Risk factors associated with hospital admission among healthy children with adenovirus infection

Punkaj Gupta[1,2], Sunali Goyal[3], Joseph D. Tobias[4,5], Parthak Prodhan[1], Prashant Purohit[2], Jeffrey M. Gossett[6], Vinca Chow[7], Natan Noviski[2]

[1]Section of Pediatric Cardiology and Critical Care, and [6]Biostatistics Program, Department of Pediatrics, [3]Department of Ophthalmology, University of Arkansas Medical Center, Little Rock, Arkansas, and [2]Division of Pediatric Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, and [4,5]Departments of Anesthesiology and Pediatrics, Nationwide Children's Hospital and the Ohio State University, Columbus, Ohio, and [7]Department of Medical Education, Stanford University Medical Center, Palo Alto, California, USA

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Adenovirus infections mimic bacterial infections on initial presentation in healthy children, leading to higher likelihood of hospital admission. The objective of this study was to identify risk factors associated with hospital admission in previously healthy children with adenovirus infection. This is a retrospective study of 125 previously healthy children, who tested positive with direct immunofluorescence assay (DFA) for adenoviral infection at our center between January 2001 and October 2007. The primary outcome of the study was the need for hospital admission. The relationship between clinical variables at initial emergency room (ER) presentation and need for hospital admission were explored using univariate and multivariate logistic regression models. The model's predictive value was investigated by calculating the area under the receiver operating characteristic (ROC) curve and Hosmer-Lemeshow test.

On stepwise multivariate logistic regression analysis, the presence of respiratory distress (odds ratio [OR]: 5.6; p=0.014), acute gastroenteritis (OR: 3.8; p=0.019) and wheezes at initial presentation (OR: 6.5; p=0.003) at the time of initial presentation in the ER were associated with need for hospital admission. For this model, the area under the ROC curve was 0.79, and there was no evidence of lack of fit on Hosmer-Lemeshow goodness-of-fit test (p=0.56). Our study identifies three risk factors, namely, respiratory distress, wheezing and acute gastroenteritis, associated with hospital admission for healthy children with adenoviral infections.

Key words: adenovirus, hospital admission, respiratory distress, wheezing, acute gastroenteritis.

Adenovirus infections occur primarily in infants and children less than five years of age. It accounts for 2-5% of all pediatric respiratory illnesses and 4-10% of childhood pneumonias[1]. The majority of children with adenovirus infection develop mild upper respiratory tract disease. Those with more severe lower respiratory tract infection (LRTI) may develop either acute pneumonitis and/or bronchiolitis. Many with a more severe clinical presentation may additionally have acute extrapulmonary manifestations, which include keratoconjuctivitis, hemorrhagic cystitis, gastroenteritis, meningoencephalitis, hepatitis, myocarditis, and life-threatening disseminated disease[2-4].

Various risk factors associated with a higher likelihood of developing severe adenoviral infection include prematurity, a younger age at presentation, presence of malnutrition or immunodeficiency, daycare attendance, environmental crowding, or the presence of a preceding viral disease[3-7]. However, none of these previous studies has assessed risk factors at initial presentation in the emergency room (ER) among healthy children with adenovirus

infection that are associated with need for hospital admissions. This is in contrast to some other well-studied viruses in children, such as respiratory syncytial virus (RSV), where several demographic, environmental and clinical characteristics are associated with a more severe clinical course and hospital admission[8-15]. Therefore, this study aimed to identify risk factors associated with a need for hospital admission in previously healthy children with adenovirus infection.

Material and Methods

Study Design and Population

This retrospective study was approved by the Institutional Review Board (IRB) of the Massachusetts General Hospital (MGH), and the criteria for informed consent were waived. All potential study subjects were identified using the microbiology records for patients who tested positive by direct immunofluorescence assay (DFA) for adenovirus during the study period. The study included all children between the ages of 1 day and 18 years who presented to the ER at MGH between January 2001 and October 2007and had a positive nasopharyngeal DFA for adenoviral infection. Patients with a history of prematurity (defined as <36 weeks of gestation), other comorbid conditions (known immunodeficiency, cardiac anomaly, chronic lung disease, neuromuscular disease, and chromosomal abnormalities), and those transported directly to the in-patient wards from outside hospitals were excluded from the study. Data on demographic features, clinical symptoms and signs, laboratory findings, and radiographic findings were collected from ER records. Data for those patients requiring subsequent hospital admission were obtained from their in-patient medical records.

Outcome Measurement and Definitions

The need for hospital admission from the ER was our defined primary outcome. This endpoint was chosen as it represents a surrogate marker of severity of illness. The need for hospital admission has been used previously to depict disease severity in RSV infection[8-15]. Children were classified as 'hospitalized' if they were admitted to the hospital with adenoviral infections within the study period. Based on the clinical condition of the patient in the ER, the need for hospitalization was based on the physicians' discretion. *A priori*-defined criteria for diagnosis of upper respiratory tract infection (URTI) included symptoms and signs of rhinitis, pharyngitis, conjunctivitis, and/or acute otitis media, while LRTI was diagnosed based on the presence of clinical symptoms and signs of pneumonia, bronchitis or bronchiolitis. Bacterial and/or viral co-infection was defined as the presence of concurrent culture-proven/serology-positive infection with another respiratory pathogen within 72 hours of a positive adenovirus DFA test. Chest radiograph findings at the time of initial presentation were categorized as either 'Hyperinflation' or 'Infiltrate' by a single experienced investigator blinded to the patient's diagnosis and other clinical variables.

Statistical Analysis

Continuous variables were presented as median (range), whereas categorical variables were presented as numbers and percentages. Initially, a univariate analysis to examine the relationship between the variables and the primary outcome variable (i.e., need for hospital admission) was performed using the Wald test. The p-value was calculated using chi-square test of independence for categorical variables and Wilcoxon rank-sum test for continuous variables. Our results were then used to carry out a multiple logistic regression analysis to predict hospital admission for patients presenting in the ER with adenoviral infection. Variables with a p-value of ≤0.2 in the univariate analysis or that were considered important for the outcome *a priori* were entered in the first multiple regression model. A Hosmer-Lemeshow approach to model building was used to construct multivariable models. Any variable with ≥20% missing values, and/or that was exceedingly rare (<5 subjects with characteristic in either cases or controls) were not considered for inclusion into the multivariate models. The model was expressed in terms of adjusted odds ratio (OR), 95% confidence interval (CI) and p-value using Wald chi-square test. A reduced multivariate model for hospital admission was created using backward selection to reduce the number of variables in the first model. A significance level of 0.05 was applied for removal of variables

Table I. Comparison of Sample Characteristics with Unadjusted Odds Ratios for Need for Hospital Admission

Variable	N	Non-hospitalized patients (N=99)	Hospitalized patients (N=26)	P-value
Male gender	125	21% (21)	31% (8)	0.3
Age ≤ 6 months	125	4% (4)	8% (2)	0.44
Weight ≤11.5 kg	125	51% (50)	35% (9)	0.15
Family history	73	32% (18)	38% (6)	0.66
Medications at home	119	86% (80)	85% (22)	0.86
Exposure to sick contacts	125	45% (45)	31% (8)	0.18
Fever	123	98% (96)	100% (25)	0.47
Pulse oximetry	68	98.3±1.4	94.9±7.2	0.14
Upper respiratory tract infection	125	88% (87)	96% (25)	0.22
Apnea	124	1% (1)	4% (1)	0.31
Respiratory distress	124	6% (6)	31% (8)	<0.001
Skin rash	125	11% (11)	12% (3)	0.95
Acute gastroenteritis	124	45% (44)	65% (17)	0.063
Wheezes	125	8% (8)	38% (10)	<0.001
Crackles	124	4% (4)	16% (4)	0.03
Tachypnea	69	24% (11)	38% (9)	0.26
Tachycardia	110	32% (27)	36% (9)	0.69
Seizures	123	3% (3)	8% (2)	0.26
Altered mental status	125	6% (6)	8% (2)	0.76
Pyuria	125	11% (11)	19% (5)	0.27
Viral coinfection	125	4% (4)	4% (1)	0.96
Bacterial coinfection	125	6% (6)	12% (3)	0.34
Hyperinflation on chest radiograph	43	25% (6)	47% (9)	0.13
Infiltrates on chest radiograph	43	29% (7)	42% (8)	0.38

from the expanded model. When the final model was identified, factors that had not been retained in the model were re-evaluated for inclusion. Several additional analyses were performed to explore the findings of the final multivariate model. The model's goodness-of-fit was evaluated using the Hosmer-Lemeshow test, and the discrimination of the model was assessed using the area under the receiver operating curve (ROC). All analyses were performed using the STATA/MP, Version 11.1 (Stata Corp LP, College Station, Texas).

Results

Baseline Characteristics

During the study period from January 2001 to October 2007, 171 children were diagnosed with adenovirus infection in the ER at MGH. Of the 171 children, 125 previously healthy children fulfilled our inclusion criteria. Forty-seven children were excluded from the analysis . those with a history of prematurity (n=16), chronic lung disease (n=9), underlying cardiac disease (n=4), underlying immunodeficiency disease (n=2), underlying chromosomal abnormality (n=8), and underlying neuromuscular disease (n=8). The majority in the study cohort were females (77%). The cohorts' median age and weight were 22 months (range: 2 months to 9.8 years) and 11.8 kg (range: 4.6 kg to 9.8 kg), respectively. Of the 125 patients, 26 (21%) required hospital admission, with the median length of hospital stay of 3.5 days (range: 1 day to 292 days). Twenty-three (88%) patients were admitted to the general pediatric ward and 3 (12%) required admission to the pediatric intensive care unit (PICU) with a median length of hospital stay of 3 days (range: 1 day to 6 days) and 11 days (range: 4 days to 292 days), respectively.

Risk Factors Associated with Hospital Admission

Table I depicts the demographics, clinical characteristics, univariate comparisons, and unadjusted ORs based on univariate logistic regressions. The variables found significant ($p<0.05$) on univariate analysis included presence of respiratory distress ($p<0.001$), acute gastroenteritis ($p=0.063$), wheezes ($p<0.001$), and crackles ($p=0.03$). Additional variables with p value ≤0.2 in the univariate analysis included exposure to sick contacts ($p=0.18$), pulse oximetry ($p=0.14$), hyperinflation on chest radiograph ($p=0.13$), and body weight ≤11.5 kg ($p=0.15$). Pulse oximetry and hyperinflation on chest radiograph were dropped from the first multivariate model, as more than 20% of values were missing from the dataset. A chest radiograph was performed in only 43 patients (34%). Focal and/or diffuse pulmonary bilateral infiltrates on chest radiograph were diagnosed in 15 children (35%), and the difference between the two groups was not statistically significant ($p=0.38$). Similarly, hyperinflation on chest radiograph was also diagnosed in 15 children (35%) and was not statistically significant between the two groups ($p=0.13$). Though the median values of pulse oximetry were different in the two groups (94.9±7.2 versus 98.3±1.4 in hospitalized versus non-hospitalized patients), it was not statistically significant ($p=0.14$). Age ≤6 months was considered clinically important *a priori* and therefore included in the multivariate model.

A multivariable logistic regression model (Table II) was developed to identify independent risk factors associated with hospital admission. The variables included in the model included age ≤6 months, weight ≤11.5 kg, respiratory distress, acute gastroenteritis, wheezes, exposure to sick contacts, and presence of crackles as predictors. Controlling for other variables in the model, the odds of hospital admission were 5.6 times higher (95% CI: 1.2 to 25.2) for subjects with respiratory distress ($p=0.025$), 3.2 times higher (95% CI: 1.0 to 10.9) for subjects with acute gastroenteritis ($p=0.059$), 9.3 times higher (95% CI: 2.3 to 36.7) for subjects with wheezes ($p=0.002$), and 1.4 times higher (95% CI: 0.2 to 9.2) for subjects with crackles ($p=0.703$). For this model, the area under the ROC curve was 0.82, and there was evidence of a good fit as suggested by the Hosmer-Lemeshow goodness-of-fit test ($p=0.25$).

Another model based on a stepwise multivariate logistic regression analysis was built (Table III). In this model, only the presence of respiratory distress, acute gastroenteritis and wheezes at initial presentation were independently associated with hospital admission. Controlling for other variables in the model, the odds of admission were 5.6 times higher in children with respiratory distress (95% CI: 1.4 to 22.4, $p=0.014$), 3.8 times higher in children with acute gastroenteritis (95% CI: 1.2 to 11.6, $p=0.019$), and 6.5 times higher in children with wheezes (95% CI: 1.9 to 22.6, $p=0.003$). For this model, the area under the ROC curve was 0.79 (Fig. 1), and there was evidence of good fit for the model as suggested by the Hosmer-Lemeshow goodness-of-fit test ($p=0.56$).

Therapies in Adenovirus Infection

Table IV shows the treatment characteristics in the ER for our study cohort. Approximately one-third (38%) of patients in our cohort of 125 children received antibiotic therapy. Hospitalized children received therapies much more frequently as compared to non-hospitalized children: antibiotic therapy (62% versus 49%, $p<0.005$), oxygen therapy (35% versus 0, p=NA), nebulizations (35% versus 6%, $p<0.001$), and corticosteroids (65% versus 3%, $p<0.001$).

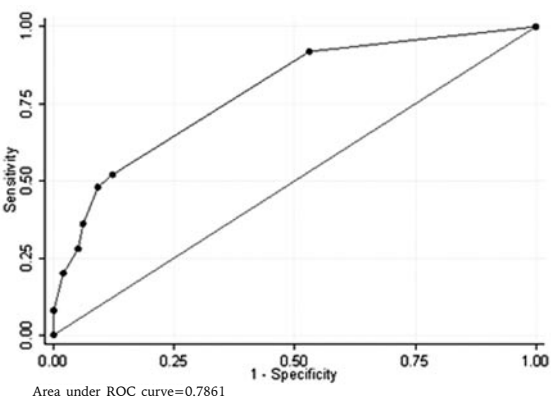

Figure 1. Receiver Operating Curve (ROC) for final model with respiratory distress, acute gastroenteritis, and wheezes as predictors.

Table II. Preliminary Multivariable Model Identifying Clinical Risk Factors for Hospital Admission in Healthy Children with Adenovirus Infection

Predictor	Odds Ratio	P-value	95% Confidence Interval	
Age ≤6 months	0.6	0.703	0.0	9.8
Weight ≤11.5 kg	0.5	0.27	0.2	1.7
Exposure to sick contacts	0.4	0.084	0.1	1.1
Respiratory distress	5.6	0.025	1.2	25.2
Wheezes	9.3	0.002	2.3	36.7
Crackles	1.4	0.735	0.2	9.2
Acute gastroenteritis	3.2	0.059	1.0	10.9

Discussion

The principal observation from this institution-specific study is that the presence of specific risk factors, namely, respiratory distress, acute gastroenteritis and wheezing, at the initial ER presentation may predict hospital admission, a surrogate for severe disease among previously healthy, adenovirus-infected children.

Previously, various authors have shown severe adenoviral disease to be associated with presentation at a younger age, presence of malnutrition or immunodeficiency, day care attendance, environmental crowding, lower socioeconomic status, or history of a preceding viral illness[1,5-7,16]. In contrast, we did not find any association of hospital admission related to gender, young age, body weight, exposure to sick contacts, or family history of reactive airway disease. In our cohort, only 21% of patients required hospital admission. This is much lower compared to the overall hospital admission rate (56%) reported by Rocholl et al[3]. In their study of 143 children, the hospital admission rate was about 50% among previously healthy children and 83% among those with underlying comorbidities.

Table III. Final Reduced Multivariable Model Identifying Clinical Risk Factors for Hospital Admission in Healthy Children with Adenovirus Infection, Using Backward Selection Method

Predictor	Odds Ratio	P-value	95% Confidence Interval	
Respiratory distress	5.6	0.014	1.4	22.4
Wheezes	6.5	0.003	1.9	22.6
Acute gastroenteritis	3.8	0.019	1.2	11.6

Respiratory distress and wheezing were found to be significant risk factors associated with need for hospital admission in our study. As reported previously, respiratory distress with or without hypoxia may reflect a more severe lower respiratory tract disease with severe adenovirus infection[3,6,7,17]. However, in contrast to these reports, hypoxia was not a significant factor in our cohort. Wheezing is a common occurrence in hospitalized children with adenovirus infection[18-20], and has been reported to occur in 18% to 23% of

Table IV. Treatment Characteristics of Children with Adenovirus Infections

Variable	Hospitalized patients (N=26)	Non-hospitalized patients (N=125)	P value
Oxygen	35% (9)	0	NA
Nebulizations	35% (9)	6% (7)	<0.001
Fluid boluses	65% (17)	3% (4)	<0.001
Antibiotics	62% (16)	49% (31)	0.005
Corticosteroids	27% (7)	2% (2)	<0.001
Vasopressors	4% (1)	0	NA
Mechanical ventilation	8% (2)	0	NA

children infected with adenovirus infection[18,20]. However, wheezing is not associated with the development of bronchiolitis obliterans (BO) in the post-adenovirus pneumonia phase[17].

Acute gastroenteritis was another risk factor associated with hospital admission in our study. It is known that human adenoviruses cause acute gastroenteritis in children worldwide. In a study of 400 cases of acute infantile gastroenteritis, enteric adenoviruses were the sole recognizable cause of diarrhea in 7.2% of the cases[21]. A review of another outbreak in several day care centers found that 38% of 249 young children had positive stool specimens for adenovirus[22]. Adenovirus may be excreted in the feces for months after a primary infection, and thus a positive stool culture for adenovirus is not usually a clinically significant cause of diarrhea. We speculate that acute gastroenteritis in children may be associated with poor oral intake and dehydration, making them more prone to be admitted by ER physicians. Similarly, children with wheezing and respiratory distress get admitted to the hospital more often than other children, as these two signs may be interpreted as signs of LRTI.

Adenoviral-positive children often mimic clinical and radiographic findings of bacterial infection[3,6,18,23]. As a result, the treatment in these children tends to very aggressive in the form of inappropriate antibiotic therapy, corticosteroids, nebulizations, oxygen therapy, and fluid boluses, eventually leading to higher likelihood of hospital admission. Severe adenovirus infection can also result in considerable morbidity and mortality[16]. In our study, three (12%) children needed PICU admission with the need for mechanical ventilation in only one (4%) patient. The patient who needed mechanical ventilation also received extracorporeal membrane oxygenation (ECMO) for 47 days and developed acute respiratory distress syndrome during the course of his prolonged hospitalization. Children who recover from adenoviral LRTIs may develop sequelae such as BO, bronchiectasis, unilateral hyperlucent lung syndrome, persistently collapsed lung, and abnormal pulmonary function tests[24-27].

This retrospective study has several limitations. First, this study was conducted in a tertiary care university hospital, and the findings may not be generalizable to all populations and regions, as regional variations in adenovirus disease genotype and severity have been well recognized previously. Second, the need for hospitalization was based on the physician's discretion, and this may have introduced some ascertainment bias in the study. Third, the principal method of diagnosis for adenovirus infection was DFA analysis, which could have missed another respiratory virus in the absence of back-up culture or more sensitive polymerase chain reaction (PCR) assays. Fourth, DFA analysis could have included healthy children who are 'carriers' of adenovirus in their nasopharynx. Fifth, typing of adenovirus isolates was not performed, and therefore conclusions cannot be drawn regarding the virulence of the various strains. Sixth, this study was also limited by missing ER documentation that was available for data collection. Seven, this study is limited in scope to addressing long-term sequelae, as we do not have long-term follow-up data for our study cohort. Given the limitations of our study, the current model needs to be validated in a future prospective multi-center clinical trial.

In conclusion, although most of the adenoviral infections are self-limited, it is important to identify serious adenoviral infection in previously healthy children, as it has the potential of rapid progression and increased morbidity and mortality. Our study identifies three risk factors, namely, respiratory distress, wheezing and acute gastroenteritis, associated with hospital admission in healthy children with adenoviral infections.

REFERENCES

1. Cherry JD. Adenoviruses. Textbook of Pediatric Infectious Diseases (4th ed). Philadelphia: WB Saunders; 1998: 1666-1684.
2. Baum S. Adenovirus. Principles and Practice of Infectious Diseases (6th ed) Vol 2. Philadelphia: Churchill Livingstone; 2005: 1835-1840.
3. Rocholl C, Gerber K, Daly J, Pavia AT, Byington CL. Adenoviral infections in children: the impact of rapid diagnosis. Pediatrics 2004; 113: e51-56.
4. Moro MR, Bonville CA, Suryadevara M, et al. Clinical features, adenovirus types, and local production of inflammatory mediators in adenovirus infections. Pediatr Infect Dis J 2009; 28: 376-380.
5. Schmitz H, Wigand R, Heinrich W. Worldwide epidemiology of human adenovirus infections. Am J Epidemiol 1983; 117: 455-466.

6. Farng KT, Wu KG, Lee YS, Lin YH, Hwang BT. Comparison of clinical characteristics of adenovirus and non-adenovirus pneumonia in children. J Microbiol Immunol Infect 2002; 35: 37-41.
7. Chuang YY, Chiu CH, Wong KS, et al. Severe adenovirus infection in children. J Microbiol Immunol Infect 2003; 36: 37-40.
8. Bulkow LR, Singleton RJ, Karron RA, Harrison LH. Risk factors for severe respiratory syncytial virus infection among Alaska native children. Pediatrics 2002; 109: 210-216.
9. Kaneko M, Watanabe J, Ueno E, Hida M, Sone T. Risk factors for severe respiratory syncytial virus–associated lower respiratory tract infection in children. Pediatr Int 2001; 43: 489-492.
10. Rietveld E, Vergouwe Y, Steyerberg EW, et al. Hospitalization for respiratory syncytial virus infection in young children: development of a clinical prediction rule. Pediatr Infect Dis J 2006; 25: 201-207.
11. Thorburn K. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. Arch Dis Child 2009; 94: 99-103.
12. Stretton M, Ajizian SJ, Mitchell I, Christopher JL. Intensive care course and outcome of patients infected with respiratory syncytial virus. Pediatr Pulmonol 1992; 13: 143-150.
13. Outwater KM, Crone RK. Management of respiratory failure in infants with acute viral bronchiolitis. Am J Dis Child 1984; 138: 1071-1075.
14. Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. J Pediatr 2003; 143: S112-117.
15. Green M, Brayer AF, Schenkman KA, Wald ER. Duration of hospitalization in previously well infants with respiratory syncytial virus infection. Pediatr Infect Dis J 1989; 8: 601-605.
16. Hong JY, Lee HJ, Piedra PA, et al. Lower respiratory tract infections due to adenovirus in hospitalized Korean children: epidemiology, clinical features, and prognosis. Clin Infect Dis 2001; 32: 1423-1429.
17. Castro-Rodriguez JA, Daszenies C, Garcia M, Meyer R, Gonzales R. Adenovirus pneumonia in infants and factors for developing bronchiolitis obliterans: a 5-year follow-up. Pediatr Pulmonol 2006; 41: 947-953.
18. García-García ML, Calvo C, Falcón A, et al. Role of emerging respiratory viruses in children with severe acute wheezing. Pediatr Pulmonol 2010; 45: 585-591.
19. Saçkesen C, Pınar A, Şekerel BE, Akyön Y, Saraçlar Y. Use of polymerase chain reaction for detection of adenovirus in children with or without wheezing. Turk J Pediatr 2005; 47: 227–231.
20. Chen HL, Chiou SS, Hsiao HP, et al. Respiratory adenoviral infections in children: a study of hospitalized cases in southern Taiwan in 2001–2002. J Trop Pediatr 2004; 50: 279–284.
21. Uhnoo I, Wadell G, Svensson L, Johansson ME. Importance of enteric adenoviruses 40 and 41 in acute gastroenteritis in infants and young children. J Clin Microbiol 1984; 20: 365-372.
22. Van R, Wun CC, O'Ryan ML, Matson DO, Jackson L. Outbreaks of human enteric adenovirus types 40 and 41 in Houston day care centers. J Pediatr 1992; 120: 516-521.
23. Han BK, Son JA, Yoon HK, Lee SI. Epidemic adenoviral lower respiratory tract infection in pediatric patients: radiographic and clinical characteristics. Am J Roentgenol 1998; 170: 1077-1080.
24. Herbert FA, Wilkinson D, Burchak E, Morgante O. Adenovirus type 3 pneumonia causing lung damage in childhood. Can Med Assoc J 1977; 116: 274-276.
25. Becroft DM. Bronchiolitis obliterans, bronchiectasis, and other sequelae of adenovirus type 21 infection in young children. J Clin Pathol 1971; 24: 72-82.
26. Wenman WM, Pagtakhan RD, Reed MH, Chernick V, Albritton W. Adenovirus bronchiolitis in Manitoba: epidemiologic, clinical, and radiologic features. Chest 1982; 81: 605-609.
27. Murtagh P, Giubergia V, Viale D, Bauer G, Pena HG. Lower respiratory infections by adenovirus in children. Clinical features and risk factors for bronchiolitis obliterans and mortality. Pediatr Pulmonol 2009; 44: 450-456.