

A Comparative Study of Severe and Critical Influenza B in Children in the 2021–2022 Winter Season

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Introduction: Influenza B viruses are less common than influenza A viruses in most seasons and cause relatively milder forms of infection that are less studied. We witnessed a dominance of influenza B in Shijiazhuang, China, in the 2021–2022 winter season. In this study, we comparatively investigated the severe and critical influenza B in pediatric patients.

Methods: Children who were hospitalized from December 2021 to January 2022 and diagnosed with influenza B were included in this study. Those who tested positive for COVID-19 were excluded. Demographic data, clinical features, underlying medical conditions, laboratory testing results, and treatment outcomes were retrieved and analyzed retrospectively. Disease severity was classified as severe or critical according to Chinese expert consensus on diagnosis and treatment of influenza in children.

Results: A significantly greater proportion of patients with critical influenza had extra-pulmonary complications and bacterial coinfections. Children with critical influenza B had substantially higher levels of procalcitonin and lactate dehydrogenase, a markedly higher neutrophil percentage and a significantly lower CD4+ lymphocyte percentage.

Conclusion: Our findings suggest that, to effectively manage critical influenza B, therapeutic regimens should consist of organ-specific supportive care, antibiotic application if bacterial coinfection is present, and anti-inflammatory and immune-boosting treatments.

Keywords: influenza B, critically ill children, extra-pulmonary complication, bacterial coinfection, treatment

Introduction

Influenza is an infectious respiratory disease caused by influenza A and influenza B viruses; it often occurs in outbreaks during the cold season and can cause severe outcomes and even death.^{1,2} Young children, elderly individuals and those with underlying medical conditions are especially vulnerable.^{3–6} It was estimated that 291,243–645,832 worldwide deaths occurred annually due to seasonal influenza during 1999–2015, and in this period of time the annual global influenza-associated respiratory mortality among children younger than 5 years ranged 9243–105,690.⁷

There were significant worldwide decreases in influenza activity during 2020 and 2021 after the onset of the COVID-19 pandemic.^{8–14} Such phenomenon was also reported in China for the 2020–2021 season along with a dramatic circulating subtype change with influenza B (Victoria strain) viruses responsible for over 99% cases.⁸ Not surprisingly, influenza B viruses (Victoria strain) were detected in the vast majority of children with influenza we treated between the end of 2021 and early 2022. Prior to the COVID-19 pandemic, co-circulation of influenza B Victoria and Yamagata strains or dominance of Yamagata B lineage were reported in some regions.^{15–17} Influenza can cause a substantial increase in outpatient visits, hospitalizations and deaths among children. Recognition of factors that contribute to influenza severity is key to improved treatment and reduced morbidity and mortality.³ The aim of this study was to identify factors associated with disease severity in children with influenza B virus infection during the COVID-19 pandemic, which has been scantily described in the literature.

Methods

Ethics Approval

This study was approved, with an approval No. 202012, by the Medical Research Ethics Committee of Children's Hospital of Hebei Province, in compliance with the principles of the Declaration of Helsinki, the Code of Ethics of the World Medical Association. Because this study is retrospective, which presents no risk of harm to subjects, and all patients are de-identified, the informed consent was waived by the Committee.

Study Subjects

Children (younger than 18 years of age) who were admitted into our hospital from December 2021 to January 2022 and diagnosed with influenza B were included in this study. Patients who tested positive for COVID-19 were excluded. Demographic data, clinical features, underlying medical conditions, laboratory testing results, and treatment outcomes were retrieved and analyzed retrospectively.

Laboratory Testing

Laboratory testing was performed in our Diagnostic Laboratory following established protocols.

Pathogen Detection

A multiplex PCR-based platform, namely the ResP-CE System, was used to simultaneously detect the following pathogens: influenza A virus, influenza B virus, respiratory syncytial virus (RSV), adenovirus (ADV), parainfluenza virus (PIV), human rhinovirus (HRV), human metapneumovirus (HMPV), human bocavirus (HBOV), human coronavirus (HCOV), Chlamydia, and *Mycoplasma pneumoniae* (MP). Multiplex PCR was performed as described elsewhere.¹⁸ Culture of respiratory secretion and blood samples for bacteria and fungi was done according to the protocols established in our diagnostic laboratory.

Disease Diagnosis and Severity Classification

Disease diagnosis and severity classification (severe or critical) were carried out according to the Chinese expert consensus on diagnosis and treatment of influenza in children (2020 Edition).¹⁹ Diagnosis was made if one of the following testing results was reported: 1) positive amplification of influenza B virus genomic nucleic acids by RT-PCR; 2) positive influenza B virus culture; and 3) a ≥ 4 -fold increase in the titer of serum influenza B virus-specific IgG antibodies. Severe influenza was determined if one or more of the following manifestations were present: 1) body temperature $>40^{\circ}\text{C}$ for 3 days or more with cough or chest pain; 2) dyspnea accompanied with cyanosis; 3) vomiting and/or diarrhea with dehydration; 4) consciousness alteration such as drowsiness or convulsion; 5) complicated pneumonia; 6) deterioration of underlying disease; or 7) hospitalization. Critical influenza was defined as having one or more of the following conditions: 1) respiratory failure; 2) sepsis shock; 3) multiple organ dysfunction syndrome; 4) acute necrotizing encephalopathy; or 5) other conditions requiring intensive care.

Treatment and Outcomes

All patients were treated according to the Chinese expert consensus on diagnosis and treatment of influenza in children (2020 Edition).¹⁹ Outcomes were recorded as recovered and discharged, improved and transferred to community hospitals, or death.

Statistical Analyses

All statistical analyses were performed using the SPSS 20.0 software. Data normality was determined by the Shapiro–Wilk test. Normally distributed data were expressed as mean $\pm$ standard deviation, and analyzed by the Student *t*-test. Non-normal data were presented as median (first quantile, third quantile), and analyzed by the Mann–Whitney test. Categorical data were analyzed by the Chi-square or Fisher's exact test. A *p* value less than 0.05 was considered statistically significant.

Results

A total of 88 patients with a median age of 48 months (range: 7–144 months) were included in this study. Of these patients, 73 had severe and 15 had critical influenza B. The demographics and clinical characteristics of the patients in the two groups are shown in Table 1. The age, the sex ratio, the fever peak and duration, and the percentage of patients with underlying conditions in the two groups were not significantly different. A significantly greater proportion of patients with critical influenza had extra-pulmonary complications (Table 1).

Laboratory testing revealed that white cell counts were not markedly different between the two groups; however, a significantly higher percentage of neutrophils and a significantly lower percentage of CD4⁺ cells were seen in the critical group (Table 2). C-reactive protein (CRP) levels in the two groups were not remarkably different; the critical group had substantially higher levels of procalcitonin (PCT) and lactate dehydrogenase (LDH) (Table 2). While children with critical conditions had substantially higher levels of serum alanine aminotransferase (ALT), levels of serum aspartate transferase (AST) were not significantly different between the two groups (Table 2). There were no significant differences in serum IL-1 β and TNF- β concentrations between children with severe and critical influenza (Table 2).

Bacterial coinfections occurred in 15 severe (15/73, 20.5%) and 7 critical cases (7/15, 46.7%). The percentage of patients with bacterial coinfection was significantly higher in the critical group ($p = 0.033$, Table 3). The most detected bacterium was *Streptococcus pneumoniae* with 7 in severe and 4 in critical patients. Viral coinfections were identified in 21 and 4 cases in the severe and critical group, respectively ($p = 0.999$), with adenovirus being the most detected. There were 21 and 3 cases positive for *Mycoplasma pneumoniae* in the severe and critical groups, respectively ($p = 0.751$) (Table 3).

Table 1 Demographic Data and Clinical Features Between Severe and Critical Patients

	Severe (n=73)	Critical (n=15)	P value
Gender (male/female)	52/21	10/5	0.72
Age (months)	42 (23, 71.5)	61 (36, 84)	0.34
Underlying disease, n	6	3	0.18
Peak fever (°C)	39.3 $\pm$ 0.7	39.0 $\pm$ 0.8	0.16
Fever duration (days)	7.0 (4.0, 8.0)	8.0 (4.8, 13.0)	0.14
Cardiovascular involvement	4	6	0.001
Neurologic involvement	4	6	0.001
Digestive system involvement	11	6	0.026

Table 2 Laboratory Testing Results

	Severe (n=73)	Critical (n=15)	P value
White cell count (10 ⁹ /L)	7.8 $\pm$ 3.9	7.6 $\pm$ 3.7	0.843
Neutrophil percent (%)	46.6 $\pm$ 20.3	69.0 $\pm$ 17.2	<0.001
CD4 ⁺ cell percent (%)	42.6 (37.9, 47.4)	33.1 (30.1, 38.4)	<0.001
CD8 ⁺ cell percent (%)	24.6 (20.9, 29.1)	26.7 (22.8, 32.6)	0.253
CRP	3.9 (1.2, 9.9)	5.56 (1.0, 24.2)	0.356
PCT (μ g/L)	0.1 (0.1, 0.2)	0.4 (0.1, 2.2)	0.024
LDH (U/L)	280 (240, 328)	331 (281, 489)	0.010
IL-1 β (pg/mL)	2.7 (1.0, 8.5)	1.2 (0.7, 2.9)	0.127
TNF- α (pg/mL)	3.9 (2.4, 5.9)	3.1 (2.7, 3.5)	0.453
ALT (U/L)	14.0 (10.3, 18.8)	23.5 (13.8, 124.5)	0.006
AST (U/L)	34.0 (26.3, 42.8)	49.0 (22.8, 183.5)	0.153

Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3 Coinfections Detected in Severe and Critical Cases

Coinfections	Severe	Critical	P value
Total bacterial coinfections, n	15	7	0.033
<i>S. pneumoniae</i> , n	7	4	
<i>M. catarrhalis</i> , n	4	0	
<i>H. influenza</i> , n	3	0	
<i>S. aureus</i> , n	1	0	
<i>S. maltophilia</i> , n	0	1	
<i>M. catarrhalis</i> + <i>S. aureus</i> , n	0	1	
<i>H. parainfluenzae</i> + <i>C. indologenes</i> , n	0	1	
Total viral coinfections, n	21	4	0.999
ADV, n	6	1	
RSV, n	4	1	
HRV, n	3	0	
PIV, n	1	1	
HBOV, n	1	0	
HCOV, n	1	0	
HMPV, n	1	0	
Influenza A virus, n	1	0	
ADV + RSV, n	2	0	
RSV + HMPV, n	1	0	
RSV + PIV, n	0	1	
Total <i>M. pneumoniae</i> coinfections, n	21	3	0.751

Abbreviations: *S. pneumoniae*, *Streptococcus pneumoniae*; *M. catarrhalis*, *Moraxella catarrhalis*; *H. influenza*, *Haemophilus influenzae*; *S. aureus*, *Staphylococcus aureus*; *S. maltophilia*, *Stenotrophomonas maltophilia*; *H. parainfluenzae*, *Haemophilus parainfluenzae*; *C. indologenes*, *Chryseobacterium indologenes*; ADV, adenovirus; RSV, respiratory syncytial virus; HRV, human rhinovirus; PIV, parainfluenza virus; HBOV, human bocavirus; HCOV, human coronavirus; HMPV, human metapneumovirus; *M. pneumoniae*, *Mycoplasma pneumoniae*.

Table 4 Treatment Outcomes

	Severe	Critical	P value
Length of hospital stay (days)	6 (4, 8)	13 (10, 15)	<0.001
Recovered	58	8	<0.001
Improved	15	3	<0.001
Death	0	4	<0.001

Notes: The number of patients who recovered, improved or died in the two groups is presented in this table.

Patients with critical conditions had a significantly greater length of hospital stay (Table 4). All children in the severe group recovered or improved, while four patients with an age range of 5–21 months died in the critical group (Table 4). Of these four patients, three had underlying medical conditions: one with developmental delay, one asthma and one spinal muscular atrophy.

Discussion

Influenza B viruses are less common than influenza A viruses in most seasons, and cause relatively milder forms of infection that are less studied.²⁰ We witnessed the dominance of influenza B Victoria strain in the 2021–2022 winter season, and characteristics of influenza B in children during the COVID-19 pandemic has not been described. In this study, we examined disease severity and its associated factors in children with influenza B between December 2021 and January 2022, and reported the following major findings: 1) a greater proportion of children who were critically ill had

extra-pulmonary complications and bacterial coinfections and 2) children with critical illness had higher levels of PCT and LDH, a higher percentage of neutrophils and a lower percentage of CD4⁺ lymphocytes.

Influenza can cause complications outside the respiratory system in both adults and children.^{21–27} A large series study of 2330 hospitalized pediatric patients with influenza A (H1N1 pdm09) during the 2009–2010 pandemic in the USA revealed that 709 (30.4%) children had complications affecting the digestive, neurological, musculoskeletal and cardiovascular systems.²³ Several recently published articles have described extra-pulmonary complications in hospitalized children with influenza B prior to the COVID-19 pandemic.^{24–27} Geerdes-Fenge et al treated 17 hospitalized children with influenza B in northern Germany in the winter season of 2017–2018, and revealed that 5 (29.4%) suffered extra-pulmonary complications,²⁴ lower than 42% (37/88) found in the present study (Table 1). A few studies focusing on neurologic involvement in hospitalized children with influenza B observed that approximately 10–15% of the patients had neurologic complications.^{25–27} A study conducted in Hong Kong found that 7.3% of the children (672/9175) between 2014 and 2018 had neurologic complications.²⁵ Frankl et al reported that, during 2010–2017, 12.9% of the hospitalized children (53/412) in a tertiary pediatric hospital in the USA had neurologic complications.²⁶ Mattila et al showed that 16.1% of hospitalized patients (18/112) in a university hospital in Finland from 2004 to 2018 had neurological system involved.²⁷ We demonstrated that 11.3% of the patients (10/88, Table 1) had neurologic manifestations. These data suggest that influenza B-associated extra-pulmonary complications are common in children prior to or during the COVID-19 pandemic. Extra-pulmonary complications can lead to high morbidity and mortality,²¹ and therefore their management should constitute a critical part of the therapeutic regimens.

Lymphocyte decrease or lymphopenia in children with influenza A or B and its association with disease severity have been reported.^{28–32} Lymphopenia negatively affects the host adaptive immune responses and prolongs the clinical course of viral infection.³¹ A recent study showed that CD4⁺ T cells promoted influenza virus-specific CD8⁺ T cell memory, and induced the differentiation of CD8⁺ cells into cytotoxic effector cells, which helped to eliminate virus.³³ In the present study, a substantially lower percentage of CD4⁺ lymphocytes was seen in critical patients than in severe patients, suggesting CD4⁺ cell decrease may reflect the disease severity.

PCT is recognized as a marker of systematic bacterial infection.^{34–36} It has been shown that children with influenza and bacterial coinfection have markedly higher levels of PCT than those who have influenza alone.^{37,38} However, comparison of PCT between severe and critically ill children with influenza B has not been described. In this study, we showed that critically ill patients had substantially higher levels of PCT, suggesting that PCT may serve as a marker for disease severity, which calls for further study.

Bacterial coinfection in critically and/or severely ill children with influenza B has been described.^{27,39} In a study aiming to evaluate the efficacy of vancomycin monotherapy for methicillin-resistant *Staphylococcus aureus* coinfection in children with influenza-related critical illness, Randolph et al showed that, during 2008–2016, 55.8% of the children (24/43) with critical influenza B had bacterial coinfection.³⁹ In another study, 34.8% (39/112) of hospitalized children with influenza B during 2004–2018 was found to have bacterial coinfection.²⁷ We observed a significantly higher rate of bacterial coinfections in the critically ill children. These results indicate that, to prevent deterioration of the illness, early recognition, and prompt and effective antibiotic treatment are important in suspected severe cases.

Due to the small sample size, especially with only 15 critical patients included in the current study, we were unable to perform a multiple regression analysis to identify factors significantly associated with disease severity. This is a limitation of the present study. Other limitations include the following: 1) this is a retrospective study involving a single center and 2) the vaccination rate among children aged under 5 years was extremely low ranging 3–4% from 2015 to 2019 in China,⁴⁰ therefore we were unable to assess the effect of vaccination in the children studied.

Conclusion

In conclusion, a substantially higher proportion of children with critical influenza B have extra-pulmonary complications and bacterial coinfection. Children who are critically ill may have higher levels of inflammation and lower levels of adaptive immunity. Therefore, therapeutic regimens for critical influenza B should consist of organ-specific supportive care, antibiotic application if bacterial coinfection is present, and anti-inflammatory and immune-boosting treatments.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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