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Clinical Characteristics of Acute Viral Lower Respiratory Tract Infections in Hospitalized Children in Seoul, 1996-1998

This study was performed to investigate the etiologic agents, age distribution, clinical manifestations and seasonal occurrence of acute viral lower respiratory tract infections in children. We confirmed viral etiologies using nasopharyngeal aspirates in 237 patients of the ages of 15 years or younger who were hospitalized for acute lower respiratory tract infection (ALRI) from March 1996 to February 1998 at Samsung Seoul Hospital, Seoul, Korea. The overall isolation rate was 22.1%. The viral pathogens identified were adenovirus (12.7%), influenza virus type A (21.1%), -type B (13.9%), parainfluenza virus type 1 (13.5%), -type 2 (1.3%), -type 3 (16.0%) and respiratory syncytial virus (21.5%). The occurrence of ALRIs was highest in the first year of life, although parainfluenza virus type 1 infection occurred predominantly in the second year of life and influenza virus caused illnesses in all age groups. The specific viruses are frequently associated with specific clinical syndromes of ALRI. The respiratory agents and associated syndromes frequently have characteristic seasonal patterns. This study will help us to estimate the etiologic agents of ALRI, and establish a program for the prevention and treatment. An annual nationwide survey is necessary to understand the viral epidemiology associated with respiratory illnesses in Korea.

Key Words: *Viruses; Respiratory tract infections; Croup; Bronchitis; Bronchiolitis; Pneumonia; Child*

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INTRODUCTION

Acute lower respiratory tract infection (ALRI) is a major cause of morbidity in developing countries (1), especially among infants and toddlers (2). The causes of ALRI were unknown in the past due to difficulties in obtaining adequate samples and lack of reliable diagnostic methods (3-4). However, much progress has been made over the past several decades in elucidating the microbial causes of acute respiratory tract infection and epidemiology of its etiologic agents. Most infections are known to be caused by viruses and bacteria, and the proportion caused by viruses is much greater.

To our knowledge the report described by Yun et al. (5) was the first one in Korea concerning viral etiology and epidemiology of acute lower respiratory tract infections in children. They included both hospitalized and non-hospitalized patients from 1990 to 1994. We started to isolate major respiratory viral pathogens including adenovirus, influenza virus-type A, -type B, parainfluenza virus-type 1, -type 2, -type 3, and respiratory syncytial virus in all the hospitalized patients with acute lower respiratory tract infection from 1996.

Our purpose is to investigate the etiologic agents, age distribution, clinical manifestations and seasonal occurrence of acute viral lower respiratory tract infections in hospitalized children. This study will help us to predict the occurrence of respiratory viral illness, estimate the etiologic agents of ALRI and establish an effective program for the prevention and treatment. In addition, we expect that this kind of etiologic study can provide us a basis for avoiding inappropriate antibiotic therapies.

MATERIALS AND METHODS

The study was performed from March 1996 to February 1998 at Samsung Seoul Hospital, Seoul, Korea. All children of the ages of 15 years or younger who were hospitalized for acute lower respiratory tract infection

Table 1. Clinical syndromes in childhood infections of lower respiratory tract

Croup	Hoarseness, cough, inspiratory stridor with laryngeal obstructions
Tracheobronchitis	Cough and rhonchi; no laryngeal obstruction or wheezing
Bronchiolitis	Expiratory wheezing with or without tachypnea, air trapping, and substernal retractions
Pneumonia	Rales or evidence of pulmonary consolidation on physical examination or radiograph

Denny FW, et al. (6)

were enrolled in this study. All the patients were classified into one of four clinical syndromes, which was described by Denny et al. (6) (Table 1).

Nasopharyngeal aspirates were collected on admission by inserting a five-French nasogastric tube into the nasopharynx and aspiration with a syringe. The aspirates were expelled into viral transport medium and delivered to the laboratory. Each specimen was centrifuged at 1,500 *g* for 10 min and 0.2 mL of the supernatant was inoculated for cell culture.

HEp-2 cells were used for isolation of adenoviruses and respiratory syncytial viruses. Madin-Darby canine kidney (MDCK) cells and LLC-MK2 cells were used for isolation of influenza viruses and parainfluenza viruses, respectively. Each cell line was maintained in minimum essential medium (MEM) supplemented with 10% fetal bovine serum, and subcultured into 24-well plate for specimen inoculation. A 0.2 mL sample of each specimen was inoculated into the wells of each cell line, and incubated at 35℃ with 5% CO_2 up to nine days.

Light Diagnostics Respiratory Panel I (Chemicon International, Inc., Temecular, CA, U.S.A.) kit was used for the qualitative identification of adenovirus, influenza A, influenza B, parainfluenza-type 1, -type 2, -type 3, and respiratory syncytial virus. This kit for indirect immunofluorescent stain contained monoclonal antibodies for each virus and FITC-conjugated secondary antibody.

Table 2. Viruses recovered from 237 patients with ALRI

Virus isolated	Number (%)
Adenovirus	30 (12.7)
Influenza virus	83 (35.0)
Type A	50
Type B	33
Parainfluenza virus	73 (30.8)
Type 1	32
Type 2	3
Type 3	38
RSV	51 (21.5)
Total	237 (100)

Each cell placed in a 24-well plate was detected using 0.05% trypsin-EDTA (ethylene diamine tetraacetic acid), spotted onto the slide after centrifugation and washing, and fixed in chilled acetone. Fixed slides were then stained by indirect immunofluorescent method using the kit. The slides were examined under magnification of 200 times with a fluorescent microscopy. Positive staining for a virus was represented by the presence of at least two or more intact cells with a type of fluorescent for each virus. Negative specimens were finally stained again at day nine.

RESULTS

During the two years of the study, 1,070 cases of ALRI were investigated, of which 237 were confirmed as having viral etiologies. The overall isolation rate was 22.1%. The viral agents recovered from children with ALRI during the study are shown in Table 2. There were no mixed infections in our cases.

The age of the hospitalized children with viral ALRI ranged from one to 175 months with median age of 15 months. The 237 patients consisted of 171 boys (72%) and 66 girls (28%). Pneumonia accounted for 44% in all patients with ALRI. Croup and bronchiolitis were 26% and 22%, respectively. Tracheobronchitis was only 8%.

Age

The occurrence of total ALRI was the highest in the first year of life. The rate in the second six months was higher than that in the first six months. In contrast, the occurrence of croup was the highest in the second year of life (Fig. 1).

The age distribution of lower respiratory tract infections caused by specific infective agents is shown in Fig. 2. Most viral infections occurred in the first five years of life, although influenza virus caused illnesses in all age groups. In particular, ALRI by respiratory syncytial virus and parainfluenza virus type 3 developed frequently in children aged one or less, compared with parainfluenza virus type 1 occurring predominantly in the second year of life. Our data showed that the occurrence of adenoviral infection peaked in infants and children between six months and five years of age, but as many as 23% (7/30) of adenoviral infection occurred in infants less than six months.

Association of respiratory viruses and clinical syndromes

The distribution of the principal viral agents recovered

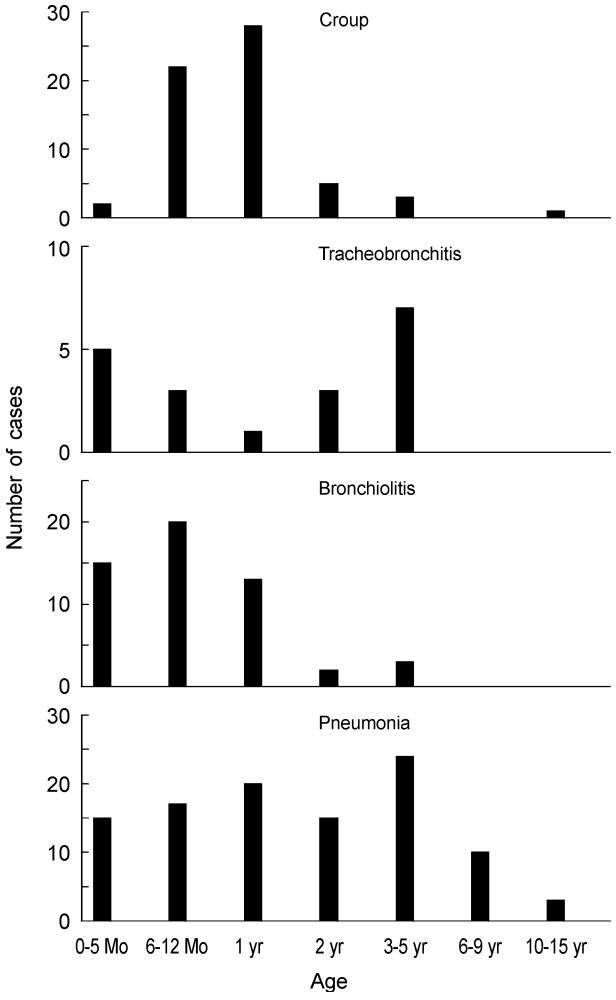

Fig. 1. Age distribution of four clinical syndromes of acute viral lower respiratory tract infection in children.

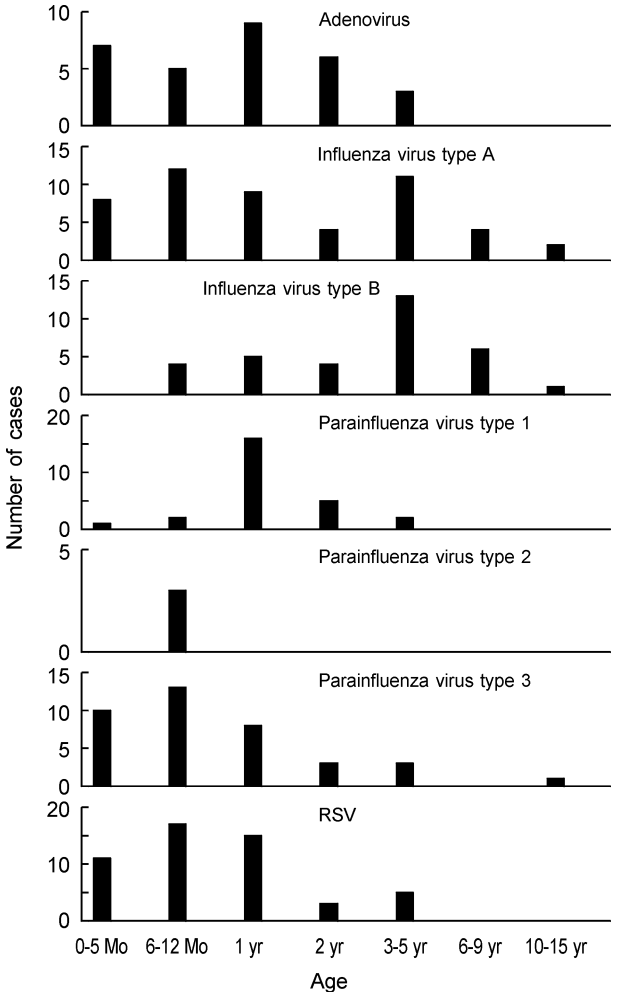

Fig. 2. Association of specific viral agents with age of patients with acute lower respiratory tract infection. RSV, respiratory syncytial virus.

from children of different respiratory syndromes is shown in Fig. 3. When clinical manifestations were presented initially as either croup or bronchiolitis and extended to pneumonia, we classified those patients as pneumonia. Croup was caused most frequently by parainfluenza viruses, especially type 1, which accounted for 38% of all isolates from our croup cases. Tracheobronchitis was associated with influenza virus type A and respiratory syncytial virus. The cause of bronchiolitis was most frequently respiratory syncytial virus. Pneumonia was caused by most of the viral agents except parainfluenza virus type 1 and 2. The distribution of specific viral agents isolated from children with pneumonia by age is shown in Fig. 4.

In our study, adenovirus and influenza virus frequently developed pneumonia (77% and 55%, respectively) (Fig. 5). In contrast, respiratory syncytial virus and parainfluenza virus type 1 were predominantly associated with bronchiolitis and croup, respectively. Parainfluenza virus type 3 caused pneumonia (47%) and croup (32%) to a similar degree.

Seasonal occurrence

Respiratory agents, and consequently associated syndromes, frequently have characteristic seasonal patterns. The monthly occurrence of ALRI, associated with respiratory viruses during the two-year study, is shown in Fig. 6.

Adenoviruses produced infections sporadically all through the year, with a peak in spring, 1996. We had another adenoviral epidemics in May, 1998 (data not shown here). Epidemics of respiratory illness caused by influenza virus occurred in late winter and early spring in 1997. As shown in Fig. 6, peak incidence of influenza virus type A in February and March, 1997 was followed by an outbreak of influenza virus type B in March and April, 1997. Parainfluenza virus type 1 caused respiratory

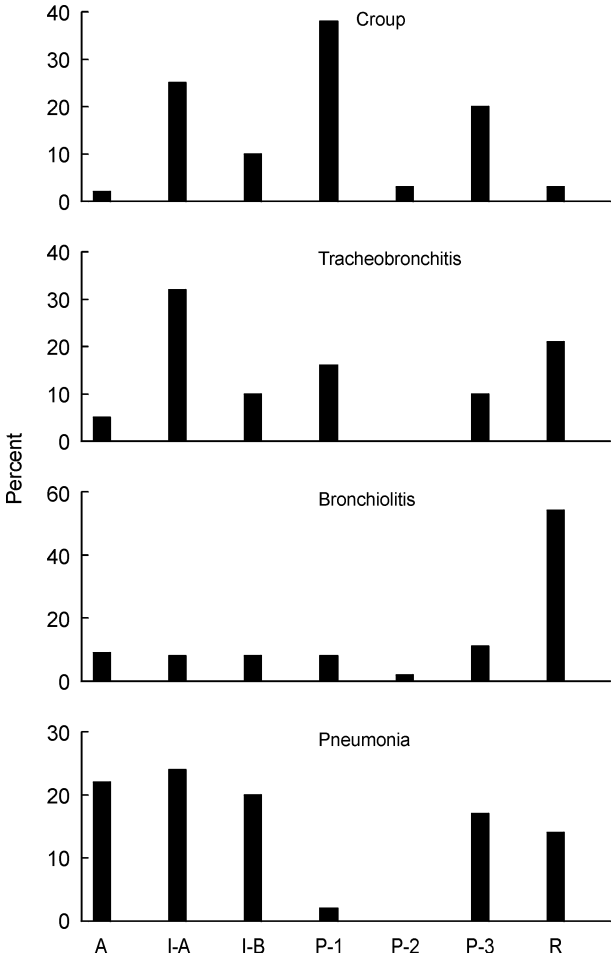

Fig. 3. Proportion of specific viral agents associated with four clinical syndromes of acute lower respiratory tract infection. A, adenovirus; I-A, influenza virus type A; I-B, influenza virus type B; P-1, parainfluenza virus type 1; P-2, parainfluenza virus type 2; P-3, parainfluenza virus type 3; R, respiratory syncytial virus.

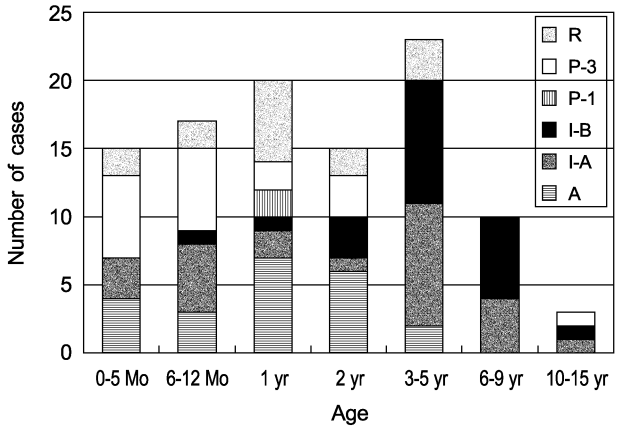

Fig. 4. Distribution of specific viral agents isolated from children with pneumonia by age. A, adenovirus; I-A, influenza virus type A; I-B, influenza virus type B; P-1, parainfluenza virus type 1; P-2, parainfluenza virus type 2; P-3, parainfluenza virus type 3; R, respiratory syncytial virus.

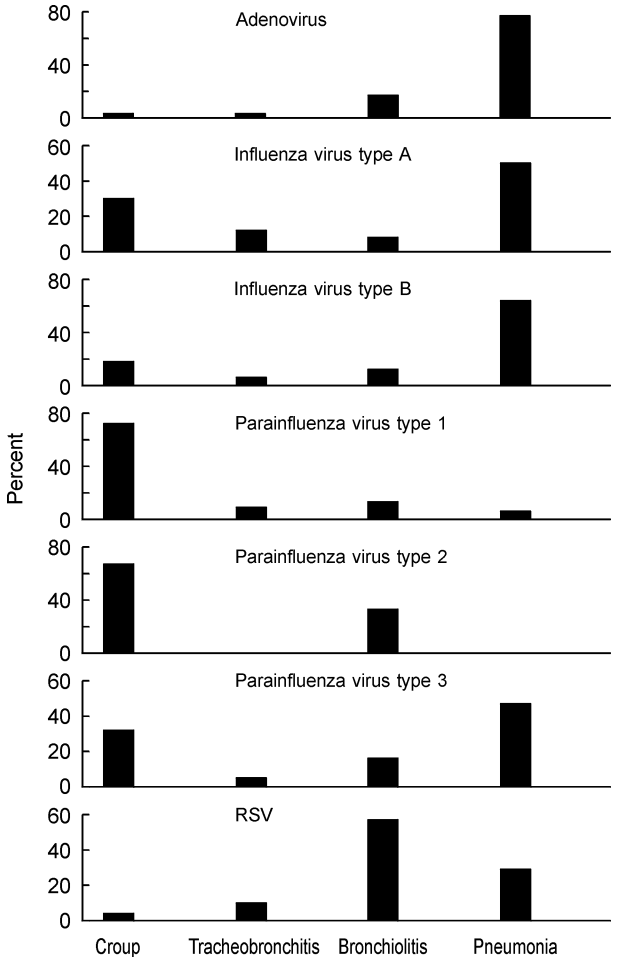

Fig. 5. Proportion of four clinical syndromes associated with specific viral agents. RSV, respiratory syncytial virus.

infections during the fall and early winter, primarily of croup. In contrast, ALRI caused by parainfluenza virus type 3 occurred between April and July every year, following epidemics of influenza virus infections. Parainfluenza virus type 3 infections were manifested mainly by pneumonia. Isolation of respiratory syncytial virus appeared in the fall and winter in 1996, but in all seasons in 1997.

DISCUSSION

The causative agents associated with ALRI are relatively well understood. All classes of microorganisms, including viruses, bacteria, fungi, parasites, and protozoa, can infect the respiratory tract. Adenoviruses, influenza viruses, parainfluenza viruses, respiratory syncytial viruses and enteroviruses are common viruses involved in ALRI. The common bacterial causes of ALRI are *Mycoplasma pneumoniae, Streptococcus pneumoniae, Haemophilus influenzae,* and *Chlamydia pneumoniae* (7-8). As bacterial infec-

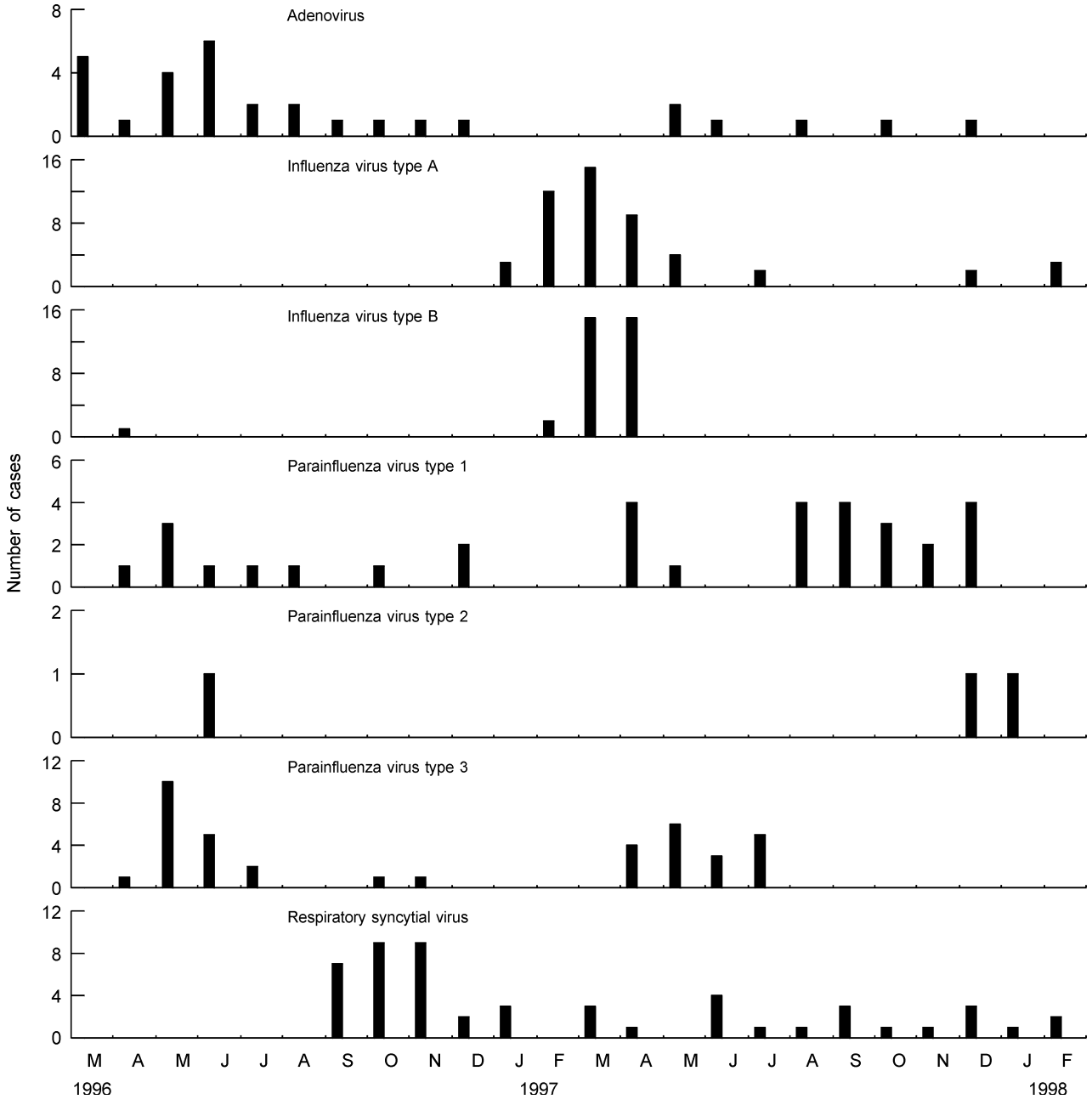

Fig. 6. Monthly occurrence of acute lower respiratory tract infection caused by specific viral agents from 1996 to 1998.

tions are readily treated by antibiotics, most practicing pediatricians also in Korea became more interested in the infections of viral origin.

According to our data respiratory viral agents was confirmed only in 22.1% of patients with lower respiratory tract infection, which is similar to or less than that of other studies (5, 9, 10-11). The reasons for this discrepancy are not clear, but procedural differences probably played a large role. The number of patients with a viral etiology would have increased by more careful collection of nasopharyngeal aspirates by a skillful person and by more prompt transport of specimen. Higher rates of virus isolation might have been achieved if children had been studied in the early stage of their illness. Other possibilities for this discrepancy are that ALRI might be caused by other viral agents such as enterovirus, and by bacteria or mycoplasma more frequently than expected in other studies. We did not perform lung aspirate studies to confirm bacterial etiologies. There were no mixed infections in our data, partly because the duration of this study is just two years. The tendency of viral agents not to cause simultaneous epidemics in a community, as demonstrated here, has been shown by others as well (12).

Most of the viral agents infected children less than five years of age. In this study, viral ALRI tended to be more common in younger children than in older children, because older children have already developed immunity. The clinical picture of ALRI in older children may have been severe enough to require hospitalization only if there was bacterial involvement, whereas in the younger children, viral respiratory infection itself may have caused symptoms requiring hospital treatment. On the other hand, in children over three years influenza viruses were the main agents causing acute lower respiratory tract infection, as in other reports (13, 14).

Most infants are known to have a neutralizing antibody to one or more of the common adenoviral types, and this appears to be protective during the first six months of life. The occurrence of adenoviral infection peaks in infants and children between six months and five years of age (15). In our study as many as 23% of adenoviral infections occurred in infants under six months of age.

The association between respiratory syndromes and infecting agents has been established (5, 7, 9, 16-18). The major cause of croup was parainfluenza virus type 1, followed by influenza virus type A and parainfluenza virus type 3 in our study. Bronchiolitis was caused predominantly by respiratory syncytial virus, accounting for 54% of the cases. Influenza virus type A and respiratory syncytial virus were the frequent causes of tracheobronchitis, although the proportion of tracheobronchitis among the patients was only 8%, because clinical symptoms of tracheobronchitis were not so severe to require hospitalization. Most respiratory viruses developed pneumonia to a similar degree except for parainfluenza virus type 1 and type 2. Pneumonia by either influenza virus type A or B occurred in all age groups, including children over three years of age. We had relatively lots of pneumonia patients infected by adenovirus and influenza virus during the study period, which was due to virus outbreaks in 1996 and 1997, respectively.

Seasonal occurrence of the respiratory viruses was similar to other reports (5-6, 12). Influenza virus epidemics was observed in the winter and early spring in 1997 with type A in February and March, followed by type B in March and April. Our result is consistent with those shown by Yun et al. (5), since influenza virus type B was isolated biennially in 1991 and in 1993 whereas type A was detected every year. Infection by parainfluenza virus type 3 was found in the spring around May, presenting mainly pneumonia or croup. Parainfluenza virus type 1 caused an outbreak in the fall and winter, usually manifested as croup, although it was also isolated in the spring like type 3. Glezen et al. (12) described that parainfluenza virus type 1 has produced biennial epidemics of croup. Our data showed similar finding, showing parainfluenza virus type 1 epidemics occurred in 1997, not in 1996. Parainfluenza virus epidemics was followed by respiratory syncytial virus epidemics in the fall and winter. Adenovirus also occurred in epidemics in spring, although it was isolated sporadically in 1996. Yun et al. (5) showed adenoviral infection occurred every year from 1990 to 1994, especially in 1993. We experienced large numbers of adenoviral infection in 1995 (19), 1996 (20) and 1998 (data not shown here), which was manifested mainly as severe pneumonia. Serotype of adenovirus isolated in some patients in 1996 was type 7 in 10 cases (21).

If the clinician considers the age of the patient and season of the year, and has some knowledge of the characteristics of respiratory illnesses, a clinical and epidemiologic estimation can be made concerning the etiology of ALRI without using definitive laboratory tools. One of the usefulness of this kind of studies is to provide a basis to avoid inappropriate antibiotic therapy. However, it should be remembered that the presence of viruses does not exclude the presence of bacteria, since previous studies have found mixed bacterial and viral infections in 5 to 37% of children with respiratory tract infections (22-27). Therefore factors such as severity of illness, other laboratory findings (e.g., leukocyte count, C-reactive protein) or seasonal epidemics should be considered before stopping antibiotic treatment.

In conclusion, the age distribution of ALRI caused by specific viruses is different from each other. The specific viruses are frequently associated with specific clinical syndromes of ALRI. Viral pneumonia predominantly occurred in children less than five years, in which adenovirus and influenza virus are frequently isolated. Respiratory agents and associated syndromes frequently have characteristic seasonal patterns.

Our study is limited to lower respiratory tract infections which require hospitalization in Seoul for only two years. Therefore, an annual nationwide survey is necessary to understand the viral epidemiology associated with respiratory illnesses in Korea, which can help the pediatricians to estimate and manage children with ALRI.

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