Original article

Clinical characteristics of adenovirus associated lower respiratory tract infection in children

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Background: **Acute lower respiratory tract infection (ALRI) due to adenovirus infection is a low frequency event but often causes severe outcome. This study was undertaken to uncover the clinical and epidemiological features of adenovirus infection in children.**

Methods: **Hospitalized children with ALRI were analyzed through continuous monitoring from 2006 to 2012. Nasopharyngeal aspirates were examined by direct immunofluorescence to detect respiratory agents including respiratory syncytial virus, adenovirus, influenza virus types A/B, parainfluenza virus types 1/2/3. *Chlamydia pneumonia*, *Mycoplasma pneumonia* and *Chlamydia trachomatis* were determined by real-time PCR. A retrospective analysis was made of 479 patients with positive infection of adenovirus.**

Results: **The positive detection rate of adenovirus was 0.63% in patients with ALRI. The incidence rate of adenovirus-associated acute lower respiratory tract infection peaked at the second six months of life. The morbidity was much higher in winter, spring and summer than in autumn. Patients with pneumonia accounted for 73.90% of the patients. More than one-third of the patients developed severe pneumonia, whereas no death was found. Features of severe adenovirus-associated lower respiratory tract infection included persistent high fever with serious infective symptoms, and hepatic dysfunction was one of the most common complications. Mixed infection of atypical pathogens was common (18.58%) in this study.**

Conclusions: **Adenovirus is a critical pathogen that can cause severe respiratory infections even in immunocompetent children. Coinfection of adenovirus with atypical pathogens is common. Antibiotic treatment with azithromycin or erythromycin is necessary in patients with mixed infection of atypical pathogens.**

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Key words: **adenovirus;**
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Introduction

Infection with adenovirus occurs worldwide and has been associated with 3%-5% of cases of acute lower respiratory tract infection (ALRI) in infants and children.[1-3] Although the positive detection rate of adenovirus in patients with respiratory infection is low, its fatal infections in immunocompromized patients arise considerable attention of pediatricians.[4,5] Currently, there are no drugs or vaccines available for the treatment of adenovirus infection. The condition of mixed infection of atypical pathogens in patients with adenovirus infection remains less understood, not to mention whether severe form of respiratory illness in adenovirus infected patients is related to this co-infection state. Here we investigated the clinical features of adenovirus associated ALRI as well as the co-infection state of adenovirus with mycoplasma and chlamydia in hospitalized children, which may provide us a basis for early clinical diagnosis or forecasting the severe condition of adenovirus infection.

Methods

Patients

The study was performed from July 2006 to June 2012 at the Children's Hospital, Zhejiang University School of Medicine. Children hospitalized for ALRI were enrolled in this study. Recognition of pediatric ALRI was based on the diagnosis of bronchitis, bronchiolitis and pneumonia.

Clinical manifestations of ALRI

ALRI was defined as respiratory symptoms lasting less than 3 weeks. Patients with chronic lung or heart

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diseases, and primary or secondary immunodeficiency were excluded. Physicians categorized the patients into groups of lower and upper respiratory tract infections according to the clinical manifestations described in the *Nelson Textbook of Pediatrics*.[6] Chart review collected by physicians was classified in two clinical ALRI episodes: non-severe ALRI and severe ALRI. The severity of ALRI was defined according to the World Health Organization criteria (Table).[7] Children who met ≥1 major or ≥2 minor criteria were considered as having severe pneumonia.

Specimens

Nasopharyngeal samples were collected on admission by inserting a nasogastric tube into the nasopharynx and aspirating with a vacuum constriction device. The aspirates were then made into slides, each of which should have at least 20 exfoliative cells. The aspirates were placed in a universal transport medium and stored at 4°C until being sent to the central laboratory of the hospital for analysis.

Table. Criteria for severity of acute lower respiratory tract infection in children

Criteria	
Major criteria	Invasive mechanical ventilation
	Fluid refractory shock
	Acute need for NIPPV
	Hypoxemia
Minor criteria	Respiratory rate higher than the World Health Organization classification for age
	Apnea
	Increased work for breathing (retractions, dyspnea, nasal flaring)
	PaO_2/FiO_2 ratio <250
	Multilobar infiltrates
	Altered mental status
	Hypotension
	Presence of effusion
	Unexpected metabolic acidosis

NIPPV: noninvasive positive pressure ventilation; FiO_2: function of inspired oxygen; PaO_2: arterial oxygen pressure.

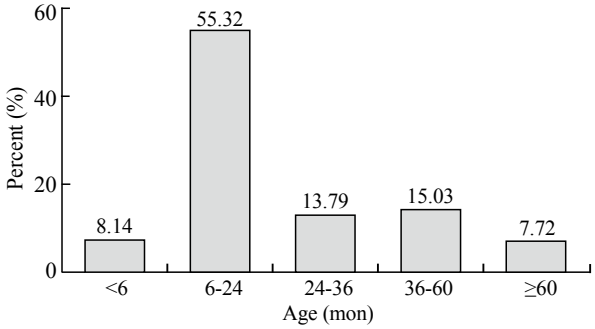

Fig. The constitution of different age in adenovirus positive lower respiratory tract infection.

Detection of viral antigens and atypical pathogens

Adenovirus, influenza A, influenza B, parainfluenza-type 1, 2, 3 and respiratory syncytial virus were identified qualitatively by the Chemicon immunofluorescence assay (IFA, respiratory viruses panel and identification kit). The slides were examined under magnification of 200 times with a fluorescent microscopy. Positive staining was represented by the presence of at least two intact cells with a type of fluorescent for certain virus. Atypical pathogens (*Chlamydia pneumonia*, *Mycoplasma pneumonia*, *Chlamydia trachomatis*) in nasopharyngeal aspirates and broncho-alveolar lavage fluid were detected using real-time PCR following the manufacturer's instructions (CP/MP/CT Fluorescent Polymerase Chain Reaction Diagnostic Kit).

Bronchoscopy and broncho-alveolar lavage procedure

Fiberoptic bronchoscopy was considered in patients with large patchy of pneumonia and persistent high fever for ≥7 days. Flexible fiberoptic bronchoscopy was performed in 55 patients who had severe symptoms with suspected mucus obstruction of airways, persistent atelectasis, and/or persistent infiltrates. Broncho-alveolar lavage was performed either in an area most prominently affected on the chest radiographs or sputum obstruction in the airway. Boluses of 1 mL/kg of sterile, nonbacterio-static saline at room temperature were instilled through the instrumentation channel.[8] The broncho-alveolar lavage fluid was gently aspirated immediately after each aliquot and collected in a sterile container and immediately placed on 4°C.

Statistical analysis

All statistical analyses were performed using SPSS software (version 16). Data were presented as the percentage or mean±SD. The Poisson method was used to compare between-group differences. A *P* value less than 0.05 was considered statistically significant.

Results

Demographics

During the study period, we investigated 76 518 patients with ALRI, of which 479 were confirmed with adenovirus infection (a positive isolation rate of 0.63%). Of the 479 patients, 331 were boys and 148 girls (a male-female ratio of 2.24:1). The age distribution of adenovirus-ALRI is shown in the Fig. The hospitalized children with adenovirus-ALRI ranged from one month to 172 months, with a median age of 16 months. The highest occurrence of adenovirus-ALRI was in the first year of life and peaked at the second six months (55.32%).

Clinical features of adenovirus-ALRI

In all patients with adenovirus-ALRI, those with pneumonia accounted for 73.90% and the rest had tracheobronchitis or laryngotracheitis. Over 90% of the patients had fever with irregular patterns (the temperature curve was intermittent without certain rule) and most of them had a high fever (>39°C) persisting for about 8 days (8.67±4.31). A quarter of the patients experienced wheezing. The complications of adenovirus-ALRI included respiratory failure (36/479), encephalopathy (36/479), cardiac failure (29/479), myocardial damage (6/479), pneumothorax (2/479), hemoptysis (1/479) and hematemesis (1/479). Serum biochemical test revealed abnormal function of the liver in 115 patients, in whom 45 had hepatosplenomegaly shown by abdominal ultrasonography. The mean length of hospital stay for patients with adenovirus-ALRI was 10.79±7.26 days. Sixty-two patients were transferred to intensive care unit or critical ward, and 18 of them needed mechanical ventilation, but no deaths occurred in this study.

Chest radiograph

Chest X-ray or computed tomography scan was taken on admission for each child. Repeated radiographs were done within 5 days when the disease was progressed. Increased shadowing occurs either in a widespread pattern or in an anatomical pattern with patchy infiltrates. Integration lesions or pneumonic consolidation was common. Some patients (95/475) developed large patchy of pneumonia which often occurred in the superior lobe of the right lung or in the inferior lobe of the left lung. Multiple segmental pneumonia (52/479) and pleural effusion (13/479) were not rare in adenovirus-ALRI patients.

Bronchoscopy and broncho-alveolar lavage

Fifty-five of all 95 patients who had large patchy of pneumonia with a persisted high fever for ≥7 days were examined by bronchoscopy and broncho-alveolar lavage. Bronchial inflammatory change or sputum obstruction was observed under a bronchoscope. Patients who underwent broncho-alveolar lavage showed improved respiratory symptoms including fever, cough, tachypnea and rales during pulmonary auscultation.

Coinfection of adenovirus with atypical pathogens

The rate of adenovirus mixed infection with atypical pathogens was 18.58% (89/479) in nasopharyngeal aspirates of the patients. Most of the patients were co-infected with *Mycoplasma pneumonia* (79/89, 88.76%), and five patients were positive for *Chlamydia pneumonia* and *Chlamydia trachomatis* (5/89, 5.62%). *Mycoplasma pneumonia* was positive in broncho-alveolar lavage fluid of 6 of 55 patients, but no patients were positive for *Chlamydia pneumonia* or *Chlamydia trachomatis* pathogen.

Discussion

The detection rate of adenovirus in ALRI patients (0.63%) was much lower in this study than in the other reports. In some tropical countries such as Cambodia, adenovirus was detected in 3% of ALRI in children of less than five years old.[9] In Oman, the detection rate of adenovirus was about 7.7% in hospitalized infants and young children with acute respiratory infection.[10] The lower detection rate in our study was partly due to the testing method as the immunofluorescence method we used was more specific but less sensitive than PCR. On the other hand, the patients enrolled in this study had a broader age spectrum (from one month to 172 months) than other studies, which may reduce the positive rate relatively.

Previous studies[11-13] have indicated the importance of adenovirus as a potential pathogen in severely immunocompromized children. In this study, over one-third of these adenovirus-infected patients with normal immune function developed severe diseases. The clinical manifestations varied. In addition to the manifestations of primary infected lesion, serious infective symptoms, including persistent high-fever, mental fatigue, headache and drowsiness, were most prominent. Another feature of adenovirus-ALRI was its chest radiograph performance, showing consolidation or integration lesions in the right upper or left lower lobe. Although unspecific, those comprehensive chest X-ray performances were indicative of aggressive clinical course of adenovirus diseases.

In our study, we found that hepatic dysfunction, followed by myocardial damage and central nervous system impairment, was the most common short-term complication of adenovirus-ALRI. In one of the related studies, researchers found that necrotizing bronchitis and bronchiolitis with diffuse alveolar damage were the most important findings in patients who died of adenovirus infection.[14] Bronchiectasis may occur in over a quarter of children with adenovirus pneumonia.[15] Chronic adenovirus infection was speculated to play an etiological role in the development of bronchopulmonary dysplasia and asthma.[16] Because of the limitations of research conditions, we did not conduct the forward evaluation of adenovirus-ALRI.

Respiratory pathogen co-infection is common in ALRI patients.[17,18] It is speculated that an additional respiratory pathogen infection can increase clinical

manifestations leading to hospitalization of a patient with *Mycoplasma pneumonia* and is linked to higher emergence of complications.[19] In our study, the incidence of adenovirus co-infected with atypical pathogens was not rare, and *Mycoplasma pneumonia* infection appeared in the first. *Mycoplasma pneumonia* is supposed to be able to act as a cofactor in severe respiratory disease by facilitating alterations in local respiratory immunity or in structure and function of epithelial cells.[20] In our study, there were no distinguishing features between adenovirus infected and co-infected patients. Since this speculation was dependent on a limited number of co-infected cases, larger and prospective studies are needed.

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References

1 Schmitz H, Wigand R, Heinrich W. Worldwide epidemiology of human adenovirus infections. Am J Epidemiol 1983;117:455-466.
2 Kim YJ, Hong JY, Lee HJ, Shin SH, Kim YK, Inada T, et al. Genome type analysis of adenovirus types 3 and 7 isolated during successive outbreaks of lower respiratory tract infections in children. J Clin Microbiol 2003;41:4594-4599.
3 Guerrier G, Goyet S, Chheng ET, Rammaert B, Borand L, Te V, et al. Acute Viral Lower Respiratory Tract Infections in Cambodian Children Clinical and Epidemiological Characteristics. Pediatr Infect Dis J 2013;32:e8-13.
4 Nakazawa H, Ito T, Makishima H, Misawa N, Okiyama W, Uehara T, et al. Adenovirus fulminant hepatic failure: disseminated adenovirus disease after unrelated allogeneic stem cell transplantation for acute lymphoblastic leukemia. Intern Med 2006;45:975-980.
5 Ozbay Hoşnut F, Canan O, Ozçay F, Bilezikçi B. Adenovirus infection as possible cause of acute liver failure in a healthy child: a case report. Turk J Gastroenterol 2008;19:281-283.
6 Orenstein DM. Acute inflammatory upper airway obstruction. In: Behrman RE, Kliegman RM, eds. Nelson textbook of pediatrics. 16th ed. Philadelphia: Pennsylvania, 2000: 1274-1279.
7 World Health Organization. A programme for controlling acute respiratory infections in children. Memorandum from a WHO meeting. Bull World Health Organ 1984;62:47-58.
8 Tang LF, Xu YC, Wang YS, Wang CF, Zhu GH, Bao XE, et al. Airway foreign body removal by flexible bronchoscopy: experience with 1027 children during 2000-2008. World J Pediatr 2009;5:191-195.
9 Guerrier G, Goyet S, Chheng ET, Rammaert B, Borand L, Te V, et al. Acute viral lower respiratory tract infections in Cambodian children: clinical and epidemiologic characteristics. Pediatr Infect Dis J 2013;32:e8-13.
10 Khamis FA, Al-Kobaisi MF, Al-Areimi WS, Al-Kindi H, Al-Zakwani I. Epidemiology of respiratory virus infections among infants and young children admitted to hospital in Oman. J Med Virol 2012;84:1323-1329.
11 Hierholzer JC. Adenoviruses in the immunocompromised host. Clin Microbiol Rev 1992;5:262-274.
12 Chakrabarti S, Mautner V, Osman H, Collingham KE, Fegan CD, Klapper PE, et al. Adenovirus infection following allogeneic stem cell transplantation: the incidence and outcome in relation to graft manipulation, immunosuppression and immune recovery. Blood 2002;100:1619-1627.
13 Walls T, Hawrami K, Ushiro-Lumb I, Shingadia D, Saha V, Shankar AG. Adenovirus infection after pediatric bone marrow transplantation: is treatment always necessary? Clin Infect Dis 2005;40:1244-1249.
14 Siminovich M, Murtagh P. Acute lower respiratory tract infections by adenovirus in children: histopathologic findings in 18 fatal cases. Pediatr Dev Pathol 2011;14:214-217.
15 Similä S, Linna O, Lanning P, Heikkinen E, Ala-Houhala M. Chronic lung damage caused by adenovirus type 7: a ten-year follow-up study. Chest 1981;80:127-131.
16 Smyth A. Pneumonia due to viral and atypical organisms and their sequelae. Br Med Bull 2002;61:247-262.
17 Ruuskanen O, Mertsola J. Childhood community-acquired pneumonia. Semin Respir Infect 1999;14:163-172.
18 Debiaggi M, Canducci F, Ceresola ER, Clementi M. The role of infections and coinfections with newly identified and emerging respiratory viruses in children. Virol J 2012;9:247.
19 Peng D, Zhao D, Liu J, Wang X, Yang K, Xicheng H, et al. Multipathogen infections in hospitalized children with acute respiratory infections. Virol J 2009;6:155.
20 Cimolai N, Wensley D, Seear M et al. Mycoplasma pneumonia as cofactor in severe respiratory infections. Clin Infect Dis 1995;21:1182-1185.

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