International Journal of Infectious Diseases 98 (2020) 390–397

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Cross-infection of adenovirus among medical staff: A warning from the intensive care unit in a tertiary care teaching hospital in China

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ARTICLE INFO

Article history:
Received 27 May 2020
Received in revised form 19 June 2020
Accepted 20 June 2020

Keywords:
Human adenovirus
Disease outbreak
HAdV-55
Epidemiology
Medical staff

ABSTRACT

Rationale: In 2019, a small HAdV55-associated outbreak of adenovirus infection occurred among the intensive care unit (ICU) staff in Xiangya Hospital of Central South University in Hunan Province, China, during the treatment of a patient.
Objective: To investigate the characteristics of a nosocomial adenovirus outbreak in an ICU.
Methods: We evaluated all the patients treated and the medical staff working in the ICU from August 1 to September 4, 2019. We further performed an epidemiological and molecular analysis for this outbreak from patient to healthcare workers and between healthcare workers. After the outbreak, we adopted exposure prevention and droplet prevention measures based on standard precautions.
Measurements and main results: Between August 1 and August 27, 2019, 27 cases of human adenovirus cross-infection were reported in our institution. Among the cases, eleven were doctors (41%), eleven were nurses (41%), three were respiratory therapists (11%), and two were caregivers (7%). The attack rate was 28.4%, and the fatality rate was 0. The results showed that contact with the index case, lack of hand hygiene or gloving adherence were risk factors for infection after adenovirus exposure. After taking specific precautions, no new cases of infection have appeared since August 27.
Conclusions: Our results show that HAdV55 in a single patient had strong transmission potential in an intensive care unit with adequate facilities and standardized operation. We provide convincing evidence indicating that attention could be highlighted on the role of standard and specific precautions for controlling the spread of adenovirus in ICUs.

Introduction

Adenovirus (AdV) is a nonenveloped virus with an icosahedral nucleocapsid containing a double-stranded DNA genome (Lynch et al., 2011). It is one of the most common pathogens causing respiratory infections in immunocompetent adults and elderly individuals (Hakim and Tleyjeh, 2008; Tan et al., 2016; Lynch and Kajon, 2016). Respiratory viruses, which account for a proportion of more than 22% of respiratory infections, are detected more frequently than bacteria in adults with acute respiratory disease (ARD) (Jain et al., 2015; Ruuskanen et al., 2011).

Since the initial isolation in 1953 (Hilleman et al., 1953; Rowe et al., 1953), more than 60 distinct adenoviral genotypes in seven species (Human adenovirus A to G) have been found to be responsible for a wide range of illnesses in humans (Lion, 2014). HAdV species A, B, C, E are most often associated with respiratory infections (Crenshaw et al., 2019). Among HAdV species B, all Subspecies B1 except for HAdV-B50 and HAdV-B14 and -B55 in subspecies B2 may cause respiratory disease (Binder et al., 2017; Scott et al., 2016; Echavarria, 2008).

The epidemiological characteristics of illness caused by a human adenovirus (HAdV) tend to occur sporadically without significant

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https://doi.org/10.1016/j.ijid.2020.06.103
1201-9712/

seasonality. Outbreaks of HAdV associated ARD have been reported globally in closed or crowded settings, including among military recruits (Lu et al., 2014; Killerby et al., 2019; Park et al., 2017; Biggs et al., 2018). According to existing reports, the incubation period for adenovirus infections does not exceed 14 days (Lynch et al., 2011; Reich et al., 2011). Clinical manifestations include upper and lower respiratory tract infections, gastroenteritis, keratoconjunctivitis, myocarditis, etc. (Primo et al., 2018; Kenmoe et al., 2018; Cederwall and Pahlman, 2020). Transmission of adenoviruses occurs mainly by direct contact and fomites, such as respiratory droplets and fecal routes. HAdV can remain in the body for several days to weeks, even after the resolution of symptomatic infection, and HAdV may survive outside of the body and in water for prolonged periods (Xu et al., 2018; Wilson and Zumla, 2019). HAdV-B subtype, especially HAdV-B55, is associated with a severe respiratory infection (Scott et al., 2016; Bautista-Gogel et al., 2017), and recently considered responsible for most outbreaks of adenovirus in China (Xu et al., 2018; Li et al., 2014; CDC, 2013; Cao et al., 2014).

Herein, we describe the identification, investigation, and successful containment of an outbreak concerning cross-transmission of HAdV-B55 from a patient in an ICU diagnosed with severe pneumonia to medical health workers from August 1 to August 27, 2019. To our knowledge (Cassir et al., 2014; Nguyen et al., 2016), the cross-transmission from a patient to more than 20 medical staff members in an adult ICU has not been previously reported.

Methods

Setting of ICU

The Central South University Xiangya Hospital is a 3500-bed tertiary referral university-affiliated teaching hospital with a 10-bed ICU that manages patients more than 18 years old with critical respiratory illnesses. The ICU is a laminar flow ward equipped with a combination of a single room and open cubicles, with approximately 360 admissions annually over the past 10 years. A negative-pressure isolated room was usually reserved for patients infected with highly infectious pathogens to protect other patients and the HCWs in this unit. The other beds are located in open cubicles, with each cubicle containing 1–2 beds. The beds are separated from each other by at least three feet. Each

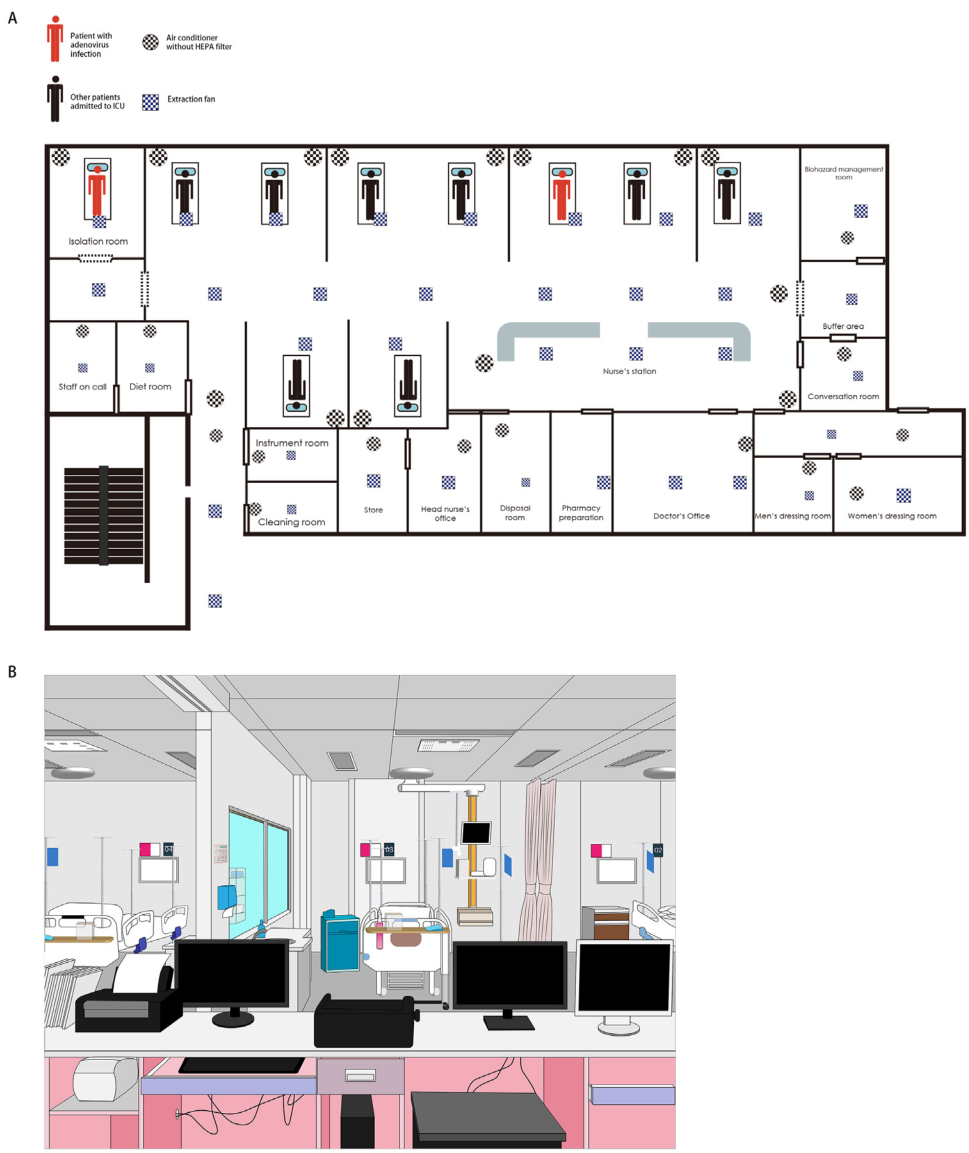

Figure 1. (A) Floor plan of the ICU and location of patient 3 during his stay in the emergency room. (B) Schematic views of bed for Patient 3.

bed is provided with a hand wash basin less than 1.5 feet from a hand sanitizer. Masks and caps from the nurse station are used (Figure 1). Our institution employs a bundle management strategy to isolate patients (detailed in Appendix 1). Specific precautions for patients with potentially communicable diseases mainly depend on the route of transmission of the pathogen (detailed in Appendix 1).

Demographic and epidemiological data

Confirmed cases were defined as those who had a positive adenovirus real-time PCR detection from respiratory tract samples, regardless of whether they were symptomatic or asymptomatic. Suspected cases were defined as only those with fever and other symptoms of infection, but that were not confirmed in the laboratory. Patients' demographic information, underlying diseases, visiting dates, stay duration, and the exact time of arrival at and departure from the ICU are collected. For healthcare workers, information about their age, gender, occupation, underlying diseases, patient contact, daily workflow, and date and time of duty were collected through interviews, an examination of the staff's work schedule, and a review of electronic signatures in patients' medical records and questionnaires. We conducted symptom screening including fever, shivers, headache, myalgia, cough, expectoration, chest pain, sore throat, dyspnea, nausea, vomiting, abdominal pain, diarrhea, and daily conjunctival redness, and we collected respiratory tract samples every 2–7 days for adenovirus using real-time PCR detection. The incidence rate was calculated by dividing the number of confirmed cases by the total number of people exposed in the ICU.

Sample collection

Respiratory tract samples from everyone exposed to the virus, including nasopharyngeal swabs and tracheal aspirates, and environmental samples were collected for laboratory screening. We randomly selected medical staff for real-time PCR positive screening, to collect venous blood for typing by NGS using the sealed, opaque envelope method. A total of 36 samples were obtained each time.

Microbiologic investigation: real-time PCR for the detection of adenovirus DNA in clinical specimens collected in viral transport media.

The samples were immediately transferred to a viral transport medium (Eagle's minimal essential medium, bovine serum albumin, and antibiotics) and Stored at 4–8 °C before transporting to the laboratory within 24 h. The tests were performed immediately after the delivery of the samples to the laboratory. Real-time PCR for the nucleic acid of adenovirus was detected, as described previously (Huh et al., 2019). Briefly, total nucleic acid was extracted from specimens mentioned above using a DNA extraction kit (Biolab, China) according to the manufacturer's protocol. Adenovirus DNA was detected by real-time PCR using TB Green Ex Taq II (Tli RNaseH Plus) (Takara Biotechnology Co. Ltd., Dalian, China) on a Real-Time PCR System (ABI ViiATM7; Applied Biosystems, Carlsbad, CA, USA) with the following cycling conditions: 1 cycle for 10 min at 45 °C, 1 cycle for 10 min at 95 °C, followed by 45 two-step cycles of 15 s at 95 °C and 45 s at 60 °C.

Next-generation sequence (NGS) was used for blood specimens and bronchoalveolar lavage fluid (BALF) to detect the pathogens. Sample DNA extraction was performed using MagPure FFPE DNA LQ Kit (Magen, China), according to the manufacturer's instructions. DNA libraries were constructed through DNA fragmentation, end-repair, adapter ligation, and PCR amplification. An agilent 2100 Bioanalyzer was used for quality control of the DNA libraries. The libraries were sequenced on the BGISEQ-50 platform. High-quality sequencing data were generated by removing low-quality and short reads (length < 35 bp), followed by computational subtraction of human host sequences, which were mapped to the human reference genome (hg19) using Burrows–Wheeler alignment.

Classification reference databases were downloaded from the National Center for Biotechnology Information (NCBI, www.ncbi.nlm.nih.gov/genomes/). The NGS results were further verified by PCR.

Assemble NGS sequencing reads to take the contig sequence. The complete sequence (of 34,738bp) is assembled according to the overlap between contigs. Sixty-one previously identified human adenovirus genomes for sequence download fromwere downloaded from the NCBI database. All samples were sequence -aligned (software: mafft-7.4). Subsequently, the Aalignment sequence was used to construct the rootless NJ evolutionary tree.–!>The complete sequence (34,738 bp) is assembled according to the overlap between contigs. Sixty-one previously identified human adenovirus genomes for sequence were downloaded from the NCBI database. All samples were sequence-aligned (software: mafft-7.4). Subsequently, the alignment sequence was used to construct the rootless NJ evolutionary tree.

Statistical analysis

Classification variables were expressed as frequency (percentage), and continuous variables were expressed as median (range, interquartile range). The incubation period was compared using Student's *t*-test. We used binary logistic regression analysis to assess the risk factors for adenovirus infection among all patient contacts. For these analyses, odds ratios and 95% confidence intervals were reported. Bilateral *P* values less than 0.05 indicated statistical significance. We performed statistical analysis using SAS version 9.2 and GraphPad Prism version 8.

Results

Description of the outbreak

Between August 1 and August 27, 2019, 27 confirmed cases of medical staff infection with human adenovirus were identified in Xiangya Hospital of Central South University in Hunan Province, China. All confirmed cases were part of a single outbreak involving an adult in the ICU.

Index case

Starting from August 5, 2019, doctors and nurses successively began to exhibit cough, fever, and other symptoms. Considering the longest incubation period of 14 days, index case investigation targeted all patients with adenovirus admitted to the ICU from July 24 to August 5. We examined people who had contact with patients 8 and 3, the two cases of adenovirus infection who were hospitalized during this period. Patient 8, a patient with severe adenovirus pneumonia, had already been admitted to the only laminar flow ward in the ICU. Therefore, patient 3 stayed in a cubicle temporarily. Only people who had contact with patient 3 showed symptoms of or tested positive for adenovirus infection (Figure 1). Therefore, we considered patient 3 to be the index case.

On August 1, 2019, a 29-year-old male with respiratory tract adenovirus infection (patient 3) was transferred to the ICU with fever, cough, and expectoration as the chief complaints. The definitive diagnosis of adenovirus infection was made 24 h after admission; examination showed that the adenovirus DNA was 2.34E+6 and sequenced as type B55 by NGS. The systemic

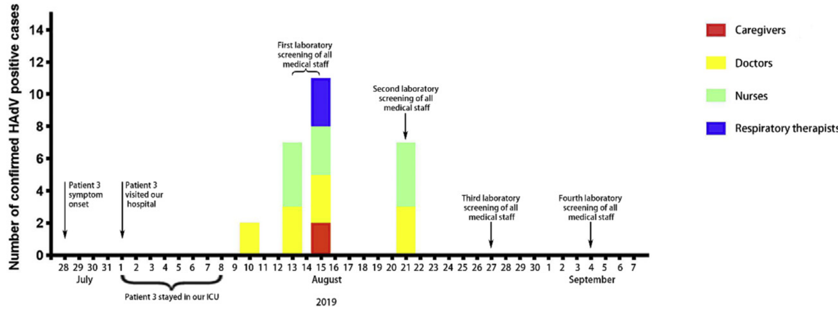

Figure 2. Confirmed cases of Adenovirus infection by date of confirmation after exposure to Patient 3.

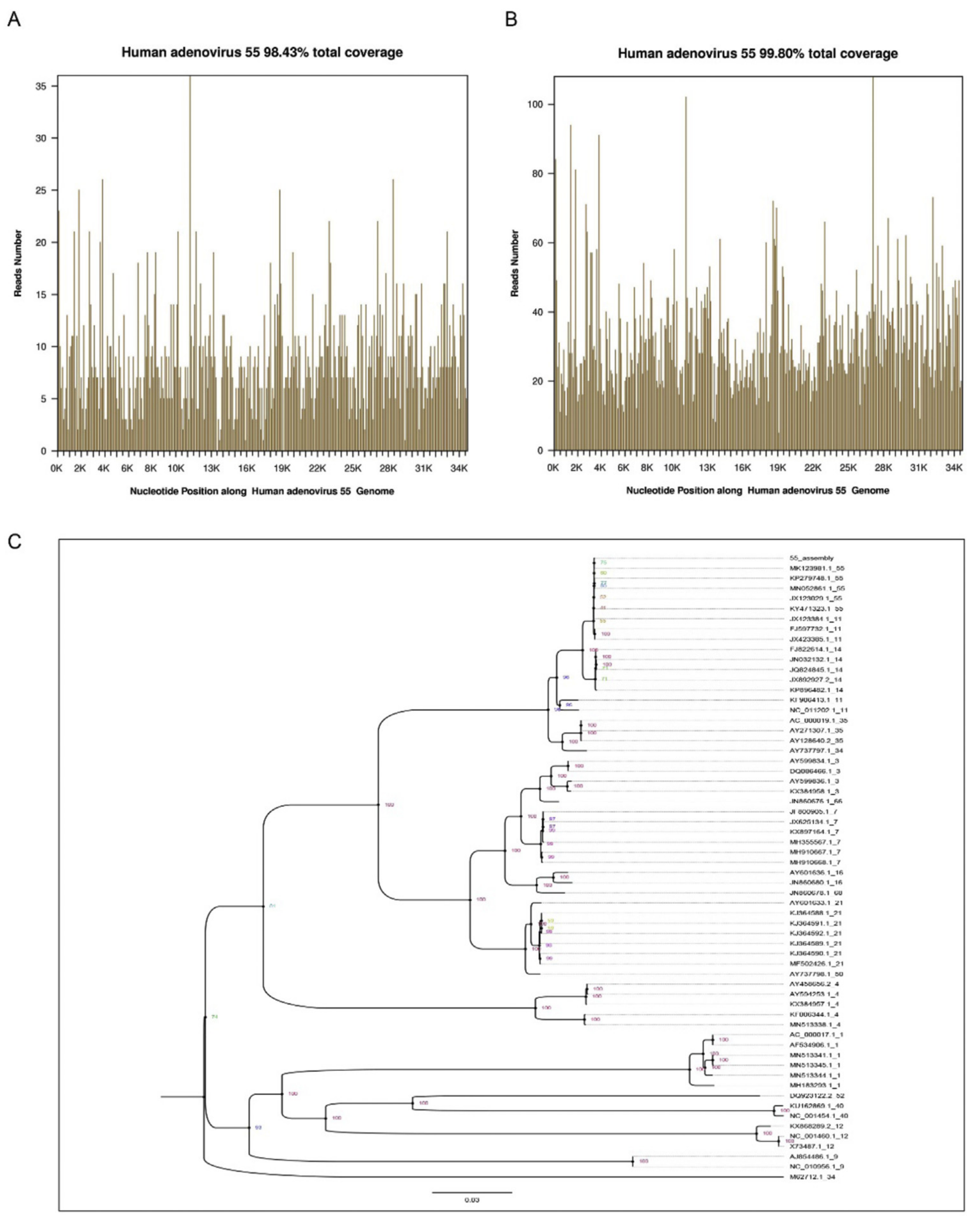

Figure 3. NGS for index case in blood (A) and BALF (B). Phylogenetic analysis of the sequences (C).

Table 1
Characteristics and symptoms of HCWs with laboratory-confirmed adenovirus infection.

Characteristics	HCWs with confirmed cases (N = 27)			
	Doctors (N = 11)	Nurses (N = 11)	Respiratory therapists (N = 3)	Caregivers (N = 2)
Male sex — no. (%)	5(45)	2(18)	2(67)	0
Age — yr				
Median	33	31	32	53.5
Range	23–41	21–40	26–36	52–55
Underlying illness — no. (%)				
Lung disease	0	0	0	0
Immunosuppressive condition	0	0	0	0
Signs and symptoms — no. (%)				
Fever	6(55)	4(36)	1(33)	1(50)
Shivers	1(9)	0	0	0
Headache	4(36)	5(45)	2(67)	0
Myalgia	4(36)	5(45)	2(67)	0
Respiratory symptoms				
Sore throat	8(73)	8(73)	3(100)	1(50)
Cough	4(36)	5(45)	3(100)	1(50)
Expectoration	3(27)	5(45)	3(100)	1(50)
Chest pain	0	1(9)	1(33)	0
Shortness of breath	0	2(18)	0	0
Gastrointestinal symptoms				
Nausea	0	4(36)	1(33)	0
Vomiting	0	3(27)	0	1(50)
Diarrhea	2(18)	1(9)	0	0
Ocular symptoms				
Redness	1(9)	1(9)	1(33)	0
Duration of signs and symptoms — no. (%)				
>7 days	6(54)	7(64)	3(100)	1(50)
≤7 days	3(27)	2(18)	0	0
Complication — no. (%)				
Pneumonia	0	1(9)	0	0
Specimen source — no. (%)				
Nasopharyngeal swab	11(100)	11(100)	3(100)	2(100)
Tracheal aspirate	0	3(27)	0	0
Blood	1(9)	4(36)	0	0
Protective measures — no. (%)				
Mask	7(64)	6(55)	3(100)	1(50)
N95-Respirator	3(27)	5(45)	0	1(50)
Protective clothing	1(9)	1(9)	0	0
Handwashing hygiene[a]	10(91)	11(100)	3(100)	0
Direct contact[b] — no. (%)	8(73)	7(64)	3(100)	1(50)
Indirect contact[c] — no. (%)	7(64)	3(27)	2(67)	1(50)
Relative infection — no. (%)	1(9)	2(18)	0	0

[a] Seven-step hand-washing method advised by our Hospital Infection Control Center using either plain or antiseptic-containing soap and water and the use of alcohol-based products (gels, rinses, foams) that do not require water. The specific steps are: (1) palms rubbing relative to each other; (2) fingers crossed, palms being rubbed against each other; (3) fingers crossing, palms rubbing relative; (4) bending finger joints rubbing palm; (5) rub thumb in palm; (6) rub fingertips in palm; (7) wash wrist if the wrist is contaminated. Timing: (1) before contacts with patients; (2) before contact with clean, sterile objects and aseptic procedures; (3) after contact with patients' blood, body fluids, secretions and feces, and after glove removal; (4) after contact with patients; (5) after contact with surrounding items of patients.

[b] (1) The HCW's skin or mucous membrane has directly contacted the patient's blood or blood-containing body fluids; (2) the HCWs have touched the patient's skin and mucous membranes with hands without gloves.

[c] (1) HCW's skin or mucous membrane has touched the equipment used by the patient (including medical equipment and daily necessities without thorough disinfection or sterilization); (2) the medical staff's skin or mucous membrane has directly contacted the patient without hand hygiene; (3) the medical staff's skin or mucous membranes come in contact with the medical staff's protective equipment such as work clothes, masks, etc. that have been infected or splashed by the patient's blood or other body fluids.

symptoms improved after treatment with cidofovir (5 mg/kg per week). The patient was then transferred to the general ward on August 8, 2019, and isolation treatment was continued. Five household contacts, including four adults, were followed up; no one was infected except the 4-year-old daughter.

Contact investigation

During his stay in the ICU, the patient's scope of activities was limited to his own bed. A total of 37 people were contacted after patient 3 was admitted to the ICU. From August 10 to August 21, 27 cases of adenovirus infection were confirmed (Figure 2). To identify the source of the first case, we randomly selected medical staff members for positive screening to collect venous blood for typing by NGS. Based on the genome sequences, we found that four of the six healthcare personnel showed positive adenovirus infection and were identified as HAdV-B55. The phylogenetic analysis of whole genomic sequences confirmed that the most closely related sequence to this clade is MK123981.1 55, which was consistent with the result of NGS (Figure 3).

Among the cases of adenovirus infection, eleven were doctors (41%), eleven were nurses (41%), three were respiratory therapists (11%), and two were caregivers (7%) (Table 1). Most of the infected cases were women, and the median ages were 33, 31, 32, and 53.5 years among doctors, nurses, respiratory therapists, and caregivers, respectively. The most common symptom was sore throat (73%, 73%, 100% and 50% of infected doctors, nurses, respiratory therapists, and caregivers, respectively), and most people's symptoms lasted more than seven days (54%, 64%, 100% and 50%). During patient 3's stay in ICU from August 1 to August 8, the exposed population was 95, including 83 workers, nine patients,

Table 2
Risk factors for transmission of adenovirus in all exposed HCWs in ICU.

All exposed HCWs (N = 83)	Odds ratio (95% CI)	P Value
Contact with the index case	4.253(1.393–12.984)	0.011
Hand hygiene adherence[a]	0.239(0.079–0.720)	0.011
Gloving adherence	0.591(0.127–2.761)	0.057
Gowning adherence	4.253(1.393–12.984)	0.57
Droplet precautions adherence[b]	—	—

[a] In addition to handwashing hygiene mentioned above, the timing also includes: (1) before wearing personal protective equipment (PPE); (2) after touching PPE while getting off work; (3) after removing and disposing of PPE.
[b] Including wearing mask or N95-Respirator.

and three visitors to the ICU during this period. The incidence rate was 28.4%, and the fatality rate was 0.

Epidemiologic investigation

The infection rate was 54% among the 35 medical workers who had contact with the primary case, and 17% for the 48 medical workers who had not.

We took 27 infected HCWs cases and 56 uninfected HCWs exposed in the ICU as Controls for Logistic regression analysis (Table 2). In the multivariate model, contact with the index case (OR 4.253; 95%CI 1.393–12.984, P = 0.011), hand hygiene adherence (OR 0.239; 95%CI 0.079–0.720, P = 0.011), gloving adherence (OR 0.591; 95%CI 0.127–2.761, P = 0.057) was independently associated with incident infection, while droplet precautions adherence and gowning adherence did not show any association with incident infection.

After investigation, we confirmed that the number of medical workers with adenovirus infection transmitted by the index case was five, and transmitted by their colleagues was 10. We compared the incubation periods in eight healthcare workers who had infections transmitted by the index case and six healthcare workers who had infections transmitted by their colleagues whose contact date and symptom occurrence date could be determined. The median incubation period was seven days (range: 4–10, interquartile range: 5–9) vs. three days (range: 1–7, interquartile range: 1.75–5.5) (Figure 4).

Infection control measures and response

Unit-based interventions. Having transferred all patients to other ICUs in our hospital, separately, we emptied the whole unit for 72 h for thorough sterilization by 75% alcohol, twice a day. Since adenovirus usually does not remain infectious at a long distance when transmitted by droplets (Musher, 2003), no special air treatment and ventilation measures were taken. During this treatment, we tested for HAdV in air and all possible contaminated devices and equipment. When all tests revealed negative results, our unit reopened, and those who were less likely infected, asymptomatic, and negative on RT-PCR could come back for clinical work. The index case was placed on contact and droplet precautions. Such precautions remained for14 days from the positive test result or until symptoms resolved. An infection control team was established, and members supervised daily medical staff's behavior at work, including wearing protective outfits (caps, masks, work clothes, isolation gown), hand hygiene, and gloving adherence. It was emphasized that medical staff should wear masks for respiratory tract isolation when talking with each other. The ICU staff members were screened for signs and symptoms of illness daily. PCR screening for staff and patients should continue every week. Any symptomatic staff members with evidence of upper respiratory infection or conjunctivitis were evaluated by the Occupational Health Department and underwent adenoviral testing. Affected staff members were furloughed for 14 days from the date of symptom onset. Symptomatic family members were identified by ICU staff and counseled not to visit until symptoms resolved. Basic prevention practices were observed and reinforced on the unit under the guidance of infection prevention and trained hand hygiene observers. Routine situational briefings were carried out to keep staff members updated and receiving recommendations in a timely manner. After taking these measures, no further new cases of infection were identified on August 27.

Discussion

This report investigates adenoviral infection among medical staff caused by patient 3 in the ICU of Xiangya Hospital of Central South University in southern China. The infection occurred in the ICU, where disease prevention measures and equipment are relatively complete. Patients had not been given any treatment approaches that might cause aerosolization, such as aerosol inhalation. In addition, the air inlets of our institution are located directly above each bed and air is discharged from the outlets on both sides of the bed. Although the positive predictive values of the detections were very low, the samples from air and the air outlets were all negative; therefore, we determined that the possibility of air transmission was not very high. We investigated the lack of preventive measures that might have occurred during or after the medical staff's contact with adenovirus patients. After analysis, it was found that the risk factors of this contact transmission were: contact with the index case, and lack of hand hygiene or gloving

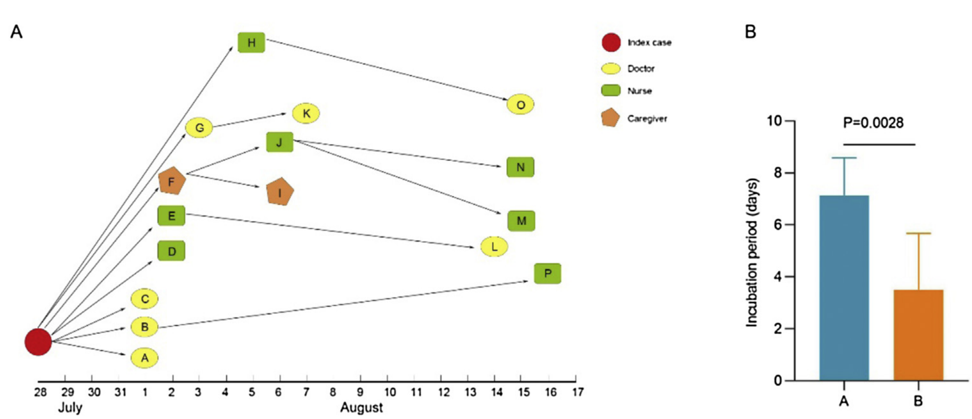

Figure 4. (A) Transmission map of outbreak of adenovirus infection and (B) incubation periods. Group A indicates eight healthcare workers who had infections transmitted by the index case and group B indicates six healthcare workers who had infections transmitted by their colleagues.

adherence. When it comes to hand hygiene, some staff would not wash or rub their hands immediately after taking off their working outfit but would rub their hands with an alcohol-based hand rub located on the door wall after changing to their casual clothes and shoes in the dressing room. During this period, their hands might have contacted their mask or work clothes and then contacted their eyes, mouth, nose, and other body parts, which may be one of the possible causes of the spread.

After the comprehensive screening conducted on August 15, seven medical workers with negative screening results showed positive results after PCR screening on August 21. After investigation, we hypothesize that these medical workers were infected by viral transmission from their colleagues, based on the following reasons: (1) There were almost no preventive isolation measures among medical staff, 87% of them did not always wear masks when communicating with their colleagues during working hours. (2) Personnel had close-range conversations without wearing masks with their colleagues who were infected with adenovirus, with the distance not exceeding 50 cm. (3) After implementing respiratory tract isolation measures for some time, no new cases were detected after August 27. Although the diagnosis of patients was rapid and timely, the response of the medical staff when symptoms occurred was not timely enough. Therefore, during an outbreak period, attention should be paid not only to patients but also to medical workers' health status, which may be one of the transmission routes (Cassir et al., 2014; Cavari et al., 2016; Hoyle et al., 2016). At the same time, prevention among medical staff should also be emphasized, which may be the most easily neglected step in ICU work.

High viral load and increased respiratory tract secretions are factors for severe acute respiratory syndrome (SARS)-related coronavirus superspreaders (Christian et al., 2004). This index case had the following characteristics: (1) The viral load was high. NGS sequencing results showed that the copy numbers of HAdV-B55 were 59,331 in the alveolar lavage fluid, and 16,556 in the blood. (2) Cough was severe and the sputum volume was moderate (about 50–100 mL/day). (2) No ventilator was used, so the respiratory tract virus could not be discharged through the ventilator pipeline. (4) The patient refused to wear a mask. However, he did not cause any more nosocomial infection after being transferred to a general ward. Perhaps the transmissibility of the adenovirus was due to various factors, such as the time of disease onset, duration of exposure, and dynamics of virus shedding. Therefore, more evidence is required for further confirmation.

We think it may be due to the difference in viral load and transmission route for the difference in incubation periods between the two groups. Of the 27 medical staff with adenovirus infection, 25 (92.6%) were wearing surgical masks or N95 respirators (Table 1) during contact with the first case, and the remaining 2 were not in contact with adenovirus patients. It was more likely that the patient's saliva or other body fluids splashed on the medical staff's personal protective equipment (PPE), and protective loopholes appeared when putting on and taking off the PPE, such as when masks or work clothes were removed and either the hands were not washed in time or hand rubbing with the use of alcohol-based hand rub was not done on time. However, the transmission of adenovirus infection by colleagues was relatively simple, and droplet transmission was more likely. There was almost no protection among the medical staff. They did not wear masks for close conversation (less than 50 cm). However, due to the lack of timely acquisition of relevant samples for viral load measurement, this is only our speculation, so more studies are needed for further confirmation.

There were some limitations to our investigation and analysis. No hand hygiene assessment was conducted; information on hand hygiene adherence during this period was obtained by questionnaires and interviews, which might be biased. The regression model to investigate risk factors for this outbreak is incomplete due to the limited sample size. Thus, this model measures only a fraction of possible explanations and does not allow a full and complete investigation of this outbreak.

In summary, we reported an outbreak of adenovirus in the ICU of a large class IIIa teaching hospital. This outbreak was triggered by an index case-patient with adenovirus, causing further spread among the medical personnel, which undoubtedly has a warning effect. In the outbreak of adenovirus, medical personnel themselves can also be part of the disease's spread. Most previous studies have emphasized the susceptibility of ICU patients to infectious diseases and the prevention and protection of patients by medical workers, often ignoring the protection of medical workers themselves and the prevention among medical workers. Medical staff should not be ignored in the formulation of preventive measures against infectious diseases.

Ethics

All examinations and screening were a part of routine clinical practice. The study was approved by the Xiangya Hospital Central South University Research Ethics Committee (No. 201912536).

Authors' contribution

Conception and design: Minhui Dai, Pinhua Pan, Hongyi Tan.

Acquisition of data: Maodan Hou, Wenzhong Peng, Guo Chen, Yi Li.

Analysis: Minhui Dai.

Drafting the manuscript for relevant intellectual content: Minhui Dai, Yanhao Wu.

Revised the manuscript: Minhui Dai, Jing Deng, Hongyi Tan, Haitao Li.

Final approval of the version submitted for publication: Minhui Dai.

Agreement to be accountable for all aspects of the work: Pinhua Pan, Jingmei Lu.

Conflict of interest

No conflict of interest to declare.

Acknowledgments

This study was supported in part by the National Key R&D Program of China (No. 2018YFC1311900 and No. 2016YFC1304204). We would like to thank Editage (www.editage.cn) and Dr. Yun Tan for English language editing, BGI for its biotechnology support, and Professor Dan Luo for her care and encouragement.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2020.06.103.

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