiratory disease	D+65	Yes	Yes
AT024	1	Probable upper respiratory disease	D+29	Probable upper respiratory disease	D+29	Yes	Yes
AT028	1	Probable colitis/enteritis	D+150	Probable colitis/enteritis	D+161	Yes	No
LC005	1	Adenovirus infection only	N/A	Adenovirus infection only	N/A	Yes	N/A
LC010	1	Probable colitis/enteritis	D+63	Probable colitis/enteritis	D+63	Yes	Yes
		Possible Pneumonitis	D+96	Possible Pneumonitis	D+96	Yes	Yes
LC019	1	Adenovirus infection only	N/A	Possible colitis/enteritis	D+69	No	N/A
	2	Adenovirus infection only	N/A	Possible colitis/enteritis	D+148	No	N/A
LC023	1	Possible cystitis	D+18	Possible cystitis	D+18	Yes	Yes
LC047	1	Possible colitis/enteritis	D+48	Probable colitis/enteritis	D+52	No	No
	2	Adenovirus infection only	N/A	Adenovirus infection only	N/A	Yes	N/A
CM018	1	Adenovirus infection only	N/A	Adenovirus infection only	N/A	Yes	N/A
CM024	1	Possible febrile syndrome	D+32	Possible febrile syndrome	D+39	Yes	No
CM041	1	Possible hepatitis	D+158	Possible hepatitis	D+158	Yes	Yes
CM044	1	Adenovirus infection only	N/A	Adenovirus infection only	N/A	Yes	N/A
SJ001	1	Possible upper respiratory infection	D+47	Possible upper respiratory infection	D+47	Yes	Yes
		Probable colitis/enteritis	D+46	Probable colitis/enteritis	D+46	Yes	Yes
SJ003	1	Probable upper respiratory infection	D+62	Probable upper respiratory infection	D+62	Yes	Yes
SJ062	1	Probable colitis/enteritis	D+3	Probable colitis/enteritis	D+3	Yes	Yes
	2	Adenovirus infection only	N/A	Probable colitis/enteritis	D+61	No	N/A
SJ064	1	Adenovirus infection only	N/A	Probable colitis/enteritis	D+5	No	N/A
	2	Probable upper respiratory infection	D+155	Probable upper respiratory infection	D+155	Yes	Yes

TABLE 2 (Continued)

Subject ID (Site ID-Study ID)	HAdV Episode	Central Review Committee #1		Central Review Committee #2		Event concordance	Onset date concordance
			Disease onset day[a]	Disease designation	Disease onset day		
SJ077	1	Possible pneumonitis	D+7	Probable upper respiratory infection	D+6	No	No
		Probable colitis/enteritis	D+7	Probable colitis/enteritis	D+6	Yes	No
		Probable hepatitis	D+15	N/A	N/A	No	N/A
TOTALS						21/28 events	14/19 events

Abbreviations: HCT, hematopoietic cell transplant; PCR, polymerase chain reaction.

[a]From date of hematopoietic cell transplant.

4 | DISCUSSION

This collaboration of pediatric infectious diseases physicians, HCT physicians, and a virologist established a set of definitions for HAdV infection and HAdV diseases by organ site and developed a central review process for applying these definitions to pediatric allo-HCT recipients with at least one positive HAdV PCR in the first 180 days after HCT. The central review process to apply these definitions to patients enrolled in a multicenter prospective study proved to be feasible and an important component of consistent application of the definitions in a research setting. In addition, the process was shown to be reproducible across two central review committees separately reviewing the same 20 patients; an assessment of inter-rater agreement revealed a kappa statistic in the substantial agreement range. The kappa statistic should be interpreted with caution as it was done post hoc, and agreement may have been biased by presence of a common member to both committees.

Currently, there are no existing medications proven to be effective for preventive, pre-emptive, or directed therapy against HAdV infection or disease. While cidofovir is often initiated in HCT recipients with HAdV infection or disease, this agent has the potential for toxicity, and there are limited comparative data documenting its effectiveness, in part due to lack of systematic definitions of outcome measures assessing efficacy.[13] The definitions for HAdV infection and disease, iteratively developed in this multidisciplinary consortium, provide a foundation for outcome measures that could be utilized in future observational studies and clinical trials aiming to assess the effectiveness or efficacy of HAdV-targeted therapies. Of note, the definitions were developed with levels of certainty, namely possible, probable, and proven, similar to definitions developed for IFD, CMV, and BK polyomavirus nephropathy.[20–23] The study members concluded that this tiered approach was necessary to convey degree of certainty for attributing a clinical presentation to HAdV.

Importantly, the definitions cannot account for every clinical scenario and therefore cannot be uniformly applied without oversight of assignment. A central review process is necessary to apply the definitions in a systematic and consistent manner across all study subjects. It is recommended that the review process be implemented using a committee of three or more physicians with experience in HAdV and with caring for immunocompromised patients. The committee needs access to laboratory, radiology, and clinical summaries of enrolled subjects. Designation of outcomes for subjects should be achieved through review of the collected data, subsequent discussion, and eventual committee consensus. It is recognized that the central review process to apply definitions of HAdV infection and disease is labor intensive and may not be possible in observational studies. In these circumstances the definitions can still serve as a useful framework to the local research team for outcome designation. It is also noted that, while our definitions incorporate level of certainty for a given disease type (i.e., possible, probable, and proven), the severity of a disease event will vary by organ involved. For example, proven HAdV hepatitis may be more life threatening than proven HAdV cystitis. Study teams

planning clinical trials to assess efficacy of an intervention should determine the targeted disease endpoints of most concern at the time of study design.

While the results of the two CRC reviews of the same subjects were similar, the final designations were discrepant on seven events. We do not have specific reasons for these discrepancies, but they highlight the challenges in assigning outcomes for HAdV infection and disease even with the same definitions and a similar review process. It is possible that the composition of CRC members could review similar information but conclude different outcomes because of unconscious cognitive biases. It is also possible that the two CRCs queried the primary sites for additional qualifying information differentially. The study did not capture whether a given CRC requested qualifying information so the impact of these queries on discordant assignments could not be determined.

One approach to limiting the impact of differential review, is to ensure the same review committee is in place for the entirety of a study so that all enrolled subjects are reviewed in as similar a fashion as possible. This would ensure consistent application of definitions within the same study; however, this would not ensure consistent application of definitions between studies with different CRC members. In considering between CRC differences, it was hypothesized that differences in outcome designation may be the result of how site investigators formatted information in clinical summaries they created and submitted for review. Site investigators were provided direction on what content to summarize for central review of HAdV positive patients at their center but a specific template form for this documentation was not provided. As such, it is possible that some information could have been either omitted or over emphasized. A template that provides structure to the clinical content submitted alongside itemized laboratory results (i.e., timing of HAdV testing and results of those tests) could further improve the consistency of the process.

Investigators aiming to apply these definitions and central review process to their studies should be aware of several limitations of the definitions and proposed process. First, absolute viral load thresholds and adenovirus specific histopathology testing (e.g., immunohistochemical staining) were not included in our definitions; this is because HAdV PCR tests were not performed using the same assay at one central laboratory leading to potential variation in viral loads across participating sites and because histopathology testing for HAdV was not routine at participating centers. In addition, a uniform HAdV PCR diagnostic approach was not mandated across all centers leading to differential indications for testing. As such, definitions could only rely on the qualitative presence or absence of HAdV by PCR testing and on relative changes in viral load from one specimen to the next. Second, our definitions had to accommodate for the fact that specimens from invasive testing (e.g., bronchoalveolar lavage fluid, cerebral spinal fluid, or tissue biopsy) are infrequently obtained owing to critical illness states that exist for many of these patients. This could result in an overly sensitive assignment of possible or probable HAdV disease entities. For example, a 50% increase in alanine aminotransferase or aspartate aminotransferase from baseline was used as a threshold for possible or probable hepatitis. This threshold was frequently achieved in this population often with multifactorial causes including immune-mediated processes, drug toxicities, or other infections. The temporal association of such an increase in transaminases relative to a positive HAdV PCR blood test does not establish a clear causal association, and thus, the hepatitis definition was likely overly sensitive. Third, our definitions only guided the assignment of new onset or recurrent HAdV infection or disease. The definitions do not provide guidance on determining clinical improvement or worsening in the follow-up period after the onset of HAdV infection or disease. Establishing definitions to guide the assessment of clinical response would be important for studies assessing outcomes of HAdV therapy started after detection of HAdV. Fourth, our definitions were developed in the context of pediatric allo-HCT recipients. While our definition framework and central review process may be adapted to adult patients and to patients from other immune-suppressed populations (e.g., solid organ transplant), adjustments to account for clinical differences between patient groups may be necessary. Any study team aiming to leverage these HAdV definitions needs to understand these limitations and appoint a central review committee that modifies the definitions a priori to align with the specific aims of the planned observational study or clinical trial. Finally, our definitions have not been endorsed by regulatory agencies as acceptable endpoints for clinical trials investigating efficacy of therapeutic agents. Those desiring to adapt these definitions for clinical trial endpoints are encouraged to engage with regulatory agencies at the time of clinical trial design.

5 | CONCLUSIONS

This collaboration established definitions for HAdV infection and disease and developed a process for systematic application of the definitions to HCT subjects enrolled in a research study. Application of definitions by two separate CRCs yielded similar but not perfectly concordant results. The definitions may need further adaptation to include guidance on when to use a central laboratory for viral testing, how to incorporate viral load thresholds, how to expand applicability to adult patients, and how to determine clinical improvement or worsening after initial diagnosis of HAdV infection or disease. A multidisciplinary team inclusive of experts in HAdV and immunocompromised hosts across the age continuum should be assembled to complete these tasks.

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CONFLICT OF INTEREST STATEMENT

Please note the following author disclosures and potential conflicts of interest for this manuscript. BTF's institution receives funding from Allovir for adenovirus related research, his institution receives funding from Pfizer and Merck for research unrelated to adenovirus, and he serves as Chair of a Data Safety Monitoring Board for Astellas for a study unrelated to adenovirus; LDI's institution receives funding from Aicuris, Astellas, Ansun-BioPharma, Pfizer, Merck and Takeda for research unrelated to adenovirus and serves as a consultant for GSK, Merck, Roche Diagnostics and Takeda for work unrelated to adenovirus; MG's institution receives funding from ADMA for work he does unrelated to adenovirus and he receives funding from Allovir for adenovirus related research and funding from Bristol Myers Squibb, ITB-Med, and the Immune Tolerance Network for research unrelated to adenovirus; MGM receives funding from Merck and Sharpe Dohme for work unrelated to adenovirus; WM's institution receives funding from Ansun-BioPharma, Astellas, AstraZeneca, Eli Lilly and Company, Enanta Pharmaceuticals, F. Hoffmann-La Roche, Gilead Sciences, Janssen Biotech, Karius, Inc., Melinta Therapeutics, Inc., Merck, Moderna, Nabriva Therapeutics, Pfizer, and Tetraphase Pharmaceuticals, Inc. for research unrelated to adenovirus and he receives funding as a consultant or as a member of an advisory board for AstraZeneca, DiaSOrin, Invivyd, and Sanofi-Pasteur for work unrelated to adenovirus. All the other authors have nothing to disclose.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Lion T. Adenovirus infections in immunocompetent and immunocompromised patients. *Clin Microbiol Rev*. 2014;27(3):441-462.
2. Lynch JP 3rd, Kajon AE. Adenovirus: epidemiology, global spread of novel types, and approach to treatment. *Semin Respir Crit Care Med*. 2021;42(6):800-821.
3. Fairchok MP, Martin ET, Chambers S, et al. Epidemiology of viral respiratory tract infections in a prospective cohort of infants and toddlers attending daycare. *J Clin Virol*. 2010;49(1):16-20.
4. Arnold JC, Singh KK, Spector SA, Sawyer MH. Undiagnosed respiratory viruses in children. *Pediatrics*. 2008;121(3):e631-e637.
5. Allen UD. Adenoviruses. In: Long SSPL, Prober GC, Fischer M, Kimberlin D, eds. *Principles and Practice of Pediatric Infectious Diseases*. 6th ed. Elsevier, Inc; 2023:1115-1119.
6. Neumann R, Genersch E, Eggers HJ. Detection of adenovirus nucleic acid sequences in human tonsils in the absence of infectious virus. *Virus Res*. 1987;7(1):93-97.
7. Garnett CT, Talekar G, Mahr JA, et al. Latent species C adenoviruses in human tonsil tissues. *J Virol*. 2009;83(6):2417-2428.
8. Kosulin K, Hoffmann F, Clauditz TS, Wilczak W, Dobner T. Presence of adenovirus species C in infiltrating lymphocytes of human sarcoma. *PLoS One*. 2013;8(5):e63646.
9. Proenca-Modena JL, Buzatto GP, Paula FE, et al. Respiratory viruses are continuously detected in children with chronic tonsillitis throughout the year. *Int J Pediatr Otorhinolaryngol*. 2014;78(10):1655-1661.
10. Flomenberg P, Babbitt J, Drobyski WR, et al. Increasing incidence of adenovirus disease in bone marrow transplant recipients. *J Infect Dis*. 1994;169(4):775-781.
11. van Tol MJ, Kroes AC, Schinkel J, et al. Adenovirus infection in paediatric stem cell transplant recipients: increased risk in young children with a delayed immune recovery. *Bone Marrow Transplant*. 2005;36(1):39-50.
12. Hiwarkar P, Gaspar HB, Gilmour K, et al. Impact of viral reactivations in the era of pre-emptive antiviral drug therapy following allogeneic haematopoietic SCT in paediatric recipients. *Bone Marrow Transplant*. 2013;48(6):803-808.
13. Fisher BT, Boge CLK, Petersen H, et al. Outcomes of human adenovirus infection and disease in a retrospective cohort of pediatric

hematopoietic cell transplant recipients. *J Pediatric Infect Dis Soc*. 2019;8(4):317-324.
14. Rustia E, Violago L, Jin Z, et al. Risk factors and utility of a risk-based algorithm for monitoring cytomegalovirus, Epstein–Barr virus, and adenovirus infections in pediatric recipients after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2016;22(9):1646-1653.
15. Anderson EJ, Guzman-Cottrill JA, Kletzel M, et al. High-risk adenovirus-infected pediatric allogeneic hematopoietic progenitor cell transplant recipients and preemptive cidofovir therapy. *Pediatr Transplant*. 2008;12(2):219-227.
16. Feghoul L, Chevret S, Cuinet A, et al. Adenovirus infection and disease in paediatric haematopoietic stem cell transplant patients: clues for antiviral pre-emptive treatment. *Clin Microbiol Infect*. 2015;21(7):701-709.
17. Hoffman JA, Shah AJ, Ross LA, Kapoor N. Adenoviral infections and a prospective trial of cidofovir in pediatric hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2001;7(7):388-394.
18. Florescu DF, Stohs EJ. Approach to infection and disease due to adenoviruses in solid organ transplantation. *Curr Opin Infect Dis*. 2019;32(4):300-306.
19. Matthes-Martin S, Feuchtinger T, Shaw PJ, et al. 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(6):555-563.
20. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group education and research consortium. *Clin Infect Dis*. 2020;71(6):1367-1376.
21. Imlay H, Baum P, Brennan DC, et al. Consensus definitions of BK polyomavirus nephropathy in renal transplant recipients for clinical trials. *Clin Infect Dis*. 2022;75(7):1210-1216.
22. Chemaly RF, Chou S, Einsele H, et al. Definitions of resistant and refractory cytomegalovirus infection and disease in transplant recipients for use in clinical trials. *Clin Infect Dis*. 2019;68(8):1420-1426.
23. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis*. 2017;64(1):87-91.
24. Limaye AP, Budde K, Humar A, et al. Letermovir vs Valganciclovir for prophylaxis of cytomegalovirus in high-risk kidney transplant recipients: a randomized clinical trial. *JAMA*. 2023;330(1):33-42.
25. Fisher BT, Zaoutis TE, Xiao R, et al. Comparative effectiveness of Echinocandins vs Triazoles or amphotericin B formulations as initial directed therapy for invasive candidiasis in children and adolescents. *J Pediatric Infect Dis Soc*. 2021;piab024. doi:10.1093/jpids/piab024

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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