

Human Adenovirus Type 7 Infection Associated with Severe and Fatal Acute Lower Respiratory Illness and Nosocomial Transmission

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A 23-year-old male died of severe pneumonia and respiratory failure in a tertiary hospital in Beijing, and 4 out of 55 close contacts developed fever. Molecular analysis confirmed human adenovirus type 7 (HAdV7) as the causative agent. We highlight the importance of early diagnosis and treatment and proper transmission control of HAdV7.

CASE REPORT

Human adenovirus type 7 (HAdV7) infection is associated with acute respiratory disease syndrome, pharyngoconjunctival fever, pneumonia, and central nervous system disease (1–4). According to the last global survey, approximately one-fifth of all HAdV infections reported to the World Health Organization (WHO) were attributed to HAdV7 (5). HAdV7 outbreaks generally occur in settings with close living conditions, such as military barracks, hospital wards, and chronic care facilities (1, 6–8). In hospitals, HAdV has emerged as a nosocomial pathogen, and nosocomial outbreaks caused by HAdV7 with fatal cases have been reported worldwide (8–10). Although some prevention measurements have been carried out to control nosocomial transmission, questions regarding the efficacy of these programs persist, and the contribution of HAdV7 (and adenoviruses in general) to nosocomial infection is likely to be underestimated. Here, we report a case of HAdV7 infection associated with severe pneumonia and fatal acute lower respiratory disease and nosocomial transmission.

The index case, a 23-year-old male in Wuhan City, Hubei Province, China, presented with a fever of approximately 39°C on 18 January 2014, but discontinuous treatment did not alleviate his symptoms. On 26 January, he was admitted to the emergency department of a tertiary hospital in Beijing. A routine blood test showed high neutrophil levels (71.4%) and elevated plasma C reactive protein (19 mg/ml), and chest radiographs revealed an increase of right lung markings. However, the use of cefoxitin sodium by injection did not prevent his condition from worsening, with symptoms including severe fever, cough, and phlegm. He was diagnosed with pneumonia and transferred to the respiratory department on 28 January. Six days later, he was transferred to an intensive care unit (ICU) because of lung consolidation, and he passed away on 5 February 2014.

During his hospitalization, 4 of 55 close contacts developed fevers higher than 38.0°C, including a family member, a bedside clinician, and two patients in the same ward (Table 1 and Fig. 1). The initial secondary case (patient 1) was his cousin, a 19-year-old girl who visited the index case on 26 January for 30 min in the emergency department and on 2 February for 5 min in the respiratory department. The distance between them was more than 2 meters, but neither wore a mask. She experienced a fever of 38.5°C on 3 February. Patient 2, a 29-year-old male with acute pancreatitis and a fatty liver, was admitted to the same ward of the emer-

gency department on 27 January. He developed a fever on 3 February, and a chest X-ray showed pulmonary shadows. Patient 3, a bedside clinician of the index case during treatment from 28 January to 3 February, developed a fever and sore throat on 6 February. During this period, both the clinician and the index case did not always wear masks during treatment and the clinician did not have close contact with other patients with fever. Patient 4, a 12-year-old boy with a respiratory infection, spent 3 h in the same room with the index case on 27 January and went home the same day. On 7 February, he developed a fever, 11 days after first contact with the index case.

Nasopharyngeal specimens were collected from the index case on 3 February and from four close contacts on 7 and 8 February. DNA and RNA were extracted from the swab specimens using the QIAamp MinElute virus spin kit (Qiagen). Commercially available multiplex PCR assays (Seeplex RV15 ACE and PneumoBacter ACE; Seegene, South Korea) were used to test for respiratory pathogens; the results showed that the index case and the four close contacts were not infected by bacteria but were positive for HAdV. Then, a portion of the hexon gene was amplified and sequenced as described by Madisch et al. (11). Nucleotide BLAST analysis of the sequences revealed that they were all HAdV7. Comparison of the nucleic acid sequences of samples from these patients indicated that the isolates were 100% identical, strongly suggesting that all isolates were derived from a common ancestor (HAdV_7_309-1B from the index case). To assess the genetic relationships of different virus serotypes and determine their origin,

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TABLE 1 Patient characteristics and laboratory results

Patient	Age (yr)	Underlying condition	Clinical symptoms	Laboratory results	X-ray results	Outcome
Index case	23	None	Fever, cough, sore throat	Neutrophilia, 71.94%; C-reactive protein, 19 mg/ml	Increase of right lung markings; later, lung consolidation developed	Death
1	19	None	Fever, sore throat	Mononucleosis, 11.14%; lymphocytosis, 54.24%	Normal	Recovered after 6 days of hospitalization and was discharged 7 days later
2	29	Acute pancreatitis, fatty liver	Fever	Normal leukocyte count; mononucleosis, 11.74%	Pulmonary shadows	Recovered after 9 days of hospitalization and was discharged 7 days later
3	29	None	Fever, sore throat	Normal leukocyte count; mononucleosis, 10.74%	Normal	Recovered after 6 days of hospitalization and was discharged 7 days later
4	12	Respiratory infections	Fever	Mononucleosis, 10.85%; lymphocytosis, 52.68%	Normal	Recovered after 7 days of hospitalization and was discharged 7 days later

phylogenetic analysis of the partial sequences was performed (Fig. 2A and B). Strain HAdV_7_309-1B displayed one substitution at position 1228 of the hexon gene, which was a silent mutation. The strains identified in this report are closely related to the predominant HAdV7 isolates reported in China in recent years (12).

As shown by the case described above, early identification and treatment of adenovirus infection is vital. Initially, the index case only presented with mild acute respiratory symptoms. However, without prompt treatment, the viral load may increase by replication in human lungs, leading to severe pneumonia (13, 14). There are no approved antiviral agents with proven efficacy for the treatment of severe pneumonia caused by HAdV (15). Thus, the patient's condition deteriorated quickly even after later antiviral and hormone therapy. In contrast, the other four patients recovered well after timely antiviral treatment with ribavirin. The combined use of Chinese patent medicines (Lianhua Qingwen capsule and

Radix Isatidis) that have antiviral curative effects may also have played a role.

Nosocomial control of HAdV7 transmission is another challenge faced by health care centers. HAdV7 transmission generally occurs through respiratory droplets and close contact, which can lead to rapid and wide-spread infection. Large community and regional outbreaks of acute respiratory disease with an increased incidence of severe and fatal outcomes caused by HAdV7 have been described in Europe and Asia (7, 12, 16, 17). Thus, control of HAdV7 spread is crucial. However, it is difficult to differentiate pneumonia caused by HAdVs from other types of viral pneumonia, and culturing and typing of HAdVs are not routinely performed in hospitals (18). Therefore, the inevitable delay of several

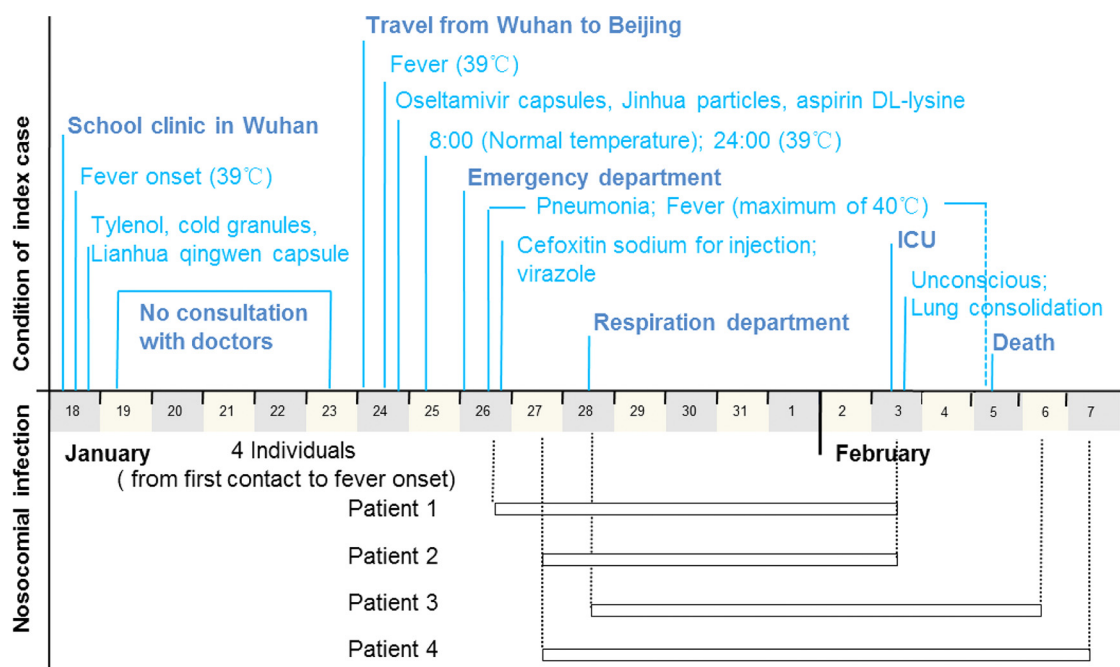


FIG 1 Timeline of critical events for the index patient and nosocomial infection. (Top) Key events during the index patient's illness are shown. (Bottom) Each bar indicates the period for an infected patient from first contact with the index case to symptom onset.

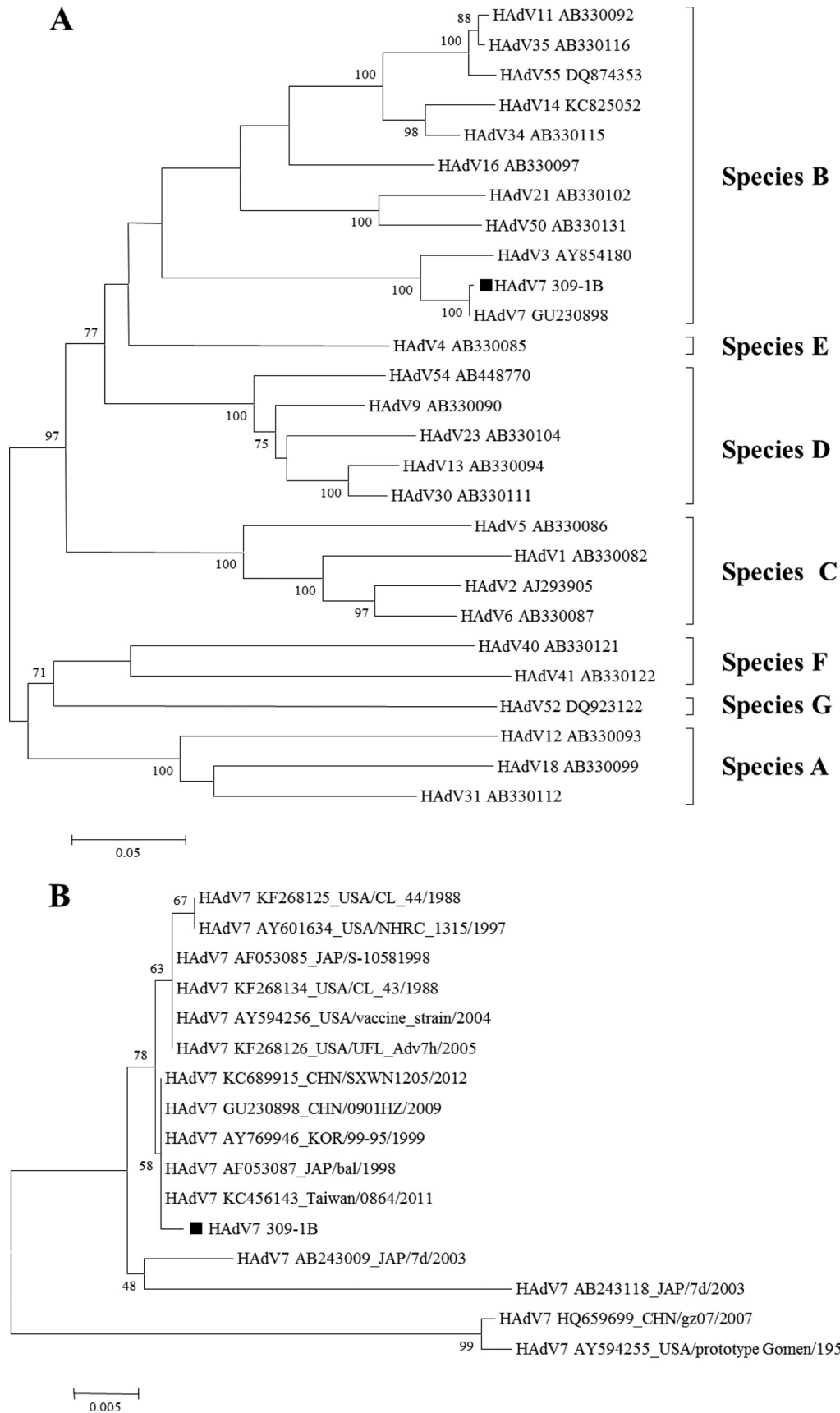


FIG 2 Phylogenetic analysis of a portion of the hexon gene for strain HAdV7 309-1B described in this study and other reference strains of adenovirus. The phylogenetic tree was generated using the neighbor-joining method. Bootstrap values are shown at branching points. Scale bars indicate nucleotide substitutions per site. (A) Strains HAdV7 309-1B compared to other subgenotype of HAdV reference strains; (B) HAdV7 309-1B compared to other HAdV7 reference strains.

days in the recognition of HAdV infections probably promoted the transmission. One study of adenovirus infection reported the incubation period to be 5 to 6 days (19), and another study of secondary infections in families found the mean incubation period to be 10 days (20). In this study, therefore, it was concluded that patient 4, who developed fever 11 days after first contact with the index case, was also infected by him. When the pathogen was identified, an infection control response was initiated immediately, on 8 February. Efforts to prevent the spread of HAdV7 included the use of disposable gowns and gloves, strict hand hygiene, and disinfection of common areas, such as floors and toilets. Furthermore, the four patients with HAdV7 infection were transferred to single rooms. The symptomatic patients had recovered well after 5 to 8 days of hospitalization and were discharged after 7 days of isolation.

In summary, we suggest that more importance should be given to the early diagnosis and treatment and proper transmission control of HAdV7, which causes acute respiratory illness. Therefore, hospitals should improve their diagnostic capabilities for rapid detection of HAdV infection, as well as their infrastructure to institute proper case management and transmission control.

Nucleotide sequence accession numbers. The hexon gene sequences of the isolates were deposited in the GenBank database (accession numbers [KJ783432](#) to [KJ783436](#)).

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The authors declare that they have no competing interests.

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