ORIGINAL ARTICLE

WILEY

Clinical characteristics and effectiveness of antiviral agents in hospitalized children with infectious mononucleosis in China: A multicenter retrospective study

Huili Hu[1*] | Huiling Deng[2*] | Jing Bi[3*] | Yi Xu[4] | Shuangjie Li[5] | Yue Xie[1] | Xinrong Sun[2] | Dongmeng Wang[3] | Xufang Li[4] | Wenxian Ouyang[5] | Bing Hu[1] | Yufeng Zhang[2] | He Tang[3] | Chunxiao Fang[4] | Hui Zhang[5] | Lingyun Guo[1] | Chen Wang[2] | Tianyi Wang[3] | Fengxia Yang[4] | Tao Jiang[5] | Zhengde Xie[6] | Gang Liu[1]

Authors' affiliations appear at the end this article.

Correspondence

Zhengde Xie, Laboratory of Infection and Virology, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
Email: xiezhengde@bch.com.cn
Gang Liu, Department of Infectious Diseases, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
Email: liugang10@hotmail.com

*These authors contributed equally to this work.

ABSTRACT

Importance: The clinical characteristics of infectious mononucleosis (IM) in Chinese children have not been evaluated in multicenter studies, and the effectiveness of antiviral treatment are controversial.

Objective: To investigate the clinical characteristics of Chinese children with IM and current status of antiviral therapy for affected patients.

Methods: Hospitalized patients with IM were enrolled between 2018 and 2020 in five children's hospitals in China. The clinical characteristics were compared among four age groups: <3 years, 3–<6 years, 6–<10 years, and ≥10 years. The clinical characteristics of IM and effectiveness of antiviral therapy were compared among patients receiving acyclovir (ACV), ganciclovir (GCV), and no antiviral therapy (i.e., non-antiviral group).

Results: In total, 499 patients were analyzed; most patients were 3–<6 years of age. The most common symptoms and signs included fever (100%), lymphadenopathy (98.6%), pharyngitis (86.4%), eyelid edema (76.8%), and snoring (72.9%). There were significant differences in rash, hepatomegaly, and liver dysfunction among the four age groups. Patients aged < 3 years had a lower incidence of liver dysfunction and a higher incidence of rash. Among the 499 patients, 50.1% were treated with GCV, 26.3% were treated with ACV, and 23.6% received no antiviral therapy. Compared with the non-antiviral group, patients in the ACV and GCV groups had longer durations of fever ($P < 0.001$). There were no significant differences in the incidences of complications among the three treatment groups.

Interpretation: The incidence of IM in Chinese children peaked at 3–<6 years of age. Clinical features of IM varied according to age. Patients receiving antiviral therapy exhibited more serious clinical manifestations than did patients without antiviral therapy. The effectiveness of antiviral therapy for IM requires further analysis.

KEYWORDS

Infectious mononucleosis, Antiviral, Ganciclovir, Acyclovir

INTRODUCTION

Infectious mononucleosis (IM) is caused by primary infection with the Epstein-Barr virus (EBV); this condition is characterized by fever, pharyngitis, lymphadenopathy, fatigue, and atypical lymphocytosis.[1,2] There is a high prevalence of EBV infection in China.[3-5] Although IM can be self-limiting, it can sometimes cause atypical and life-threatening manifestations. Clinical manifestations in children with EBV infection involve multiple systems and can cause severe illness; thus, there is a need for careful attention during diagnosis and treatment.[1,2,6]

There are differences in the age at onset among patients according to their geographic region. In Western countries, most patients with primary EBV infections (especially infants and children <6 years of age) are asymptomatic. Approximately 50% of primary infections in adolescents and adults result in IM.[6] IM is generally expected to intensify as the age at onset increases,[7] but recent studies have shown that EBV infection is more common in younger children.[8,9] In contrast to Western countries, IM mainly occurs in children 3–<6 years of age in China.[3-5]

Thus far, antiviral medications such as ganciclovir (GCV) and acyclovir (ACV) have been shown to inhibit EBV replication,[10-12] but the clinical effectiveness of antiviral therapy for IM is controversial.[10,13,14] The results of studies in Western countries have not conclusively demonstrated the effectiveness of ACV treatment. However, multiple studies of GCV treatment in China have shown that it can shorten the course of IM and relieve symptoms.[15,16] Importantly, few patients were included in the studies of GCV, and many studies have not included controls who received no antiviral therapy. To our knowledge, there have been no comparative studies among the three types of treatments: ACV, GCV, and general systemic treatment (i.e., no specific antiviral therapy).

The clinical characteristics of IM in Chinese children have not been evaluated in multicenter studies, and the effectiveness of antiviral treatment are controversial. In this multicenter retrospective study, we investigated the clinical characteristics of Chinese children with IM and current status of antiviral therapy for affected patients.

METHODS

Ethical approval

This study was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University (2020-Z-125) and the Medical Ethical Committees of the selected hospitals (Xi'an Children's Hospital: 20210028; Baoding Children's Hospital: 202017; Guangzhou Women and Children's Medical Center: 202061401; Hunan Children's Hospital: HCHLL-2015-089).

Study population and setting

This study included hospitalized patients from five tertiary children's hospitals between 1 and 18 years of age who met the inclusion and exclusion criteria for IM (described below) between 1 January 2018 and 31 October 2020. Clinical data were retrospectively collected from the patients' medical records by clinicians in each hospital; these data included demographic factors, clinical presentations, laboratory parameters, disease management methods, and outcomes.

Diagnostic criteria for IM

The definition of IM in this study was based on published diagnostic criteria for IM.[17] These criteria were as follows: the presence of $\geq$ 3 characteristic symptoms (i.e., fever, cervical lymph node swelling, hepatomegaly, splenomegaly, pharyngeal tonsillitis, and eyelid edema); atypical lymphocyte number $\geq$ 10% of the total lymphocytes and/or total lymphocyte count $\geq 5.0 \times 10^9$/L in peripheral blood; and the presence of specific antibodies: (1) anti-viral capsid antigen (VCA)-IgM and anti-VCA-IgG antibodies were positive while anti-EBV nuclear antigen (EBNA)-IgG antibody was negative; (2) anti-VCA-IgM antibody was negative but anti-VCA-IgG antibody was positive with low-affinity.

Inclusion criteria

Patients were included in the study if they met the following criteria: confirmed diagnosis of IM and documented fever $\geq$ 37.5°C within 5 days before admission.

Exclusion criteria

Patients were excluded from the study if they met the following criteria: presence of serious underlying diseases (e.g., primary immunodeficiency, malignancy, and/or other systemic diseases) and/or absence of complete medical records.

Definition of complications

Liver dysfunction was defined as an increase in serum alanine aminotransferase (ALT) level two fold greater than the upper limit of the reference interval that could not be explained by other sources of liver dysfunction.[18]

Myocardial damage was based on the Beijing Children's Hospital group consensus regarding the diagnosis and treatment of myocardial damage (2014 edition): the patient is asymptomatic or exhibits one of the following manifestations: shortness of breath, chest tightness, chest pain, palpitation, and/or fatigue after activities; serum myocardial enzyme levels are increased in the acute phase, especially creatine phosphokinase and creatine kinase-MB (CK-MB); serum troponin test results are often

negative; electrocardiography findings are nonspecific or demonstrate various abnormalities that are not characteristic of myocarditis.

Neutropenia was defined as a neutrophil count $< 1.5 \times 10^9$/L.

Gastrointestinal discomfort included abdominal pain and abdominal distension.

Thrombocytopenia was defined as a thrombocyte count $< 100 \times 10^9$/L.

Analysis of clinical features

The clinical features were compared among four age groups: <3 years, 3–<6 years, 6–<10 years, and ≥10 years. Demographic data and clinical characteristics were obtained from each patient's record; this information included the presenting symptoms and signs, complications, laboratory parameters, treatments, and outcomes.

Application of antiviral agents and their clinical effectiveness

To analyze the current status and clinical effectiveness of antiviral therapies, patients were divided into three treatment groups: ACV, GCV, and non-antiviral, according to the antiviral therapy that they had received. At 12-hour intervals, GCV was intravenously infused at a dosage of 5 mg per kilogram body weight. At 8-hour intervals, ACV was intravenously infused at a dosage of 10 mg per kilogram body weight. Patients in the non-antiviral group were only administered general systemic treatment; they received no antiviral drugs.

The clinical characteristics of patients with IM were compared among the three treatment groups.

Statistical analysis

Kolmogorov-Smirnov test was used to determine whether the data exhibited a normal distribution. The data were expressed as means and standard deviations (SDs) for normally distributed variables; otherwise, data were expressed as medians and interquartile ranges (IQRs). Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. Continuous variables were compared between groups the Mann–Whitney U test for nonparametric data. P values <0.05 were considered statistically significant. All statistical analyses were conducted using SPSS Statistics, version 23.0 (IBM Corp., USA).

RESULTS

Patients

Among 2170 hospitalized patients who were newly diagnosed with IM at the participating hospitals during the study period, 499 eligible patients (23.0%) were included in our study. Of the 499 patients, 309 (61.9%) were boys, and 190 (38.1%) were girls; the male-to-female ratio was 1.6:1. In total, 107 (21.4%) patients were from rural areas; 392 (78.6%) patients were from urban areas. The age at onset ranged from 1 to 18 years, with a median age of 4 years (IQR, 3–6 years). Among the patients, 120 (24.0%) were < 3 years of age, 244 (48.9%) were 3–<6 years of age, 112 (22.4%) were 6–<10 years of age, and 23 (4.6%) were ≥ 10 years of age (Table 1).

Clinical characteristics

The clinical features of each age group are shown in Table 1. The symptoms included fever, lymphadenopathy, pharyngitis, eyelid edema, snoring, hepatomegaly, splenomegaly, and rash. The median duration of fever was 3.0 (IQR, 2.0–5.0) days. Complications were present in 261 (52.3%) patients, including liver dysfunction, myocardial damage, neutropenia, gastrointestinal discomfort (e.g., abdominal pain and/or abdominal distension), and thrombocytopenia. There were significant differences in rash, hepatomegaly and liver dysfunction among the four age groups. The incidence of hepatomegaly was higher in preschool children than among children in other age groups ($P = 0.017$). The incidence of rash was higher in younger patients ($P = 0.014$); the incidence decreased with increasing age. In contrast, patients aged < 3 years had a lower incidence of liver dysfunction ($P = 0.005$). The incidence of liver dysfunction decreased in patients aged > 10 years.

Among the 499 patients, 345 (69.1%) were treated with antibiotics; 263 (52.7%) had antibiotic treatment before admission. Among the 58 patients with a skin rash, 30 (51.7%) were treated with antibiotics; of the 30 patients, 20 (66.7%) were administered cephalosporin, four (13.3%) were administered penicillin, and three (10%) were administered penicillin and a cephalosporin.

At admission, 452/499 (90.6%), 298/478 (62.3%), 173/499 (34.7%) and 345/445 (77.5%) patients had elevated white blood cell (WBC) count, atypical lymphocytes ≥10%, ALT ≥80 U/L (Table 1), and EBV-DNA, respectively (Table 2). There were significant differences in WBC count ($P = 0.013$), ALT level ($P = 0.001$), and CK-MB level ($P < 0.001$) (Table 2) among the four age groups. Higher total WBC count was more common in younger patients than in older patients ($P = 0.013$). ALT level ranged from 6.0 to 969.0 IU/L, with a median of 52.1 (IQR, 27.9–108.0) IU/L. The ALT level was significantly lower in children < 3 years than among children in other age groups. In contrast, the CK-MB level decreased with increasing age ($P < 0.001$). The median atypical lymphocytes proportion was 12% (IQR, 8%–18%); this did not differ among the four age groups ($P = 0.370$). The proportion of CD4+ T cells decreased and the proportion of CD8+ T cells increased; these did not differ among the

TABLE1 Clinical features among different age groups in 499 patients with infectious mononucleosis

Characteristics	Total (n = 499)	<3 y (n = 120)	3–<6 y (n = 244)	6–<10 y (n = 112)	≥10 y (n = 23)	P
Male	309 (61.9)	70 (58.3)	156 (63.9)	70 (62.5)	13 (56.5)	0.711
Clinical features						
Snoring	364 (72.9)	88 (73.3)	185 (75.8)	76 (67.9)	15 (65.2)	0.362
Eyelid edema	383 (76.8)	97 (80.8)	190 (77.9)	79 (70.5)	17 (73.9)	0.282
Rash	58 (11.6)	23 (19.1)	24 (9.8)	10 (8.9)	1 (4.3)	0.014
Pharyngitis	431 (86.4)	101 (84.2)	208 (85.2)	101 (90.2)	21 (91.3)	0.455
Hepatomegaly	310 (62.1)	74 (61.7)	161 (66.0)	67 (59.8)	8 (34.8)	0.017
Splenomegaly	215 (43.1)	41 (34.2)	111 (45.5)	54 (48.2)	9 (39.1)	0.121
Lymphadenopathy	492 (98.6)	118 (98.3)	241 (98.8)	110 (98.2)	23 (100.0)	0.906
T 38.0–39.0 °C	243 (48.7)	59 (49.2)	117 (48.0)	56 (50.0)	11 (47.8)	0.986
T 39.1–40.0 °C	180 (36.1)	45 (37.5)	85 (34.8)	40 (35.7)	10 (43.5)	0.844
Complications						
Liver dysfunction (ALT ≥80U/L)	173 (34.7)	29 (24.2)	89 (36.5)	50 (44.6)	5 (21.7)	0.005
Gastrointestinal discomfort	10 (2.0)	3 (2.5)	4 (1.6)	3 (2.7)	0 (0.0)	0.790
Myocardial damage	41 (8.2)	13 (10.8)	19 (7.8)	5 (4.5)	4 (17.4)	0.121
Neutropenia	31 (6.2)	10 (8.3)	12 (4.9)	7 (6.3)	2 (8.7)	0.599
Thrombocytopenia	6 (1.2)	1 (0.8)	1 (0.4)	4 (3.6)	0 (0.0)	0.072

Data are shown as n (%). ALT, alanine aminotransferase.

TABLE 2 Laboratory data among different age groups in 499 patients with infectious mononucleosis

Variables	<3 y (n = 120)	3–<6 y (n = 244)	6–<10 y (n = 112)	≥10 y (n = 23)	P
WBC ($\times10^9$/L)	16.69 (13.35–21.45)	16.01 (12.83–19.88)	15.09 (12.38–18.32)	12.90 (10.80–17.18)	0.013
Monocytes (%)	7.4 (5.3–10.0)	7.8 (5.2–10.0)	6.7 (4.8–9.0)	8.0 (4.8–11.4)	0.175
ALC (%)	13.0 (8.0–20.0)	10.0 (6.0–18.0)	12.0 (7.0–17.0)	10.0 (6.0–15.0)	0.370
ALC ≥10%	80/118 (67.8)	139/233 (60.0)	65/104 (62.5)	14/23 (60.9)	0.525
CK-MB (U/L)	22.0 (17.3–26.0)	18.1 (15.0–24.0)	17.0 (13.0–21.0)	13.0 (9.8–16.7)	<0.001
ALT (U/L)	41.9 (22.0–81.0)	54.0 (26.8–120.8)	65.7 (35.3–154.9)	62.0 (38.0–79.4)	0.001
LDH (U/L)	460.0 (386.0–541.0)	462.0 (377.0–560.0)	462.0 (398.0–540.0)	513.0 (350.0–602.0)	0.963
EBV-DNA[†] (copies/mL)	6.14×10^3 (1.60×10^3–3.30×10^4)	1.71×10^3 (5.00×10^2–8.40×10^3)	2.39×10^3 (5.00×10^2–7.60×10^3)	3.50×10^3 (7.10×10^2–6.40×10^3)	0.893
CD4 (%)	15.7 (10.8–21.6)	15.5 (11.7–23.6)	14.1 (11.6–17.9)	14.0 (11.9–25.1)	0.343
CD8 (%)	64.6 (56.5–71.7)	64.5 (55.6–73.0)	63.9 (56.5–70.1)	58.3 (47.5–70.0)	0.382

Data are shown as n/N (%) or median (interquartile range). WBC, white blood cell; ALC, atypical lymphocytes; ALT, alanine aminotransferase; CK-MB, creatine kinase-MB; LDH, lactate dehydrogenase. [†]EBV-DNA refers to EBV-DNA in serum/plasma.

four age groups. All patients showed improvement and were eventually discharged.

Application of antiviral agents and their clinical effectiveness

Among the 499 patients, 250 (50.1%) were treated with GCV, 131 (26.3%) were treated with ACV, and 118 (23.6%) did not receive antiviral therapy (Table 3). The total course of treatment was 1–14 days, with a median of 7 (IQR, 5–7) days.

At admission, clinical features and laboratory data were compared among the ACV, GCV, and non-antiviral groups (Table 3). All patients had a fever; it was between 38°C and 39°C in 243 (48.7%) patients, while it was between 39.1°C and 40°C in 180 (36.1%) patients. More patients in the ACV and GCV groups had a temperature >39.1°C (P <0.001), compared with patients in the non-antiviral group. Additionally, the incidences of pharyngitis (P = 0.001), snoring (P = 0.010), and atypical lymphocytosis ≥10% (P = 0.016) were higher among patients in the ACV and GCV groups, which suggested that patients in these

groups exhibited more serious clinical manifestations than did patients in the non-antiviral group.

Regarding the durations of symptoms (Table 4), there were significant differences among the three treatment groups in terms of fever (P <0.001), snoring (P = 0.047), and splenomegaly (P = 0.002). Pairwise comparisons among the three treatment groups showed that the durations of fever, snoring, and splenomegaly were significantly longer in the ACV group (P <0.001, P = 0.037, and P = 0.005, respectively) and GCV group (P < 0.001, P = 0.019, and P = 0.001, respectively) than in non-antiviral group; these differences may have been related to the more serious disease manifestations exhibited by patients who received antiviral treatment. No significant differences in any symptoms were observed between the ACV and GCV groups. There were no significant differences in the incidences of complications among the three treatment groups (Table 4).

DISCUSSION

To our knowledge, this is the first large multicenter study

to evaluate the clinical characteristics of hospitalized pediatric patients with IM in China, as well as the antiviral treatment outcomes among these patients.

In this study, most patients with IM were younger than 6 years of age; the peak incidence occurred at 3–<6 years of age, similar to the findings in previous studies.[4,19,20] The most common symptoms and signs included fever, lymphadenopathy, pharyngitis, eyelid edema, and snoring; the incidences varied among age groups. The incidence of hepatomegaly was higher in preschool children than among children in other age groups, while the incidence of rash was higher in younger patients than in older patients.

In this study, approximately half of the patients with IM had nonlife-threatening complications, which mainly included liver dysfunction, myocardial damage, gastrointestinal discomfort, and neutropenia. Patients aged <3 years had a lower incidence of liver dysfunction. Similar results were found in two previous studies.[19,20] These results are presumably because cellular immune responses are crucial in the pathogenesis of EBV

infections.[1,2,6] Primary EBV infection targets B cells and is accompanied by a prominent reactive expansion of T cells.[11,21] Most symptoms and complications of IM are not caused by the direct toxic effects of EBV on the infected tissue; they result from an abnormal immune response. This study showed that infants had a significantly lower incidence of liver dysfunction than did older children, which may be related to the degree of immune system maturity. However, the incidence of liver dysfunction decreased in patients aged >10 years, presumably because fewer such patients were included in the study.

Multiple studies in Western countries have demonstrated controversial findings regarding the use of antiviral treatment in patients with IM.[9,22-25] Torre D et al[26] published a meta-analysis that included five randomized controlled trials (RCTs) regarding IM patients treated with the ACV. The meta-analysis revealed a trend suggestive of clinical effectiveness, but no statistically significant results were observed; thus far, clinical data do not support the use of ACV for the treatment of acute IM. In 2016, De Paor et al[13] published a meta-analysis that studied antiviral therapy

TABLE 3 Baseline clinical data of acyclovir, ganciclovir versus non-antiviral therapy in 499 patients with infectious mononucleosis

Variables	Total ($n = 499$)	Non-antiviral ($n = 118$)	Ganciclovir ($n = 250$)	Acyclovir ($n = 131$)	P
Male	309 (61.9)	71 (60.2)	161 (64.4)	77 (58.8)	0.508
Age (years)	4.3 (3.0–6.0)	2.3 (1.9–2.6)	4.4 (2.4–5.9)	3.4 (2.5–5.6)	0.387
Symptoms and signs					
Fever (T >37.5°C)	499 (100.0)	118 (100.0)	250 (100.0)	131 (100.0)	NA
T 38.0–39.0°C	243 (48.7)	43 (36.4)	139 (55.6)	61 (46.6)	0.002
T 39.1–40.0°C	180 (36.1)	20 (16.9)	95 (38.0)	65 (49.6)	<0.001
Snoring	364 (72.9)	75 (63.6)	196 (78.4)	93 (71.0)	0.010
Pharyngitis	431 (86.4)	91 (77.1)	228 (91.2)	112 (85.5)	0.001
Hepatomegaly	310 (62.1)	79 (66.9)	153 (61.2)	78 (59.1)	0.443
Splenomegaly	215 (43.1)	46 (39.7)	102 (40.8)	67 (50.8)	0.090
Lymphadenopathy	492 (98.6)	116 (98.3)	247 (98.8)	129 (98.5)	0.922
WBC $\geq 10 \times 10^9$/L	452 (90.6)	102 (86.4)	225 (90.0)	125 (95.4)	0.048
Elevated ALC	454/478 (95.0)	105/110 (95.5)	223/239 (93.3)	126/129 (97.7)	0.181
ALC ≥10%	298/478 (62.3)	58/110 (52.7)	163/239 (68.2)	77/129 (59.7)	0.016
Antibiotic therapy	345 (69.1)	86 (72.9)	165 (66.0)	94 (71.8)	0.309

Data are shown as n (%) or n/N (%) or median (interquartile range). WBC, white blood cell; ALC, atypical lymphocytes; NA, not applicable.

TABLE 4 Clinical effectiveness of acyclovir, ganciclovir versus non-antiviral therapy in 499 patients with infectious mononucleosis

Variables	Total ($n = 499$)	Non-antiviral ($n = 118$)	Ganciclovir ($n = 250$)	Acyclovir ($n = 131$)	P
Duration[†] (d)					
Fever	3.0 (2.0–5.0)	2.0 (1.0–3.5)	3.0 (3.0–5.0)	3.0 (2.0–5.0)	<0.001[*]
Snoring	5.0 (4.0–6.0)	5.0 (3.0–5.5)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	0.047[**]
Pharyngitis	5.0 (3.0–6.0)	4.0 (3.0–5.0)	5.0 (3.0–6.0)	5.0 (3.0–6.0)	0.194
Hepatomegaly	7.0 (6.0–8.0)	5.0 (4.0–10.0)	7.0 (6.0–8.0)	8.0 (5.5–9.0)	0.290
Splenomegaly	7.0 (5.0–8.0)	5.0 (4.0–6.0)	7.0 (6.0–8.0)	8.0 (5.8–9.0)	0.002[***]
Lymphadenopathy	6.0 (5.0–8.0)	5.5 (4.0–8.3)	6.0 (5.0–9.0)	6.0 (4.0–7.0)	0.638
Complications					
Liver dysfunction (ALT ≥80U/L)	173 (34.7)	43 (36.4)	87 (34.8)	43 (32.8)	0.834
Gastrointestinal discomfort	10 (2.0)	1 (0.8)	5 (2.0)	4 (3.1)	0.463
Myocardial damage	41 (8.2)	7 (5.9)	17 (6.8)	17 (13.0)	0.067
Neutropenia	31 (6.2)	7 (5.9)	19 (7.6)	5 (3.8)	0.344

Data are shown as n (%) or median (interquartile range). ALT, alanine aminotransferase. [†]Duration means the days since symptom onset to disappearing. [*]Ganciclovir vs. non-antiviral group: $P < 0.001$; acyclovir vs. non-antiviral group: $P < 0.001$. [**]Ganciclovir vs. non-antiviral group: $P = 0.019$; acyclovir vs. non-antiviral group: $P = 0.037$. [***]Ganciclovir vs. non-antiviral group: $P = 0.001$; acyclovir vs. non-antiviral group: $P = 0.005$.

in patients with IM. Among the seven RCTs included in that meta-analysis, the antiviral agents used were ACV, valomaciclovir, and valacyclovir. Only two studies have shown that patients in the treatment group benefited from antiviral therapy. In terms of EBV infections, GCV maybe more efficacious than ACV, but this conclusion is based on the results of *in vitro* studies and a few limited case reports (often involving patients with EBV-related post-transplant disorders); thus, no substantial recommendations can be made.[27-30] In China, some studies regarding GCV have shown that GCV could shorten the course of IM and improve symptom severity.[15,16]

The results of this retrospective study showed that 381 (76.4%) of 499 patients with IM were administered antiviral medications, including ACV and GCV; GCV was administered to 250 (65.6%) patients, consistent with the findings in our previous single-center study.[31] These findings demonstrate the current status of antiviral therapy for IM in Chinese children. Compared with the non-antiviral group, patients in the ACV and GCV groups had longer durations of fever, snoring, and splenomegaly. These results may be related to the serious disease manifestations exhibited by patients who received antiviral treatment. Notably, there were no significant differences in the incidences of complications among the three treatment groups.

This study had several limitations. First, this was a hospital-based retrospective review, which might have led to bias in the results. Second, the baseline data of the three treatment groups demonstrated that disease manifestations were more serious at admission among patients who received antiviral treatment, compared with patients who did not receive such treatment. Third, complete follow-up data were not collected. Therefore, it is impossible to compare the rates of improvement in the symptoms, complications, and laboratory parameters among time periods, and our conclusions may not reflect the full outcomes of treatment.

In conclusion, the peak incidence of IM in Chinese children was at 3–<6 years of age. Clinical features of IM varied according to age. Most children with IM in China were treated with antiviral therapy, mainly GCV. The effectiveness of ACV and GCV for patients with acute IM remain unclear because the disease manifestations were more serious at admission among patients who received antiviral treatment, compared with patients who did not receive such treatment. Further prospective multicenter RCTs of IM treatment are warranted.

AFFILIATIONS

[1]Key Laboratory of Major Diseases in Children, Ministry of Education, Research Unit of Critical Infection in Children, Chinese Academy of Medical Science, Department of Infectious Diseases, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[2]Department of Infectious Diseases, Xi'an Children's Hospital, Xi'an, Shaanxi, China
[3]Department of Infectious Diseases, Baoding Children's Hospital, Baoding, Hebei, China
[4]Guangzhou Women and Children's Medical Center, Guangzhou, Guangdong, China
[5]Hepatology Center, Hunan Children's Hospital, Changsha, Hunan, China
[6]Beijing Key Laboratory of Pediatric Respiratory Infectious Diseases, Key Laboratory of Major Diseases in Children, Ministry of Education, National Clinical Research Center for Respiratory Diseases, Research Unit of Critical Infection in Children, Chinese Academy of Medical Sciences, 2019RU016, Laboratory of Infection and Virology, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

No conflicts of interest are declared with regard to this article.

REFERENCES

1. Luzuriaga K, Sullivan JL. Infectious mononucleosis. N Engl J Med. 2010;362:1993-2000.
2. Dunmire SK, Hogquist KA, Balfour HH. Infectious mononucleosis. Curr Top Microbiol Immunol. 2015;390:211-240.
3. Gao LW, Xie ZD, Liu YY, Wang Y, Shen KL. Epidemiologic and clinical characteristics of infectious mononucleosis associated with Epstein-Barr virus infection in children in Beijing, China. World J Pediatr. 2011;7:45-49.
4. Gao LW, Xie ZD, Yuan Y, Yang S, Liu YY, Wang Y, et al. Clinical characteristics of infectious mononucleosis associated with Epstein-Barr virus infection in children. J Appl Clin Pediatr. 2010; 25:725-727. (in Chinese)
5. Xiong G, Zhang B, Huang MY, Zhou H, Chen LZ, Feng QS, et al. Epstein-Barr virus (EBV) infection in Chinese children: a retrospective study of age-specific prevalence. PLoS One. 2014;9:e99857.
6. Cohen JL. Epstein-Barr Virus infection. N Engl J Med. 2000;343:481-492.
7. Fourcade G, Germi R, Guerber F, Lupo J, Baccard M, Seigneurin A, et al. Evolution of EBV seroprevalence and primary infection age in a French hospital and a city laboratory network, 2000-2016. PLoS One. 2017;12:e0175574.
8. Chen CY, Huang KY, Shen JH, Tsao KC, Huang YC. A large-scale seroprevalence of Epstein-Barr virus in Taiwan. PLoS One. 2015;10:e0115836.
9. Topp SK, Rosenfeldt V, Vestergaard H, Christiansen CB, Von Linstow ML. Clinical characteristics and

laboratory findings in Danish children hospitalized with primary Epstein-Barr virus infection. Infect Dis (Lond). 2015;47:908-914.

10. Pagano JS, Whitehurst CB, Andrei G. Antiviral drugs for EBV. Cancers (Basel). 2018;10:197.

11. Pagano JS, Sixbey JW, Lin JC. Acyclovir and Epstein-Barr virus infection. J Antimicrob Chemother. 1983;12 Suppl B:113-121.

12. Andersson J, Britton S, Ernberg I, Andersson U, Henle W, Sköldenberg B, et al. Effect of acyclovir on infectious mononucleosis: a double-blind, placebo-controlled study. J Infect Dis. 1986;153:283-290.

13. De Paor M, O'Brien K, Brien K, Fahey T, Smith SM. Antiviral agents for infectious mononucleosis (glandular fever). Cochrane Database Syst Rev. 2016;12:CD011487.

14. Andrei G, Trompet E, Snoeck R. Novel therapeutics for Epstein-Barr virus. Molecules. 2019;24:997.

15. Li R, Liu X, Lei L, Shu C, Peng X, Liu P, et al. Clinical efficacy of ganciclovir in the treatment of infectious mononucleosis in children. J Clin Med Pract. 2019;23:96-99. (in Chinese)

16. Shan M, Hu J, Mu Y, Zhou K, Tian Y, Xia C. Curative effect of Ganciclovir combined with interferon-α1b inhalation in treating children with infectious mononucleosis. Chin J Appl Clin Pediatr. 2017;32:1174-1178. (in Chinese)

17. Subspecialty Group of Infectious Diseases, the Society of Pediatrics, Chinese Medical Association; National Group of EpsteinBarr Virus Associated Diseases in Children. Principle suggestions for diagnosis and treatment of main nontumorous Epstein-Barr virus-associated diseases in children. Chin J Pediatr. 2016;54:563-568. (in Chinese)

18. U. S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/ CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed July 30, 2021.

19. Wang Y, Li J, Ren YY, Zhao H. The levels of liver enzymes and atypical lymphocytes are higher in youth patients with infectious mononucleosis than in preschool children. Clin Mol Hepatol. 2013;19:382-388.

20. Cheng CC, Chang LY, Shao PL, Lee PI, Chen JM, Lu CY, et al. Clinical manifestations and quantitative analysis of virus load in Taiwanese children with Epstein-Barr virus-associated infectious mononucleosis. J Microbiol Immunol Infect. 2007;40:216-221.

21. Kimura H, Cohen JI. Chronic active Epstein-Barr virus disease. Front Immunol. 2017;8:1867.

22. Tynell E, Aurelius E, Brandell A, Julander I, Wood M, Yao QY, et al. Acyclovir and prednisolone treatment of acute infectious mononucleosis: a multicenter, double-blind, placebo-controlled study. J Infect Dis. 1996;174:324-331.

23. van der Horst C, Joncas J, Ahronheim G, Gustafson N, Stein G, Gurwith M, et al. Lack of effect of peroral acyclovir for the treatment of acute infectious mononucleosis. J Infect Dis. 1991;164:788-792.

24. Andersson J, Sköldenberg B, Ernberg I, Britton S, Henle W, Andersson U. Acyclovir treatment in primary Epstein-Barr virus infection. A double-blind placebo-controlled study. Scand J Infect Dis Suppl. 1985;47:107-115.

25. Balfour HH Jr, Hokanson KM, Schacherer RM, Fietzer CM, Schmeling DO, Holman CJ, et al. A virologic pilot study of valacyclovir in infectious mononucleosis. J Clin Virol. 2007;39:16-21.

26. Torre D, Tambini R. Acyclovir for treatment of infectious mononucleosis: a meta-analysis. Scand J Infect Dis. 1999;31:543-547.

27. Ville S, Imbert-Marcille BM, Coste-Burel M, Garandeau C, Meurette A, Cantarovitch D, et al. Impact of antiviral prophylaxis in adults Epstein-Barr virus-seronegative kidney recipients on early and late post-transplantation lymphoproliferative disorder onset: a retrospective cohort study. Transpl Int. 2018;31:484-494.

28. Goldani LZ. Treatment of severe infectious mononucleosis with famciclovir. J Infect. 2002;44:92-93.

29. Auwaerter PG. Recent advances in the understanding of infectious mononucleosis: are prospects improved for treatment or control? Expert Rev Anti Infect Ther. 2006;4:1039-1049.

30. Yager JE, Magaret AS, Kuntz SR, Selke S, Huang ML, Corey L, et al. Valganciclovir for the suppression of Epstein-Barr virus replication. J Infect Dis. 2017;216:198-202.

31. Chen T, Miao Y, Geng Z, Hu H, Hu B, Chen H, et al. Clinical features of primary Epstein-Barr virus infection in inpatients younger than 3 years old. Chin J Appl Clin Pediatr. 2016;31:1700-1704. (in Chinese)