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**Original Article**

# Coxsackieviruses infection in northern Taiwan — epidemiology and clinical characteristics

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**Background and purpose:** The epidemiology of coxsackievirus has rarely been investigated in Taiwan. This study was performed to ascertain the epidemiological and clinical characteristics of coxsackievirus infections in Taiwan.

**Methods:** 457 patients treated at a medical center in northern Taiwan who were positive for coxsackievirus were enrolled in this retrospective study. Patients' medical charts were reviewed for clinical diagnosis, physical examination, laboratory findings, and clinical manifestations.

**Results:** Three serotypes of coxsackievirus A (A9, 5.3%; A10, 7.2%; A16, 87.5%) were identified among 265 patients, 27.4% of whom were admitted to hospital. The mean (± standard deviation [SD]) duration of fever and hospital stay was 2.6 ± 0.5 days and 4.0 ± 2.1 days, respectively. Complications were noted in 14 patients (5.3%), all of which involved the central nervous system (CNS). All 6 serotypes of coxsackievirus B (B1, 2.6%; B2, 7.8%; B3, 55.7%; B4, 2.1%; B5, 12.5%; B6, 1.0%; non-typable, 18.2%) were identified in 192 patients, 45.3% of whom were admitted to hospital. The mean (± SD) duration of fever and hospital stay was 4.1 ± 1.0 and 3.4 ± 0.9 days, respectively. Thirty seven patients (19.3%) had complications, including 34 with CNS involvement. Patients with coxsackievirus B infection had higher hospital admission rates ($p < 0.001$), more CNS involvement ($p < 0.001$), and longer fever duration ($p < 0.001$) than those with coxsackievirus A infection. Patients with coxsackievirus A infection tended to have more skin manifestations ($p < 0.001$) and oral ulcers ($p < 0.001$).

**Conclusions:** The most common serotypes were coxsackieviruses A16 and B3. Patients with coxsackievirus B infection were more likely to be admitted to hospital, had longer fever duration, and more CNS involvement than patients with coxsackievirus A infection.

**Key words:** Central nervous system infections; Coxsackievirus infections; Diagnosis; Enterovirus; Infant, newborn; Signs and symptoms

## Introduction

Coxsackieviruses belong to the picornaviridae family and the enterovirus genus, and are one of the most important pathogens in children [1,2]. Hand-foot-mouth disease (HFMD) is the best known enterovirus disease, and is a common presentation of coxsackievirus A16. However, coxsackieviruses have multiple serotypes and can cause a wide variety of diseases, including fever, exanthema, enteritis, encephalitis, aseptic meningitis, myocarditis, and respiratory infections [3]. To date, 23 serotypes from group A and 6 serotypes from group B have been identified [4].

Neonatal enterovirus infections are likely to become critical [5], and coxsackievirus B and echovirus account for most infections during this period. Neonatal coxsackievirus infections usually involve the central nervous system (CNS) and may cause serious complications of myocarditis or fulminant hepatitis [3]. Despite a moderate mortality rate, patients usually recover without sequelae [6-8]. The diversity of clinical outcomes [9] may be the result of viral virulence [10],

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viral loads, and host factors such as host immunity. The most common coxsackievirus infections in the United States are coxsackieviruses B5 (11.5% of all enterovirus infection), A9 (6.6%), B2 (6.2%), B4 (4.4%), and B3 (4.0%) [11]. The epidemiological characteristics and the different clinical manifestations of each serotype have rarely been reported in Taiwan. This study was performed to investigate the epidemiological and clinical characteristics of coxsackievirus infections in Taiwan.

## Methods

### Patients

468 patients who were positive for coxsackievirus at the National Taiwan University Hospital, Taipei, Taiwan, from January 1999 to December 2006 were included in this retrospective study. Eleven patients were excluded due to underlying diseases. Coxsackievirus was isolated from the throat, rectum, nasopharyngeal aspirate, and/or cerebrospinal fluid (CSF) of 457 patients. These patients were enrolled in the study.

There were 281 boys (61.5%) and 176 girls (38.5%). The mean (± standard deviation [SD]) age was 46.4 ± 45.1 months, and the median age was 38.6 months (range, 0.2 to 356 months).

### Data collection

The patients' medical charts were reviewed, and the demographic data, clinical symptoms, laboratory findings, radiographic reports, and treatment were analyzed. Clinical symptoms and physical examination findings, including oral ulcer, skin manifestations, tonsil exudates, acute otitis media, abnormal breathing sounds, and neck lymphadenopathy (defined as >1.5 cm in diameter) were recorded. Biphasic fever was defined as fever that subsided after 2 or more days, but flared up again. The incidence of fever was calculated for all patients, but fever duration and biphasic fever patterns were only recorded and analyzed for inpatients.

### Diagnostic definitions

Aseptic meningitis was defined as CSF pleocytosis (leukocytes >30 cells/$mm^3$ in neonates and >5 cells/$mm^3$ beyond the neonatal period), with negative bacterial culture of CSF or positive virus isolation from CSF with normal CSF cell count. Encephalitis was defined as consciousness change lasting greater than 24 h or focal neurologic signs with abnormal electroencephalography or neurological imaging findings. Poliomyelitis-like syndrome was defined as acute limb weakness plus decreased reflex and muscle power. Encephalomyelitis included both encephalitis and poliomyelitis-like syndrome. Myocarditis was defined as ejection fraction <50% on echocardiogram, arrhythmia, and an elevation in the cardiac fraction of creatine kinase. Hepatic necrosis with coagulopathy (HNC) was defined as aspartate aminotransferase >3 times the upper limit of normal plus platelet count $<10^5/mm^3$. Complications included myocarditis, HNC, shock, and CNS involvement of aseptic meningitis, encephalitis, polio-like syndrome, and encephalomyelitis.

### Virus isolation and serotyping

Throat swabs, rectal swabs, nasopharyngeal aspirate, and CSF were collected and used to inoculate human embryonic fibroblasts (MRC-5), rhesus monkey kidney cells (LLC-MK2), human laryngeal carcinoma cells (Hep2), and rhabdomyosarcoma cells. The inoculated cells were observed every day for the presence of a cytopathic effect. If a cytopathic effect involved more than 50% of the established monolayers, the culture cells were scraped and virus antigen was detected by indirect immunofluorescence assay staining with both pan-enteroviral antibody and serotype-specific antibody (Chemicon International, Inc, Temecula, CA, USA).

### Statistical analysis

Continuous variables were analyzed by Mann-Whitney *U* test and nominal variables were assayed by chi-squared test or Fisher's exact test. Analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 13.0; SPSS, Chicago, IL, USA). Significance was defined as $p < 0.05$ (2-tailed).

## Results

Coxsackievirus A infection had 2 peaks during the year, with a major peak during the summer and a minor peak during the winter. Coxsackievirus B had only 1 peak, during the summer period, especially June. Overall, the incidence of coxsackievirus peaked during the summer (Fig. 1). The most common coxsackievirus infections were A16 (50.7%), B3 (23.4%), B5 (5.2%), and A10 (4.1%) [Fig. 2].

### Demographic data

Thirty eight percent of patients were admitted to hospital and 62% were treated as outpatients. The mean (± SD)

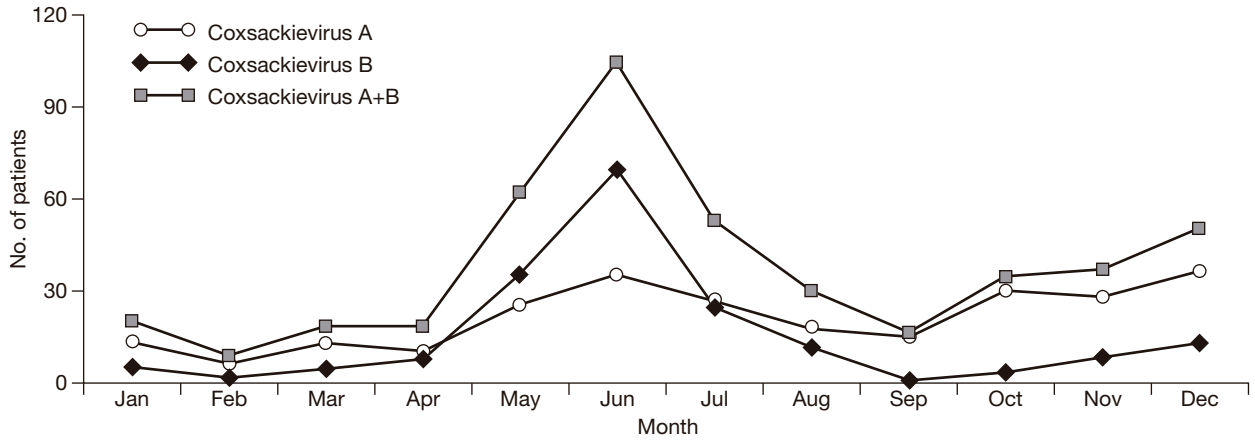


**Fig. 1.** Mean seasonal distribution of coxsackieviruses A and B infections.

duration of hospital stay was 5.0 ± 3.47 days. No patients died.

Three serotypes of coxsackievirus A (A9, 5.3%; A10, 7.2%; and A16, 87.5%) were identified in 265 patients. All 6 serotypes of coxsackievirus B (B1, 2.6%; B2, 7.8%; B3, 55.7%; B4, 2.1%; B5, 12.5%; B6, 1.0%; non-typable, 18.2%) were identified in 192 patients. The demographic and clinical data are shown in Table 1. Fig. 3 illustrates the age distribution of patients with coxsackieviruses A16 and B. Infants younger than 3 months tended to have coxsackievirus B infection rather than A16 infection.

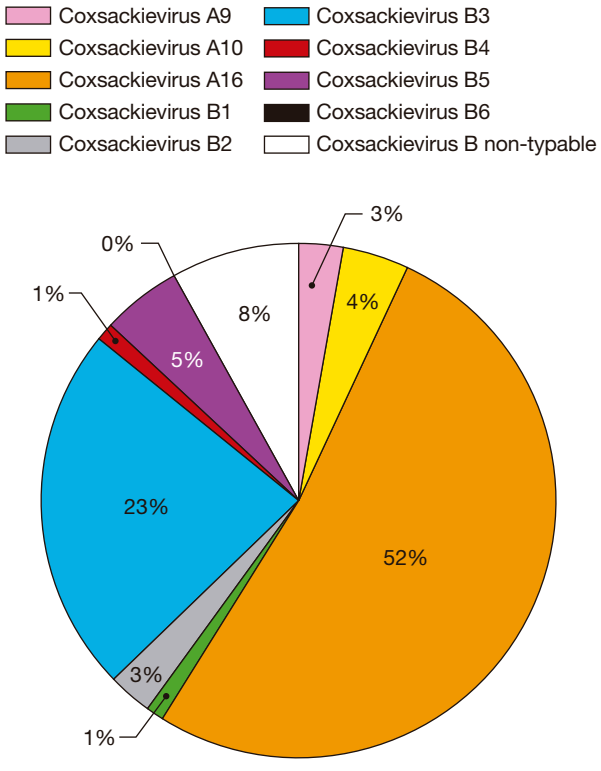


**Fig. 2.** Proportion of each coxsackievirus serotype.

## Comparison between coxsackieviruses A and B

There was a significant difference in clinical manifestations between coxsackieviruses A and B (Table 2). Patients with coxsackievirus B infection had higher hospital admission rates (45.3% vs 27.5%; $p < 0.001$), and longer duration of fever (4.1 vs 2.7 days; $p < 0.001$) than patients with coxsackievirus A infection. Coxsackievirus A infection resulted in more skin manifestations (74.0% vs 9.9%; $p < 0.001$) and oral ulcers (86.4% vs 24.5%; $p < 0.001$) than coxsackievirus B. Patients with coxsackievirus B infection had more complaints of chest pain (8.3% vs 0.8%; $p < 0.001$) and abdominal pain (19.8% vs 2.6%; $p < 0.001$) than patients with coxsackievirus A. Respiratory symptoms and tonsil exudates were more prominent in coxsackievirus B infection.

Clinical diagnoses of coxsackievirus A and B infections also exhibited variation (Table 3), with 177 coxsackievirus A infections (66.8%) being diagnosed as HFMD, while only 5 coxsackievirus B infections (2.6%) had this diagnosis ($p < 0.001$). Herpangina was diagnosed in 46 patients with coxsackievirus A infection (17.4%) and in 40 with coxsackievirus B infection (20.8%), but the difference was not statistically significant ($p = 0.396$). Furthermore, patients with coxsackievirus B infection had more CNS involvement (17.7%) than patients infected with coxsackievirus A (5.3%) [$p < 0.001$]. Although the CSF pleocytosis did not differ significantly between patients infected with coxsackieviruses A and B, the CSF virus isolation rate was much higher in coxsackievirus B infection ($p = 0.028$).

**Table 1.** Demographic and clinical characteristics of coxsackieviruses A and B.

| Characteristic | Coxsackievirus A (n = 265) | Coxsackievirus B (n = 192) | *p* |
|---|---|---|---|
| Age (months) | | | |
| Mean ± SD | 42.4 ± 32.4 | 51.9 ± 49.7 | 0.110 |
| Median (range) | 36.2 (0.28-333) | 42.5 (0.16-356) | |
| Sex (%) | | | |
| Male | 168 (63.4) | 113 (58.6) | 0.325 |
| Female | 97 (36.6) | 79 (41.4) | |
| Hospital admission (%) | 73 (27.5) | 87 (45.3) | <0.001 |
| Duration of hospital stay (days; mean ± SD) | 4.0 ± 2.1 | 6.0 ± 4.1 | <0.001 |
| White blood count (/mm$^3$; mean ± SD) | 12950 ± 5108 (79) | 10140 ± 4624 (107) | <0.001 |
| Platelets (10$^3$/mm$^3$; mean ± SD) | 287.5 ± 64.6 (79) | 294.5 ± 113 (107) | 0.908 |
| C-reactive protein (mg/dL; mean ± SD) | 2.0 ± 2.2 (68) | 1.4 ± 2.0 (100) | 0.246 |
| Aspartate aminotransferase (U/L; mean ± SD) | 38.9 ± 16.6 (59) | 107.9 ± 594.7 (88) | 0.341 |
| Alanine aminotransferase (U/L; mean ± SD) | 16.6 ± 6 (39) | 40.8 ± 97.8 (65) | 0.134 |
| Red blood cells in CSF (/mm$^3$; mean ± SD) | 0.2 ± 0.56 (16[a]) | 80.7 ± 242.6 (40[a]) | 0.027 |
| White blood cells in CSF (/mm$^3$; mean ± SD) | 16.6 ± 7 (16[a]) | 77 ± 109.9 (41[a]) | 0.676 |
| CSF pleocytosis (%) | 68.8 (11[a]) | 80.5 (33[a]) | 0.483 |
| Protein in CSF (mg/dL; mean ± SD) | 35.1 ± 24.6 (14[a]) | 68.2 ± 50.9 (39[a]) | 0.024 |
| Sugar in CSF (mg/dL; mean ± SD) | 56.6 ± 10.6 (15[a]) | 57.3 ± 15.7 (38[a]) | 0.744 |
| Positive CSF virus isolation (%) | 35.7 (14) | 71.1 (38) | 0.028 |
| Treatment (%) | | | |
| Inotropic agents | 1 (0.4) | 1 (0.5) | 0.819 |
| Antibiotic agents | 24 (9.1) | 89 (46) | <0.001 |
| Intravenous immunoglobulin | 3 (1.1) | 1 (0.5) | 0.642 |

[a]Two patients were excluded due to difficulty in performing lumbar puncture.
Abbreviations: SD = standard deviation; CSF = cerebrospinal fluid

## Clinical spectrum of each coxsackievirus serotype

The patients' demographic data and clinical diagnosis for each serotype are summarized in Table 4.

### *Coxsackievirus A9*

Among 265 patients with coxsackievirus A infection, 14 (5.3%) had coxsackievirus A9 infection. The most common diagnoses were viral exanthema (n = 5, 35.7%), herpangina (n = 2, 14.3%), and tonsillitis/pharyngitis (n = 2, 14.3%). Three patients (21.4%) had complications of aseptic meningitis. The most common symptoms were fever (78.6%) and skin rash (50.0%), 83% of which manifested on the trunk. Only 14.3% of patients had oral ulcer.

### *Coxsackievirus A10*

Nineteen patients (7.2%) had coxsackievirus A10 infection. The most common diagnosis was herpangina

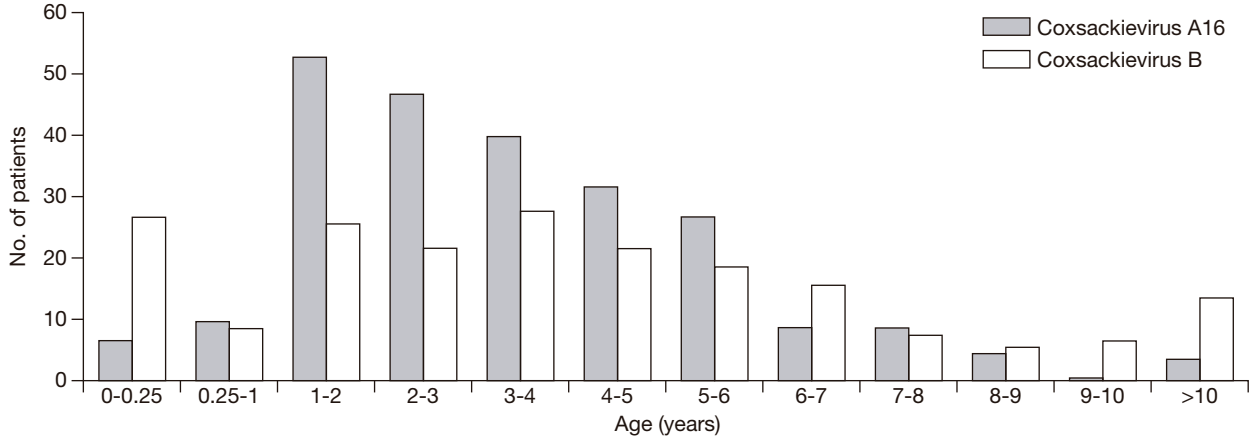


**Fig. 3.** Age distribution of patients with coxsackieviruses A16 and B.

**Table 2.** Comparison of clinical manifestations of coxsackieviruses A and B.

| Manifestation | Coxsackievirus A (n = 265) No. (%) | Coxsackievirus B (n = 192) No. (%) | *p* |
|---|---|---|---|
| Fever duration (mean ± SD) | 2.7 ± 0.5 | 4.1 ± 1.0 | <0.001 |
| Biphasic fever pattern | 0 (0) | 8 (4.2) | <0.001 |
| Fever | 170 (64.2) | 184 (95.3) | <0.001 |
| Headache | 17 (6.4) | 32 (16.7) | <0.001 |
| Nausea/vomiting | 25 (9.4) | 49 (25.5) | <0.001 |
| Oral ulcer | 229 (86.4) | 47 (24.5) | <0.001 |
| Rash | 196 (74.0) | 19 (9.9) | <0.001 |
| Jerk | 19 (7.2) | 7 (3.6) | 0.108 |
| Myalgia | 5 (1.9) | 7 (3.6) | 0.246 |
| Chest pain | 2 (0.8) | 16 (8.3) | <0.001 |
| Cough | 75 (28.3) | 77 (40.1) | 0.008 |
| Rhinorrhea | 61 (23.0) | 64 (33.3) | 0.015 |
| Sore throat | 29 (10.9) | 30 (15.6) | 0.141 |
| Tonsil exudates | 10 (3.8) | 50 (26.0) | <0.001 |
| Acute otitis media | 4 (1.5) | 6 (3.1) | 0.334 |
| Abnormal breath sounds | 11 (4.2) | 17 (8.9) | 0.039 |
| Diarrhea | 23 (8.7) | 28 (14.6) | 0.048 |
| Abdominal pain | 7 (2.6) | 38 (19.8) | <0.001 |
| Ocular involvement[a] | 1 (0.4) | 10 (5.2) | 0.012 |
| Neurological signs | 4 (1.5) | 12 (6.3) | 0.009 |

[a]Includes conjunctivitis, conjunctival erythema, and ocular discharge.
Abbreviation: SD = standard deviation.

**Table 3.** Diagnoses and complications of coxsackieviruses A and B.

| Diagnosis | Coxsackievirus A (n = 265) No. (%) | Coxsackievirus B (n = 192) No. (%) | *p* |
|---|---|---|---|
| Hand-foot-mouth disease | 177 (66.8) | 5 (2.6) | <0.001 |
| Herpangina | 46 (17.4) | 40 (20.8) | 0.396 |
| Epidemic pleurodynia | 0 (0) | 11 (5.7) | <0.001 |
| Complication | 14 (5.3) | 37 (19.3) | <0.001 |
| Central nervous system involvement[a] | 14 (5.3) | 34 (17.7) | <0.001 |
| Aseptic meningitis | 11 (4.2) | 29 (15.1) | <0.001 |
| Encephalitis | 1 (0.4) | 4 (2.1) | 0.167 |
| Encephalomyelitis | 1 (0.4) | 1 (0.5) | 0.819 |
| Polio-like syndrome | 1 (0.4) | 0 (0) | 0.394 |
| Myocarditis | 0 (0) | 2 (1.0) | 0.176 |
| Hepatic necrosis with coagulopathy | 0 (0) | 1 (0.5) | 0.42 |

[a]Including aseptic meningitis, encephalitis, encephalomyelitis, and polio-like syndrome.

(n = 8, 42.1%). Six patients (31.6%) had complications, including aseptic meningitis (n = 5) and polio-like syndrome (n = 1). The most common symptoms were fever (94.7%), oral ulcer (47.4%), cough (47.4%), nausea/vomiting (31.6%), and rhinorrhea (31.6%). Only 10.5% of patients had skin rash.

### *Coxsackievirus A16*

232 patients (87.5%) had coxsackievirus A16 infection. The most common diagnoses were HFMD (n = 176, 75.9%) and herpangina (n = 36, 15.5%). Five patients (2.2%) had complications, including aseptic meningitis (n = 3), encephalitis (n = 1), and encephalomyelitis (n = 1). The most common symptoms were oral ulcer (94.0%), skin rash (80.6%), and fever (60.3%). A comparison of the characteristics of these patients according to age group is shown Table 5. Fever was more common in the younger age groups: 83.3% of infants aged 0 to 3 months and 78.8% of those aged 12 to 24 months had fever, but only 58.1% of children developed fever. In addition, children aged between 12 and 24 months had the longest duration of fever.

**Table 4.** Patients' demographics and diagnoses for each coxsackievirus serotype.

| Serotype | A9 (n = 14) | A10 (n = 19) | A16 (n = 232) | B1 (n = 5) | B2 (n = 15) | B3 (n = 107) | B4 (n = 4) | B5 (n = 24) | B6 (n = 2) |
|---|---|---|---|---|---|---|---|---|---|
| Male-to-female ratio | 2.5 | 2.2 | 1.7 | 1.5 | 1.5 | 1.4 | 3 | 1.9 | 1 |
| Age (months; mean ± SD) | 31.6 ± 29.3 | 40.2 ± 26.0 | 43.3 ± 6.4 | 36.4 ± 32.4 | 40.4 ± 29.9 | 51 ± 41.0 | 34.3 ± 22.2 | 60.7 ± 79.8 | 196 ± 226 |
| Hospital admission rate (%) | 50.0 | 26.3 | 26.3 | 60.0 | 40.0 | 44.8 | 75.0 | 66.7 | 50.0 |
| Admission (days; mean ± SD) | 3.4 ± 1.3 | 3.4 ± 0.9 | 4.2 ± 2.3 | 5 ± 0 | 4 ± 1.4 | 5.8 ± 4.6 | 5.7 ± 0.6 | 6.6 ± 4.4 | 5 |
| Fever (days; mean ± SD) | 2.7 ± 1 | 2.25 ± 1 | 2.7 ± 0.5 | 2.2 ± 1 | 2.1 ± 0.9 | 4.4 ± 2.1 | 8 ± 1.7 | 3.2 ± 1.2 | 3 |
| Clinical symptom (%) | | | | | | | | | |
| Fever | 78.6 | 94.7 | 60.3 | 100.0 | 100.0 | 96.3 | 100.0 | 91.7 | 100.0 |
| Headache | 28.6 | 26.3 | 3.4 | 0 | 0 | 12.1 | 50.0 | 33.3 | 0 |
| Nausea/vomiting | 35.7 | 31.6 | 6.0 | 20.0 | 33.3 | 24.3 | 50.0 | 29.2 | 0 |
| Oral ulcer | 14.3 | 47.4 | 94.0 | 0 | 20.0 | 23.4 | 0 | 12.5 | 0 |
| Rash | 50.0 | 10.5 | 80.6 | 0 | 6.7 | 8.4 | 75.0 | 12.5 | 0 |
| Lethargy | 0 | 0 | 1.1 | 0 | 0 | 2.8 | 25.0 | 12.5 | 0 |
| Cough | 28.5 | 47.4 | 26.3 | 20.0 | 66.7 | 41.1 | 25.0 | 41.7 | 0 |
| Rhinorrhea | 21.4 | 31.6 | 22.0 | 40.0 | 53.3 | 36.4 | 25.0 | 29.2 | 0 |
| Sore throat | 7.1 | 0 | 12.1 | 0 | 13.3 | 16.8 | 0 | 12.5 | 50.0 |
| Chest pain | 0 | 0 | 0.9 | 0 | 6.7 | 10.3 | 0 | 8.3 | 0 |
| Abdominal pain | 7.1 | 5.3 | 2.1 | 20.0 | 6.7 | 23.4 | 0 | 16.7 | 0 |
| Diarrhea | 28.5 | 15.8 | 6.8 | 0 | 6.7 | 17.8 | 0 | 16.7 | 0 |
| Myalgia | 7.1 | 0 | 1.7 | 0 | 6.7 | 2.8 | 0 | 4.2 | 50.0 |
| Myoclonic jerk | 0 | 0 | 8.2 | 0 | 0 | 4.0 | 0 | 4.2 | 0 |
| Seizure | 0 | 0 | 0.8 | 0 | 0 | 5.6 | 0 | 4.2 | 50.0 |
| Consciousness change | 0 | 0 | 0.4 | 0 | 0 | 0.9 | 25.0 | 0 | 0 |
| Ocular discharge | 0 | 0 | 0 | 0 | 0 | 1.9 | 0 | 0 | 0 |
| Conjunctivitis | 0 | 0 | 0.4 | 0 | 13.3 | 1.9 | 25.0 | 0 | 0 |
| Acute otitis media | 0 | 0 | 1.7 | 0 | 13.3 | 2.8 | 0 | 0 | 0 |
| Tonsil exudates | 7.1 | 0 | 3.9 | 20.0 | 33.3 | 30.8 | 0 | 8.3 | 50.0 |
| Abnormal breath sounds | 7.1 | 0 | 4.3 | 20.0 | 13.3 | 9.3 | 0 | 0 | 0 |
| Diagnosis (%) | | | | | | | | | |
| Hand-foot-mouth disease | 0 | 5.3 | 75.9 | 0 | 0 | 2.8 | 0 | 0 | 0 |
| Herpangina | 14.3 | 42.1 | 15.5 | 0 | 20.0 | 19.6 | 0 | 12.5 | 0 |
| Tonsillitis/pharyngitis | 14.3 | 5.3 | 2.2 | 0 | 20.0 | 27.1 | 0 | 16.7 | 50.0 |
| Exanthema | 35.7 | 5.3 | 1.7 | 0 | 0 | 0.9 | 25.0 | 0 | 0 |
| Febrile convulsion | 0 | 0 | 0.4 | 0 | 0 | 1.9 | 0 | 0 | 0 |
| Seizure/complex febrile convulsion | 0 | 0 | 0 | 0 | 0 | 2.8 | 0 | 0 | 0 |
| Epidemic pleurodynia/ chest pain | 0 | 0 | 0 | 0 | 6.7 | 7.5 | 50.0 | 4.2 | 0 |
| Acute otitis media | 0 | 0 | 2.2 | 0 | 0 | 4.7 | 0 | 0 | 0 |
| Sinusitis | 0 | 0 | 0.4 | 0 | 13.3 | 1.9 | 0 | 4.2 | 0 |
| Lower respiratory tract infection | 7.1 | 5.3 | 3.8 | 20.0 | 6.7 | 7.4 | 0 | 8.4 | 0 |
| Upper respiratory tract infection | 0 | 10.5 | 0 | 0 | 0 | 7.5 | 0 | 4.2 | 0 |
| Acute gastroenteritis | 0 | 0 | 0 | 0 | 0 | 2.8 | 0 | 0 | 0 |
| Complication | 21.4 | 31.6 | 2.2 | 40.0 | 13.3 | 11.2 | 50.0 | 58.3 | 50.0 |
| Aseptic meningitis | 21.4 | 26.3 | 1.3 | 40.0 | 13.3 | 7.5 | 0 | 50.0 | 50.0 |
| Encephalitis | 0 | 0 | 0.4 | 0 | 0 | 1.9 | 25.0 | 4.2 | 0 |
| Encephalomyelitis | 0 | 0 | 0.4 | 0 | 0 | 0 | 25.0 | 0 | 0 |
| Polio-like syndrome | 0 | 5.3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Myocarditis | 0 | 0 | 0 | 0 | 0 | 0.9 | 0 | 4.2 | 0 |
| Hepatic necrosis with coagulopathy | 0 | 0 | 0 | 0 | 0 | 0.9 | 0 | 0 | 0 |

Abbreviation: SD = standard deviation.

**Table 5.** Characteristics of patients with coxsackievirus A16 in each age group.

| Variable | Age group | | | | | | | | Average |
|---|---|---|---|---|---|---|---|---|---|
| | 0-3 months | 3-12 months | 1-2 years | 2-3 years | 3-4 years | 4-5 years | 5-10 years | >10 years | |
| Male sex (%) | 66.7 | 75.0 | 67.3 | 63.0 | 59.0 | 64.5 | 56.5 | 33.3 | 62.5 |
| Admission (%) | 83.3 | 50.0 | 34.6 | 39.1 | 28.2 | 6.5 | 4.3 | 0 | 26.3 |
| Duration of fever (days) | 2.4 | 2.5 | 3.5 | 2.5 | 2.3 | 2.0 | 2.3 | - | 2.7 |
| Symptom (%) | | | | | | | | | |
| Fever | 83.3 | 66.7 | 78.8 | 69.6 | 59.0 | 58.1 | 34.8 | 0 | 60.3 |
| Oral ulcer | 50.0 | 91.7 | 94.2 | 95.7 | 92.3 | 96.8 | 93.5 | 66.7 | 93.4 |
| Rash | 66.7 | 83.3 | 80.8 | 67.4 | 84.6 | 83.9 | 84.8 | 100.0 | 80.6 |
| Myoclonic jerk | 0 | 25.0 | 13.5 | 15.2 | 7.7 | 0 | 0 | 0 | 8.2 |
| Seizure | 0 | 8.3 | 1.9 | 2.2 | 0 | 0 | 0 | 0 | 0.8 |
| Nausea/vomiting | 0 | 0 | 5.8 | 4.3 | 7.7 | 9.7 | 6.5 | 0 | 6.0 |
| Diarrhea | 0 | 16.7 | 11.5 | 13.0 | 2.6 | 3.2 | 0 | 0 | 6.9 |
| Abdominal pain | 0 | 0 | 0 | 2.2 | 7.7 | 3.2 | 0 | 0 | 2.2 |
| Total no. | 6 | 12 | 52 | 46 | 39 | 31 | 46 | 3 | 232 |

***Coxsackievirus B1***

Among 192 patients with coxsackievirus B infection, 5 (2.6%) had coxsackievirus B1. The diagnoses were aseptic meningitis (n = 2), atypical pneumonia (n = 1), abdominal pain (n = 1), and acute glomerulonephritis (n = 1). All 5 patients had fever, but none had oral ulcers or skin manifestations.

***Coxsackievirus B2***

Fifteen patients (7.8%) had coxsackievirus B2 infection. The most common diagnoses were herpangina (20%), tonsillitis/pharyngitis (20%), sinusitis (13.3%), and pharyngoconjunctival fever (13.3%). Two patients (13.3%) had complications of aseptic meningitis. All patients had fever. Oral ulcer and skin rash were present in only 20.0% and 6.7% of patients, respectively. Respiratory symptoms were prominent (cough, 66.7%; rhinorrhea, 53.3%). Tonsil exudates and acute otitis media were present in 33.3% and 13.3% of patients, respectively.

***Coxsackievirus B3***

107 patients (55.7%) had coxsackievirus B3 infection. The most common diagnoses were tonsillitis/pharyngitis (27.1%) and herpangina (19.6%). Epidemic pleurodynia, myocarditis, and chest pain were diagnosed in 7, 1, and 1 patients, respectively. Twelve patients (11.2%) had complications, including aseptic meningitis (n = 8), encephalitis (n = 2), myocarditis (n = 1), and HNC (n = 1). The most common symptom was fever (96.3%). Skin rash developed in 8.4% of patients, oral ulcer in 23.4%, tonsil exudates in 30.8%, and abnormal breath sounds in 9.3%.

***Coxsackievirus B4***

Four patients (2.1%) had coxsackievirus B4 infection. Viral exanthema (n = 1) and Kawasaki disease (n = 1) were diagnosed. Two patients (50.0%) had complications, including encephalitis (n = 1) and encephalomyelitis (n = 1). The most common symptoms were fever (100.0%), skin rash (75.0%), and vomiting (50.0%).

***Coxsackievirus B5***

Twenty four patients (12.5%) had coxsackievirus B5 infection. The most common complication was aseptic meningitis (50.0%). The most common symptom was fever (91.7%).

***Coxsackievirus B6***

Two patients (1.0%) had coxsackievirus B6 infection. One patient was a 30-year-old woman with pharyngitis and the other was a 3-year-old boy with aseptic meningitis.

## Discussion

Coxsackieviruses can cause a wide variety of diseases, particularly in infants and young children. During the first year of life, enterovirus infections occur mostly in infants younger than 3 months [11]. In this study, infants younger than 3 months accounted for 7.7% of the study population and most coxsackievirus infections (90.1% for coxsackievirus A16 and 76% coxsackievirus B) occurred before the age of 6 years. Boys were more likely to be infected than girls (male-to-female ratio was 1.73:1 for coxsackievirus A and 1.43:1 for coxsackievirus B), a finding in accordance with previous

reports [3,4,11]. In temperate countries, enterovirus infections primarily occur in the summer and autumn [12], but seasonal fluctuations are not so obvious in tropical areas. In this study, coxsackievirus B infections peaked in the summer. However, a considerable number of coxsackievirus A infections were still noted in winter.

Enterovirus is usually transmitted via the fecal-oral route and respiratory aerosols. Enteroviruses can be found in the respiratory tract 1 to 2 weeks after infection and in feces for up to 11 weeks [13]. It is believed that enterovirus initially proliferates in the distal bowel and upper respiratory tract. Minor viremia occurs as a result of viral spread to distant lymph nodes and major viremia could occur, leading to spread of the virus to many target organs [4]. In this study, a biphasic fever pattern was noted in 4.2% of inpatients with coxsackievirus B, but was not noted in patients with coxsackievirus A. This may indicate that minor viremia in coxsackievirus A has less impact than coxsackievirus B, but the mechanism requires further investigation. The longer duration of fever associated with coxsackievirus B infection may reflect a more virulent virus, leading to more complications.

Enterovirus is the most important pathogen of aseptic meningitis. Coxsackievirus B and echovirus accounted for more than 90% of infections [14-16], while coxsackievirus A accounted for less than 5% [17]. CSF leukocyte counts in patients with enterovirus aseptic meningitis range from 10 to 500/mm$^3$, but may occasionally exceed 1000/mm$^3$ [3]. In this study, 61 patients underwent lumbar puncture and only 2 patients had CSF leukocyte counts >500/mm$^3$ (1333/mm$^3$ and 554/mm$^3$; neither patient had a traumatic lumbar puncture). Overall, the CSF glucose concentration was normal and the CSF protein concentration was normal or slightly elevated. However, other studies have found that 18% to 33% of patients may have hypoglycorrhachia [3,18,19]. In this study, none of the patients with coxsackievirus A had hypoglycorrhachia, but 6 of 43 patients with coxsackievirus B who underwent lumbar puncture had hypoglycorrhachia (CSF glucose ≤40 mg/dL). Among these 6 patients, 5 were younger than 3 months. The CSF virus isolation yield from patients with aseptic meningitis is 30% to 35% [3]. In this study, positive virus isolation was noted in 35.7% coxsackievirus A infections and 71.1% in coxsackievirus B infections. Based on CSF pleocytosis, the sensitivities of CSF virus isolation were 25% for coxsackievirus A and 79.4% for coxsackievirus B.

Neonates with enterovirus infections usually have CNS involvement and exhibit 2 characteristic clinical syndromes, myocarditis or fulminant hepatitis. In this study, 66.7% of neonates (100% for coxsackievirus B, 33.3% for coxsackievirus A) and 64.3% of infants younger than 2 months (76.2% for coxsackievirus B and 28.6% for coxsackievirus A infection) had aseptic meningitis. Coxsackievirus B infection exhibited more CNS involvement than coxsackievirus A ($p < 0.001$). Among the 30 infants younger than 2 months, only 1 developed hepatic necrosis. According to Lin et al, 146 neonates in northern Taiwan had non-polio enterovirus infections, 61 had aseptic meningitis, and 42 had HNC [5]. In the study by Khetsuriani et al, neonates infected with coxsackievirus B4 had a higher risk of death (odds ratio [OR], 6.5; 95% confidence interval, 2.4-17.7) than those infected with other enteroviruses [10]. In addition, the time of onset of illness may play an important role since trans-placental infections may have more serious clinical presentations. The incubation period for enterovirus disease is usually 3 to 5 days (range, 2 to 12 days) and the onset of disease within 2 days of life denotes trans-placental infection. Onset beyond 12 days old indicates post-natal infection, which tends to be milder. In this study, only 2 patients presented with illness within 2 days of birth, thus trans-placental transmission occurred in a very small proportion of cases. Lin et al also noted that earlier onset of illness was a significant factor associated with HNC [5]. In their study, neonates presenting with infection within 7 days of birth had an OR of 49.1 for development of HNC compared with those who presented with infection after 7 days. Although enterovirus infections during early infancy may cause serious complications, survivors appear to have a good prognosis without sequelae [6-8]. In this study, all patients recovered without sequelae.

In conclusion, this study showed that the dominant coxsackieviruses were A16 (50.7%), B3 (23.4%), B5 (5.2%), and A10 (4.1%). Children younger than 6 years were most likely to be affected. Patients with coxsackievirus B infection had higher hospital admission rates, more CNS involvement, and longer duration of fever. In contrast, patients with coxsackievirus A infection had more skin manifestations and oral ulcers.

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The microbiology, epidemiology, and pathogenesis of these infections are discussed separately. (See "Enterovirus and parechovirus infections: Epidemiology and pathogenesis".) Poliovirus infection and prevention are discussed in detail elsewhere.Â  An atypical presentation of HFM caused by coxsackievirus A6 and characterized by vesiculobullous lesions with wider cutaneous distribution and a higher risk of onychomadesis (nail shedding) has been observed in the United States and elsewhere [12-14]. HFM is discussed in detail elsewhere.Â  In infants, the characteristic symptoms and signs of meningitis are difficult to elicit by history and examination. The most common clinical manifestations are fever and irritability [27]. Rotavirus Infections: Epidemiology, Clinical Characteristics and Treatment Options. Carissa D. Zeni (Editor). Series: Allergies and Infectious Diseases BISAC: MED022090.Â  Chapter 6 - VHH Technology: A Potential Passive Immune Therapy to Control Rotavirus Infections in Human Infants (pp. 117-156) Lorena Garaicoechea, Celina Vega and Viviana ParreÃ±o (Instituto de VirologÃa-INTA Castelar, Buenos Aires, Argentina). Chapter 7 - Neurological Presentation of Rotavirus Infection: Epidemiology and Possible Pathophysiology (pp. 157-176) Jung Sook Yeom and Hee-Shang Youn (Department of Pediatrics, Gyeongsang National University School of Medicine, Gyeongsang Institute of Health Science, Jinju, Korea). Index. You have not viewed any product yet. Clinical and epidemiologic features of coxsackievirus A6 infection in children in northern Taiwan between 2004 and 2009. J Microbiol Immunol Infect. 2011;44:252â€“257.Â  Epidemiology and clinical characteristics of hand foot, and mouth disease in a Shenzhen sentinel hospital from 2009 to 2011. BMC Infect Dis. 2013;13:539.