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ORIGINAL ARTICLE

Prolonged shedding of type 55 human adenovirus in immunocompetent adults with adenoviral respiratory infections

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Abstract

Human adenovirus (HAdV) is a common pathogen causing respiratory infections with outbreaks reported in the military and community. However, little information is available on the shedding kinetics. We performed a prospective study of immunocompetent adults confirmed with HAdV respiratory infection by multiplex real-time PCR during an outbreak of HAdV-55. Consecutive respiratory specimens of sputum or nasopharyngeal swab were collected from each patient every 2 days. Viral load was measured by real-time quantitative PCR. Of 32 enrolled patients, 27 (84.4%) had pneumonia. Five patients (15.6%) received cidofovir. Viral load was highest in the earliest samples at 8.69 $\log_{10}$ copies/mL. In a linear regression model, viral load declined consistently in a log-linear fashion at the rate of − 0.15 $\log_{10}$ copies/mL per day (95% confidence interval (CI): − 0.18, − 0.12; $R^2 = 0.32$). However, the regression model estimated the viral shedding duration to be 55 days. The rate of decline in viral load did not differ between patients who received cidofovir and who did not. Patients with prominent respiratory symptoms or extensive involvement on chest radiograph had higher volume of viral excretion. Prolonged viral shedding was observed in otherwise healthy adults with HAdV-55 respiratory infection. This finding should be considered in the establishment of infection control and prevention strategies.

Keywords Adenovirus · Pneumonia · Respiratory infections · Virus shedding

Abbreviations

CI	Confidence interval
CVL	Cumulative viral load
GMVL	Geometric mean viral load
HAdV	Human adenovirus

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Introduction

Human adenovirus (HAdV) is a common cause of respiratory infections, ranging from uncomplicated upper respiratory tract infections to life-threatening pneumonia [1]. Since the clinical application of molecular diagnostic methods, the importance of HAdV along with other viruses is increasingly recognized in adult respiratory infections [2, 3]. Although HAdV infections are usually mild and self-limiting in healthy adults, severe pneumonia or even mortalities have been reported [4–6]. While military personnel are well known to be vulnerable to respiratory infections caused by HAdV [7–9], the mechanism underlying the particularly higher transmissibility of HAdV compared to other respiratory viruses more common in the community remains unclear.

Despite the clinical characteristics are well-established, studies on the kinetics of viral shedding in patients with HAdV respiratory infections are scarce. Although previous reports suggested that HAdV could be detected from body fluids in a prolonged duration, the generalizability and reliability are limited by their small sample sizes and heterogeneous methodologies [5, 10, 11]. Lack of evidence on this issue resulted in the establishment of unclear guidelines on the necessary duration of respiratory precaution in healthcare settings, which has critical importance in infection control [12].

Furthermore, the emergence of novel type of HAdV has been implicated in outbreaks in both military and community settings, in which high number of severe manifestations and poorer outcome have been observed [13–15]. HAdV type 55 (HAdV-55) is another emerging type reported in China, Turkey, Spain, Singapore, and Israel [7, 16–19]. We also observed an outbreak of febrile respiratory infections caused by HAdV-55 in the Republic of Korea military, which has been previously reported [8].

Thus, we examined the kinetics of viral shedding in immunocompetent adults with HAdV respiratory infections by real-time quantitative polymerase chain reaction (PCR) during an HAdV-55 outbreak. Additionally, we sought to determine the factors associated with the larger amount of viral shedding and the effect of cidofovir on viral load.

Materials and methods

Study design

Armed Forces Capital Hospital is a 660-bed acute care medical facility that serves as a referral center of the Korean military healthcare system. Patients who were admitted for acute febrile respiratory infection were screened daily from February to April 2016. The inclusion criteria were as follows: (1) body temperature ≥ 38 °C accompanied by either cough or sore throat, (2) identification of HAdV in respiratory specimens by multiplex real-time PCR, and (3) willingness to participate in the study and ability to provide informed consent. Patients meeting any of the following criteria were excluded: (1) presence of any immunocompromising conditions, including the use of corticosteroids with dose equivalent of prednisolone 20 mg/day or higher, immunosuppressants, or biologics; (2) unwillingness to participate; and (3) inability to maintain hospitalization or return to outpatient clinic for follow-up.

Respiratory samples (sputum or nasopharyngeal swab) were collected at admission for the detection of HAdV and measurement of initial viral load. Subsequent respiratory samples were collected every other day until discharge, then at each outpatient visit until the end of follow-up. Sputum was the preferred specimen, and nasopharyngeal swab was collected only when the patient was unable to expectorate. All collected samples were stored at 4 °C before weekly transportation to laboratory for real-time quantitative PCR. This study was approved by the Institutional Review Board of the Armed Forces Medical Command (AFMC-16011-IRB-16-008). Informed consents were obtained from all participating patients. All methods were performed in accordance with the relevant guidelines and regulations.

Detection, quantification, and typing of HAdV

HAdV infection was diagnosed by the detection of HAdV from respiratory samples using multiplex real-time PCR. DNA were extracted from the respiratory specimens using MagNA Pure LC 2.0 (Roche Diagnostics, Mannheim, Germany), and multiplex real-time PCR for 15 respiratory viruses including HAdV was conducted using Real-Q RV Detection Kit (Biosewoom, Inc., Seoul, Korea) on a LightCycler 480 II (Roche Diagnostics, Mannheim, Germany) following the manufacturer's instruction [8]. For the quantitation of AdV, DNA was extracted from 200 μl of sputum or viral transport medium in nasopharyngeal swab kit using Nextractor NX-48 (Genolution Inc., Seoul, Korea) automated extractor.

Measurement of HAdV viral load was performed by real-time quantitative PCR in duplicates using LightCycler 480 II (Roche Diagnostics, Mannheim, Germany). Real-Q AdV Quantification Kit (Biosewoom, Inc., Seoul, Korea) was used and 25 μl of reaction medium contained 12.5 μl PCR reaction mixture (2×), probe and primer mixture, sterile water, and 5 μl DNA. This kit also contains the plasmid DNA with defined copy number for HAdV to be used as standards. Viral load was calculated by multiplication of dilution factor and AdV concentration in the PCR reaction to show AdV concentration in the original respiratory samples. The lower limit of viral load detection was 2820 copies/mL. HAdV type was determined by the sequencing of hypervariable region 7 of hexon gene and fiber gene, as described previously [8, 20]. Typing of HAdV from 23 patients was conducted as a part of a previously published study, so nine additional samples were typed for this study [8].

Clinical characteristics and definitions

Data regarding clinical parameters, laboratory and imaging findings, and clinical course were obtained from electronic medical records. For symptomatologic analysis, we counted the daily number of symptoms among the following: fever, sore throat, cough, sputum, rhinorrhea, and dyspnea [21]. Hypoxia was defined as oxygen saturation < 95% by pulse oximetry while breathing ambient air or requirement of supplemental oxygen due to dyspnea. Definition of mechanical

ventilation included not only conventional mechanical ventilation but also high flow oxygen therapy. Day of defervescence was defined as the first day of two consecutive days with body temperature < 38 °C regardless of antipyretics use.

Statistical analysis

Statistical analyses were performed using Stata Release 12 (StataCorp LLC, College Station, TX, USA) and SPSS Statistics 20 (IBM, Armonk, NY, USA). Viral load was log-transformed, and linear regression models were constructed to estimate the rate of viral load decline. The cumulative viral load (CVL) was calculated as the area under curve of viral loads during the first 10 days since fever onset using the "pkexamine" command of Stata. The peak viral load was defined as the highest measured viral load during the first 10 days since fever onset. Student's *t* test was used to compare viral loads among different groups of patients. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Patient and virological characteristics

Sixty patients who were admitted with acute febrile respiratory infections were screened for possible inclusion into the study (Fig. 1). Among these patients, HAdV was not detected from respiratory samples of 25 patients, and one patient missed the screening. All 34 eligible patients agreed to participate and thus were enrolled. Two patients dropped from the study after enrollment: one was transferred to other hospital, and the other withdrew. Finally, 32 patients were included in the analyses.

All patients were healthy young male without comorbidities (Table 1). Majority were current (43.8%) or past smokers (18.8%). At presentation, all patients had sputum; other common symptoms were sore throat (87.5%) and rhinorrhea (68.8%). Twenty-seven (84.4%) patients had radiologic evidence of pneumonia, among which 30% had multilobar involvement. Six patients (18.8%) were admitted to the intensive care unit, but only one patient (3.1%) required high flow oxygen therapy. No patient was intubated or died. Cidofovir was administered in 5 patients (15.6%). All 32 HAdV were determined as type 55 by sequencing of the hexon and fiber genes.

Viral load kinetics

A total of 188 respiratory samples were collected during the study period. The median number of samples per patient was 5.5 (range, 2–10), and the median days of the first and last tests since the fever onset were 4.5 days (range, 2–8) and 16.0 days (range, 8–52), respectively. Sputum comprised 71.8% of all samples and the rest (28.2%) were nasopharyngeal swabs.

Viral load peaked at presentation and declined in log-linear kinetics (Fig. 2a). The geometric mean viral load (GMVL) at

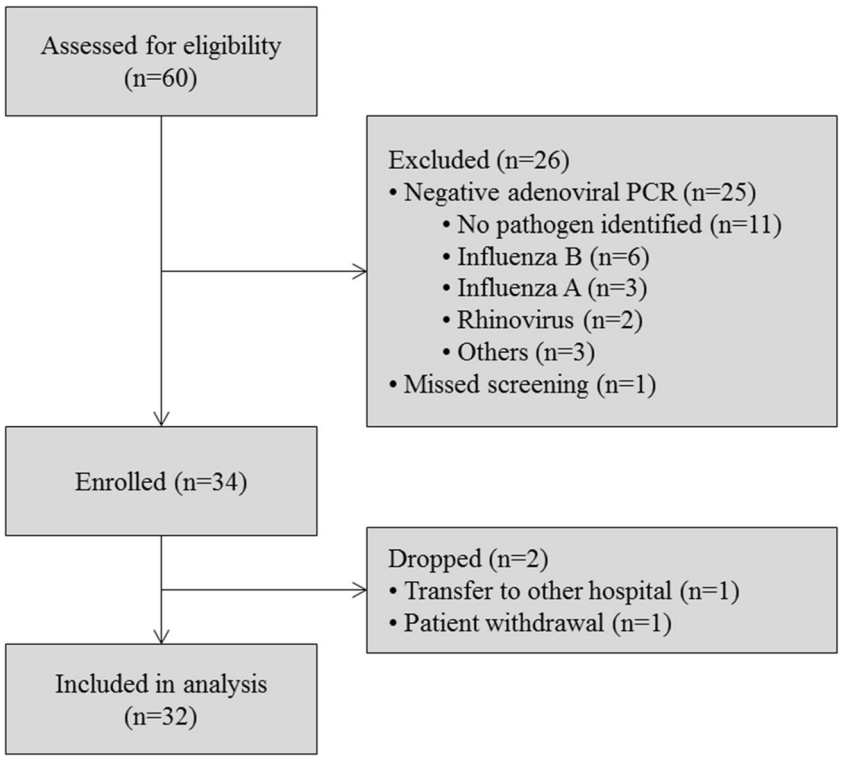

Fig. 1 STROBE diagram of study enrollment and analysis

Table 1 Characteristics of 32 patients with acute febrile respiratory infection by human adenovirus type 55

Characteristic	Number (%)
Male sex	32 (100.0)
Age, years (median, range)	20 (18–24)
Comorbidities	0 (0.0)
Smoking	
Current smoking	14 (43.8)
Previous history of smoking	6 (18.8)
Presence at presentation	
Cough	31 (96.9)
Sputum	32 (100.0)
Sore throat	28 (87.5)
Rhinorrhea	22 (68.8)
Dyspnea	6 (18.8)
Confusion	0 (0.0)
Clinical, laboratory, and radiologic findings at presentation	
Initial body temperature (°C; mean, SD)	38.5 (0.7)
Respiratory rate (mean, SD)	18.4 (3.5)
Hypoxia	4 (12.5)
Lowest systolic blood pressure (mean, SD)	112 (11.6)
Lowest diastolic blood pressure (mean, SD)	62 (11.0)
Pneumonia	27 (84.4)
Bilateral involvement	5 (18.5)
Multilobar involvement	8 (29.6)
Lower lobe involvement	22 (81.5)
Pleural effusion	6 (22.2)
Blood urea nitrogen (mean, SD)	10.2 (2.8)
Monocyte count (mean, SD)	560.6 (296.7)
Clinical course	
Duration of fever (days; mean, SD)	6.3 (1.8)
Intensive care	6 (18.8)
Mechanical ventilation	1 (3.1)
Extracorporeal membrane oxygenation	0 (0.0)
Cidofovir use	5 (15.6)
Death	0 (0.0)

SD, standard deviation

the earliest test (2 days after fever onset) was 8.69 $\log_{10}$ copies/mL. Viral loads at 7 days and 14 days after fever onset were 6.96 $\log_{10}$ copies/mL and 5.51 $\log_{10}$ copies/mL, respectively. The rate of decline was estimated to be -0.15 $\log_{10}$ copies/mL per day in a linear regression model (95% confidence interval (CI): -0.18, -0.12; $R^2 = 0.32$). Viral loads did not fall below the detection limit up to the last samples in all patients, except in one case where it became undetectable 52 days after the fever onset. The regression model estimated that the viral load will reach zero 55 days after the fever onset.

The examination of the viral load kinetics in relation with defervescence showed that the viral load started to decrease early in the course before the fever resolution (Fig. 2b). GMVL on the day of defervescence was 7.39 $\log_{10}$ copies/mL, and GMVL on 7 days after defervescence were 5.51 $\log_{10}$ copies/mL. The rate of decline was comparable with that of the previous model (aligned at the fever onset) at -0.18 $\log_{10}$ copies/mL per day (95% CI: -0.21, -0.14; $R^2 = 0.38$). The temporal trend of the body temperature (Fig. 2c) and number of symptoms (Fig. 2d) showed that most patients became afebrile and minimally symptomatic 10 days after the fever onset.

Among the enrolled patients, 5 received cidofovir. Since cidofovir was administered within 2 days after presentation except in one patient (4 days after presentation), the rates of decline in viral load before and after cidofovir administration could not be compared. Instead, the viral load kinetics of cidofovir-treated patients was compared with cidofovir-untreated patients (Fig. 3 and Table 2). The rate of decline in cidofovir-treated patients during 10 days since administration was -0.33 $\log_{10}$ copies/mL per day (95% CI: -0.49, -0.18, $R^2 = 0.48$). There was no statistically significant difference compared to the rate of viral load decline in cidofovir-untreated patients during the first 10 days since presentation, which was -0.30 $\log_{10}$ copies/mL per day (95% CI: -0.40, -0.21, $R^2 = 0.28$).

Factors associated with viral load

We compared geometric mean cumulative viral load and peak viral load in patients with various clinical and radiologic factors (Table 3). The cumulative viral load during the first 10 days since fever onset was significantly high in patients who had cough (58.53 $\log_{10}$ copies vs. 34.51 $\log_{10}$ copies, $p = 0.027$) or lower lobe involvement in radiologic imaging (61.57 $\log_{10}$ copies vs. 44.71 $\log_{10}$ copies, $p < 0.001$). The peak viral load was also high in those with cough (8.47 $\log_{10}$ copies vs. 5.88 $\log_{10}$ copies, $p = 0.025$), dyspnea (9.39 $\log_{10}$ copies vs. 8.16 $\log_{10}$ copies, $p = 0.016$), and bilateral (9.33 $\log_{10}$ copies vs. 8.17 $\log_{10}$ copies, $p = 0.020$) or multilobar involvement (9.03 $\log_{10}$ copies vs. 8.12 $\log_{10}$ copies, $p = 0.032$). Prolonged duration of fever (≥ 8 days) or smoking was not shown to be associated with both the total and peak viral loads.

Discussion

To the best of our knowledge, this is the first study primarily purposed to investigate the duration and pattern of viral shedding in immunocompetent adults with HAdV respiratory infection. The most noteworthy finding in our study is the prolonged duration of HAdV shedding in respiratory specimens. Influenza virus, one of the most common and extensively studied respiratory viruses, was detected for 3–7 days

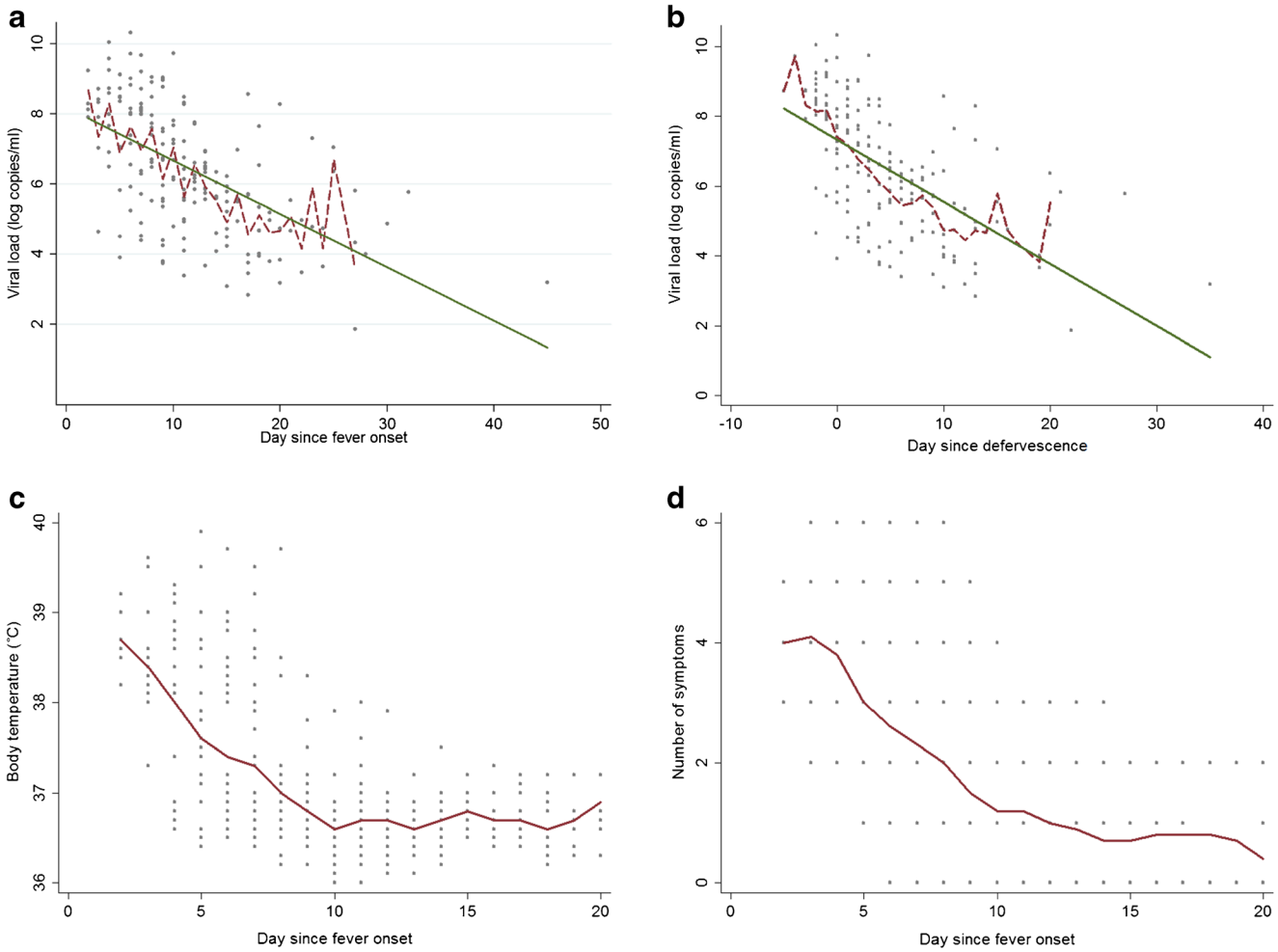

Fig. 2 Temporal patterns of viral load and clinical symptoms in adenoviral febrile respiratory infections. Viral load by day relative to fever onset (**a**) and to defervescence (**b**). Viral load (dots), geometric mean viral load (dashed line), and fitted line with linear regression (solid line). **c** Tympanic body temperature (dots) and mean body temperature (line) by day relative to fever onset. **d** Number of symptoms (dots) and mean number of symptoms (line) by day relative to fever onset

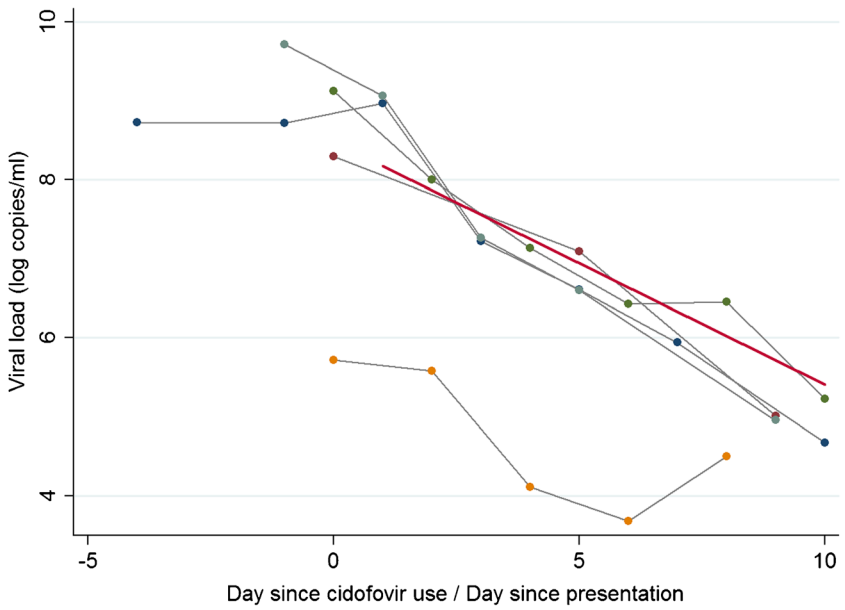

Fig. 3 Temporal patterns of viral load according to the use of cidofovir. Viral load in time relative to the administration of cidofovir is shown in gray lines and dots. Line of best fit by linear regression for viral load in patients without cidofovir use in time relative to the day of presentation is shown in red line for comparison

Table 2 Slope and correlation (R^2) between viral load and day since fever onset in patients with or without the use of cidofovir in a linear regression model

Treatment	Slope	95% CI	R^2
Cidofovir	− 0.33	− 0.49, − 0.18	0.48
No cidofovir	− 0.30	− 0.40, − 0.21	0.28

and up to 13–18 days in the respiratory specimens of community-based patients and those requiring intensive care, respectively [22]. Also, respiratory syncytial virus and rhinovirus were shown to be detected for the mean durations of 4 and 11 days, respectively, in previously healthy patients. Compared to those studies, the estimated shedding duration of 55 days is considerably longer [23, 24].

Although detailed information on HAdV shedding kinetics is scarce in the literature, previous studies support our findings. Fox et al. reported that 36% of newly infected patients with HAdV showed viral excretion for more than 30 days [10]. Nevertheless, the interpretation of results requires caution since specific information on participating individuals is lacking and specimens were obtained with biweekly interval. Another study revealed that HAdV was recovered from throat swab for up to 21 days in 8 adult patients with acute respiratory infection [11]. Our data has its strength compared with those of previous studies in that a relatively large number of otherwise healthy patients were enrolled and viral load was measured in a short interval using real-time PCR.

Another important implication of our results is that all HAdV identified in our study was type 55. HAdV-55 is a novel type previously reported in Turkey, Spain, Singapore, Israel, and China [7, 16–19]. Outbreaks of severe pneumonia and even death in healthy, young adults by HAdV-55 have been reported [25, 26]. Although it is yet unclear why certain novel HAdV types show higher virulence and transmissibility, it has been suggested that the lack of immunity to novel types is an important factor which leads to the increased host susceptibility [27]. This might explain why the immune system takes longer time to clear the virus from respiratory system. However, studies on endemic types of HAdV are required to determine whether the prolonged shedding observed in our study is a unique characteristic of HAdV-55 or a general feature of all HAdV types.

The persistent HAdV shedding implies considerable significance in infection control and clinical practice. First, our results necessitate attention in development of infection control strategies. The knowledge on viral shedding kinetics is necessary to determine the duration of isolation/respiratory precaution, which is the core element of infection control [28]. However, existing guidelines lack specific recommendations on the minimum duration of precautions for viral infections owing to the scarcity of data, with an exception for influenza [12]. Considerably prolonged duration of viral shedding in our study compared to other common respiratory viruses may suggest a possibility of prolonged duration of infectivity which requires an extended period of precaution and isolation. Second, HAdV detection warrants careful interpretation, especially in patients with recent history of febrile respiratory infection. Although HAdV is detected, it may not be the culprit of the current infection in those patients, considering its prolonged presence in the respiratory specimens.

In this study, we also examined the factors associated with higher viral excretion. Cough and extensive lung involvement as shown on chest radiograph in patients with pneumonia served as markers for excessive shedding, which is similar to influenza [29]. Thus, more extensive precaution should be

Table 3 Clinical and radiologic factors associated with higher viral shedding. Cumulative viral load was defined by the area under curve of viral load during 10 days since fever onset ($AUC_{0,10}$). Viral load was measured by real-time polymerase chain reaction of respiratory specimens (log_{10} copies/mL)

Symptoms and signs	Cumulative viral load ($AUC_{0,10}$)			Peak viral load (log_{10} copies/mL)		
	No	Yes	*p*	No	Yes	*p*
Current or ex-smoking	59.28	56.87	0.552	8.46	8.35	0.797
Sore throat	55.09	58.16	0.605	8.78	8.34	0.480
Cough	34.51	58.53	0.027	5.88	8.47	0.025
Rhinorrhea	57.03	58.12	0.797	7.81	8.65	0.055
Dyspnea	56.06	65.23	0.061	8.16	9.39	0.016
Hypoxia	57.62	58.85	0.837	8.39	8.37	0.965
Fever ≥ 8 days	57.06	59.61	0.560	8.41	8.34	0.887
Pneumonia	54.14	58.45	0.424	8.41	8.39	0.978
Multilobar involvement*	56.90	62.14	0.211	8.12	9.03	0.032
Bilateral involvement*	57.62	62.10	0.367	8.17	9.33	0.020
Lower lobe involvement*	44.71	61.57	< 0.001	7.18	8.66	0.102
Pleural effusion*	56.63	64.81	0.071	8.20	9.05	0.073

*Only patients with radiologic findings compatible with pneumonia were included ($n = 27$)

taken when caring for patients with severe involvement on radiologic imaging.

Only a limited number of antiviral agents are available to treat HAdV infection [30]. Among these, cidofovir has the greatest in vitro activity against HAdV [31]. Successful treatment of HAdV infection with cidofovir has been reported in small studies [32, 33]; however, at this time, there has been no randomized controlled trial to demonstrate the efficacy of cidofovir. In our study, no significant difference in the rate of decline in viral load was observed between patients who received cidofovir and those who did not. However, the number of patients was too small to draw conclusion on the effectiveness of cidofovir.

There are some limitations in our study. First, virus culture was not performed. Thus, some proportion of HAdV detected in our study may have been fragments of non-viable viruses. However, if a considerable accumulation of non-viable viral particles occurred, viral load kinetics would have shown initial increase before turning to decline later in the course. Consistent decline in viral load from the initial presentation observed in our study suggests the absence of significant effect of non-viable DNA fragments. Second, negative conversion of viral shedding was not observed except in one patient because the prolonged shedding duration had not been expected. Longer follow-up duration would have provided more accurate information on terminal phase of viral load kinetics.

In conclusion, our study has demonstrated that the viral shedding duration was prolonged in young immunocompetent patients with respiratory infections by HAdV-55. The amount of viral excretion was correlated with the degree of respiratory symptoms or extent of pulmonary involvement.

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Compliance with ethical standards

Conflict of interest I.K is an employee for Biosewoom, Inc., which is a manufacturer and distributor of a commercial diagnostic kit using multiplex PCR for respiratory virus used in this study. All other authors have nothing to declare.

Ethical approval This study was approved by the Institutional Review Board of the Armed Forces Medical Command (AFMC-16011-IRB-16-008).

Informed consent Written informed consents were obtained from all participating patients.

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References

1. Lynch JP 3rd, Kajon AE (2016) Adenovirus: epidemiology, global spread of novel serotypes, and advances in treatment and prevention. Semin Respir Crit Care Med 37:586–602. https://doi.org/10.1055/s-0036-1584923
2. Jennings LC, Anderson TP, Beynon KA, Chua A, Laing RT, Werno AM, Young SA, Chambers ST, Murdoch DR (2008) Incidence and characteristics of viral community-acquired pneumonia in adults. Thorax 63:42–48. https://doi.org/10.1136/thx.2006.075077
3. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, Reed C, Grijalva CG, Anderson EJ, Courtney DM, Chappell JD, Qi C, Hart EM, Carroll F, Trabue C, Donnelly HK, Williams DJ, Zhu Y, Arnold SR, Ampofo K, Waterer GW, Levine M, Lindstrom S, Winchell JM, Katz JM, Erdman D, Schneider E, Hicks LA, McCullers JA, Pavia AT, Edwards KM, Finelli L (2015) Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med 373:415–427. https://doi.org/10.1056/NEJMoa1500245
4. Ryan MA, Gray GC, Smith B, McKeehan JA, Hawksworth AW, Malasig MD (2002) Large epidemic of respiratory illness due to adenovirus types 7 and 3 in healthy young adults. Clin Infect Dis 34:577–582. https://doi.org/10.1086/338471
5. Gu L, Qu J, Sun B, Yu X, Li H, Cao B (2016) Sustained viremia and high viral load in respiratory tract secretions are predictors for death in immunocompetent adults with adenovirus pneumonia. PLoS One 11:e0160777. https://doi.org/10.1371/journal.pone.0160777
6. Heo JY, Lee JE, Kim HK, Choe KW (2014) Acute lower respiratory tract infections in soldiers, South Korea, April 2011-March 2012. Emerg Infect Dis 20:875–877. https://doi.org/10.3201/eid2005.131692
7. Kajon AE, Dickson LM, Metzgar D, Houng HS, Lee V, Tan BH (2010) Outbreak of febrile respiratory illness associated with adenovirus 11a infection in a Singapore military training cAMP. J Clin Microbiol 48:1438–1441. https://doi.org/10.1128/jcm.01928-09
8. Yoo H, Gu SH, Jung J, Song DH, Yoon C, Hong DJ, Lee EY, Seog W, Hwang IU, Lee D, Jeong ST, Huh K (2017) Febrile respiratory illness associated with human adenovirus type 55 in South Korea military, 2014-20161. Emerg Infect Dis 23:1016–1020. https://doi.org/10.3201/eid2306.161848
9. Jeon K, Kang CI, Yoon CH, Lee DJ, Kim CH, Chung YS, Kang C, Choi CM (2007) High isolation rate of adenovirus serotype 7 from South Korean military recruits with mild acute respiratory disease. Eur J Clin Microbiol Infect Dis 26:481–483. https://doi.org/10.1007/s10096-007-0312-6
10. Fox JP, Brandt CD, Wassermann FE, Hall CE, Spigland I, Kogon A, Elveback LR (1969) The virus watch program: a continuing surveillance of viral infections in metropolitan New York families. VI. Observations of adenovirus infections: virus excretion patterns, antibody response, efficiency of surveillance, patterns of infections, and relation to illness. Am J Epidemiol 89:25–50
11. Naghipour M, Hart CA, Dove W, Leatherbarrow AJ, Cuevas LE (2009) Adenovirus infections within a family cohort in Iran. Pediatr Pulmonol 44:749–753. https://doi.org/10.1002/ppul.20785
12. Siegel JD, Rhinehart E, Jackson M, Chiarello L (2007) 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control 35:S65–S164. https://doi.org/10.1016/j.ajic.2007.10.007
13. Kajon AE, Lu X, Erdman DD, Louie J, Schnurr D, George KS, Koopmans MP, Allibhai T, Metzgar D (2010) Molecular epidemiology and brief history of emerging adenovirus 14-associated respiratory disease in the United States. J Infect Dis 202:93–103. https://doi.org/10.1086/653083
14. Scott MK, Chommanard C, Lu X, Appelgate D, Grenz L, Schneider E, Gerber SI, Erdman DD, Thomas A (2016) Human

adenovirus associated with severe respiratory infection, Oregon, USA, 2013-2014. Emerg Infect Dis 22:1044–1051. https://doi.org/10.3201/eid2206.151898
15. Zhao S, Wan C, Ke C, Seto J, Dehghan S, Zou L, Zhou J, Cheng Z, Jing S, Zeng Z, Zhang J, Wan X, Wu X, Zhao W, Zhu L, Seto D, Zhang Q (2014) Re-emergent human adenovirus genome type 7d caused an acute respiratory disease outbreak in Southern China after a twenty-one year absence. Sci Rep 4:7365. https://doi.org/10.1038/srep07365
16. Zhu Z, Zhang Y, Xu S, Yu P, Tian X, Wang L, Liu Z, Tang L, Mao N, Ji Y, Li C, Yang Z, Wang S, Wang J, Li D, Xu W (2009) Outbreak of acute respiratory disease in China caused by B2 species of adenovirus type 11. J Clin Microbiol 47:697–703. https://doi.org/10.1128/JCM.01769-08
17. Hierholzer JC, Pumarola A (1976) Antigenic characterization of intermediate adenovirus 14-11 strains associated with upper respiratory illness in a military camp. Infect Immun 13:354–359
18. Salama M, Amitai Z, Amir N, Gottesman-Yekutieli T, Sherbany H, Drori Y, Mendelson E, Carmeli Y, Mandelboim M (2016) Outbreak of adenovirus type 55 infection in Israel. J Clin Virol 78:31–35. https://doi.org/10.1016/j.jcv.2016.03.002
19. Chmielewicz B, Benzler J, Pauli G, Krause G, Bergmann F, Schweiger B (2005) Respiratory disease caused by a species B2 adenovirus in a military camp in Turkey. J Med Virol 77:232–237. https://doi.org/10.1002/jmv.20441
20. Sarantis H, Johnson G, Brown M, Petric M, Tellier R (2004) Comprehensive detection and serotyping of human adenoviruses by PCR and sequencing. J Clin Microbiol 42:3963–3969. https://doi.org/10.1128/jcm.42.9.3963-3969.2004
21. Ip DK, Lau LL, Chan KH, Fang VJ, Leung GM, Peiris MJ, Cowling BJ (2016) The dynamic relationship between clinical symptomatology and viral shedding in naturally acquired seasonal and pandemic influenza virus infections. Clin Infect Dis 62:431–437. https://doi.org/10.1093/cid/civ909
22. Fielding JE, Kelly HA, Mercer GN, Glass K (2014) Systematic review of influenza A(H1N1)pdm09 virus shedding: duration is affected by severity, but not age. Influenza Other Respir Viruses 8:142–150. https://doi.org/10.1111/irv.12216
23. Okiro EA, White LJ, Ngama M, Cane PA, Medley GF, Nokes DJ (2010) Duration of shedding of respiratory syncytial virus in a community study of Kenyan children. BMC Infect Dis 10:15. https://doi.org/10.1186/1471-2334-10-15
24. Peltola V, Waris M, Kainulainen L, Kero J, Ruuskanen O (2013) Virus shedding after human rhinovirus infection in children, adults and patients with hypogammaglobulinaemia. Clin Microbiol Infect 19:E322–E327. https://doi.org/10.1111/1469-0691.12193
25. Sun B, He H, Wang Z, Qu J, Li X, Ban C, Wan J, Cao B, Tong Z, Wang C (2014) Emergent severe acute respiratory distress syndrome caused by adenovirus type 55 in immunocompetent adults in 2013: a prospective observational study. Crit Care 18:456. https://doi.org/10.1186/s13054-014-0456-6
26. Tan D, Zhu H, Fu Y, Tong F, Yao D, Walline J, Xu J, Yu X (2016) Severe community-acquired pneumonia caused by human adenovirus in immunocompetent adults: a multicenter case series. PLoS One 11:e0151199. https://doi.org/10.1371/journal.pone.0151199
27. Gray GC, Chorazy ML (2009) Human adenovirus 14a: a new epidemic threat. J Infect Dis 199:1413–1415. https://doi.org/10.1086/598522
28. Kwong JC (2016) Editorial commentary: symptoms and viral shedding in naturally acquired influenza infections. Clin Infect Dis 62:438–439. https://doi.org/10.1093/cid/civ914
29. Giannella M, Alonso M, Garcia de Viedma D, Lopez Roa P, Catalan P, Padilla B, Munoz P, Bouza E (2011) Prolonged viral shedding in pandemic influenza A(H1N1): clinical significance and viral load analysis in hospitalized patients. Clin Microbiol Infect 17:1160–1165. https://doi.org/10.1111/j.1469-0691.2010.03399.x
30. Ison MG, Hayden RT (2016) Adenovirus. Microbiol Spectr 4. https://doi.org/10.1128/microbiolspec.DMIH2-0020-2015
31. Naesens L, Lenaerts L, Andrei G, Snoeck R, Van Beers D, Holy A, Balzarini J, De Clercq E (2005) Antiadenovirus activities of several classes of nucleoside and nucleotide analogues. Antimicrob Agents Chemother 49:1010–1016. https://doi.org/10.1128/AAC.49.3.1010-1016.2005
32. Hoffman JA, Shah AJ, Ross LA, Kapoor N (2001) Adenoviral infections and a prospective trial of cidofovir in pediatric hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 7:388–394
33. Ganapathi L, Arnold A, Jones S, Patterson A, Graham D, Harper M, Levy O (2016) Use of cidofovir in pediatric patients with adenovirus infection. F1000Res 5:758. https://doi.org/10.12688/f1000research.8374.1