

Nonsevere Acute Respiratory Syndrome Human Coronaviruses in Children Hospitalized with Acute Lower Respiratory Infection

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Abstract

Background: The nonzoonotic (nonsevere acute respiratory syndrome (SARS)/Middle East respiratory syndrome) human coronaviruses (HCoVs) are usually considered as the causative agent for acute respiratory infection. We studied the characteristics and outcome of children with non-SARS HCoV acute lower respiratory infection (ALRI). **Methods:** This was a cross-sectional study from a tertiary care teaching hospital in eastern India. **Results:** Of 137 samples tested positive for respiratory viruses, 13 were due to HCoV (7 boys, median age: 2 years). Cough was the most common symptom, followed by breathing difficulty and fever. An underlying comorbid condition present in 38.4%. Co-infection with other viruses was seen in 69% of cases. Chest radiograph was abnormal in 69.3% of children. Antibiotics were administered in 53.8%. The median length of hospitalization was 5 d, irrespective of underlying disease. There was no mortality. **Conclusions:** HCoV is an uncommon but increasingly recognized cause of ALRI in hospitalized children. No severe illness was found in children with underlying comorbidities. This study underscores the importance of HCoV in causation of childhood ALRI, necessitating a surveillance system in India.

Keywords: Hospitalization, human coronaviruses, lower respiratory infection, pediatric, polymerase chain reaction, respiratory virus

INTRODUCTION

Worldwide, acute respiratory infections (ARIs) cause more than 3 million deaths annually.^[1,2] Although the pathogens causing ARIs vary, viruses play a major role.^[3,4] In a recent systematic review, the most common respiratory viruses identified were respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, metapneumovirus, and rhinovirus (RV).^[3] Over the past decade, new viral etiologies like the human coronavirus (HCoV) have been identified. HCoV is gaining attention, and two broad types have been identified till date: nonzoonotic (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) and zoonotic (severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome coronavirus).^[5,6] Of the published studies on viral etiologies of ARI including HCoV from India, no study has specifically described the profile of children hospitalized with non-SARS HCoV acute lower respiratory infection (ALRI) from eastern India.

METHODS

This cross-sectional study included children (1 month to 12 years) with ALRI admitted to a tertiary care teaching hospital of eastern India over 1-year period (March 2019–2020). ARI was clinically diagnosed in the presence of fever, cough, coryza, and nasal catarrh (<1-week duration). ALRI was defined as per the revised WHO classification.^[7] SARI was defined as ARI with breathlessness requiring hospitalization. Hypoxemia was defined as SpO₂ <92% in room air. Children were managed as per the hospital protocol.

Respiratory samples (combined nasal and throat swabs) were collected in viral transport medium and were aliquoted

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How to cite this article: Das RR, Fajrudheen M, Mohanty M, John J, Rath S, Satapathy AK, *et al.* Nonsevere acute respiratory syndrome human coronaviruses in children hospitalized with acute lower respiratory infection. *J Global Infect Dis* 2021;13:33-5.

Received: 03 August 2020 **Revised:** 09 September 2020

Accepted: 17 September 2020 **Published:** 29 January 2021

Access this article online

Quick Response Code:



Website:
www.jgid.org

DOI:
10.4103/jgid.jgid_252_20

and stored at -70°C . Testing was done with the use of a real-time reverse transcriptase-polymerase chain reaction assay. Demographic, clinical, laboratory, epidemiologic, and radiologic data were retrieved from the case records. The data were anonymized to protect the privacy of the admitted children. The study was approved by the Institute Ethics Committee.

Statistical analysis

The data were managed on Microsoft Excel and analyzed. Only descriptive data presented as numbers (%).

RESULTS

Of 357 children hospitalized, respiratory samples were obtained from 283 children. Of 283 samples, 137 (48.4%) were positive for respiratory viruses, and HCoV were positive in 13 samples (13/137) with a prevalence of 9.5% (mono-infection = 4 and co-infection = 9) [Figure 1]. Of 4 mono-infections, 3 were due to HCoV-HKU1 and 1 due to HCoV-OC43. Of 9 co-infections, HCoV-OC43 was identified in 5 and HCoV-NL63 in 4 cases. RSV and RV were the most common viruses found in co-infection. Of 3 children infected with HCoV-HKU1 only, 2 were <6 months and 1 was of 2 years of age. All 6 children infected with HCoV-OC43 were ≥ 2 years of age. Of 4 children infected with HCoV-NL63, 3 were infants (<1 year of age) and 1 was of 6 years of age. Majority of the samples were collected from November to January (41.7%), followed by August to October (24.2%).

Of 13 children, 7 (53.8%) were boys. The median age was 2 y (range, 2 months–6 years), with 5 being infants (<1 year) (38.4%) [Table 1]. About 23% of children were prematurely born. Cough (54%) was the most common symptom, followed by breathing difficulty (48%) and fever (31%). Other symptoms were cold, poor feeding, diarrhea, and lethargy. The mean (\pm standard deviation [SD]) duration of symptoms was 3.6 (± 2) days. Five (38.4%) children had underlying comorbid conditions: mild asthma, interstitial

lung diseases, cystic fibrosis (CF), gastroesophageal reflux diseases, and trachea-bronchomalacia.

Regarding the laboratory parameters, the mean (SD) total leukocyte count was 8135 (2741)/ mm^3 , and mild leucopenia ($<5000/\text{mm}^3$) was observed in 2 (15.4%) children. The liver and renal function tests were within normal limits. C-reactive protein was found elevated in 3 children (23%). Chest radiograph was normal in 31% of children. In rest, the most common features were hyperinflation with infiltrates, either unilateral or bilateral. No bacterial co-infections were detected including in blood cultures.

In 7 (53.8%) children, antibiotics were started due to severe symptoms, chest symptoms, or possible infection/sepsis. Of 10 (76.9%) children having respiratory distress, 4 (30.7%) were hypoxic at admission (required oxygen therapy), but no children required mechanical ventilation. The median duration of hospital stay was 5 days (range, 2–9 days). There was no mortality.

DISCUSSION

The present hospital-based study found a prevalence of 9.5% of non-SARS HCoV ALRI among children from eastern India. The prevalence is higher than that of other studies (including children and adults with SARI) from India.^[6] The present study prevalence is even much higher than previously published studies including children with ARI.^[4,8] Infants (<1 year) constituted 38.4% of the study population, which is lower than the figure reported by a previously published study.^[9]

Like previous studies, majority of the isolated strains in the present study included HCoV-OC43.^[9] The most common co-infecting viruses identified were RSV and RV, like previous studies.^[9,10] In children, HCoV-NL63 has been associated with conjunctivitis, croup, asthma exacerbations, and febrile seizures; HCoV-HKU1 with febrile seizures; and HCoV-OC43 with ALRI.^[5] In the present study, similar findings were noted: majority of the children with HCoV-OC43 infection presented with ALRI and received antibiotics, and those with HCoV-NL63 infection presented with wheezing or asthma exacerbation and received nebulization commonly. No child presented with febrile seizure.

The clinical presentations of mono-infection were compared with co-infections, and the findings were as follows: mono-infection group commonly had crackles on auscultation, whereas fever was more common in co-infections. This is similar to findings from previous studies.^[9] It is likely that co-infection with more than one respiratory virus predisposes to the development of fever. In addition, crackles were commonly heard among patients with HCoV-OC43 infection, emphasizing the fact that ALRI was common with this strain of HCoV.^[5,9]

The major strengths of the present study include the largest study from India till date reporting exclusively about non-SARS HCoV ALRI cases among hospitalized children from a single center. The limitations are retrospective nature of

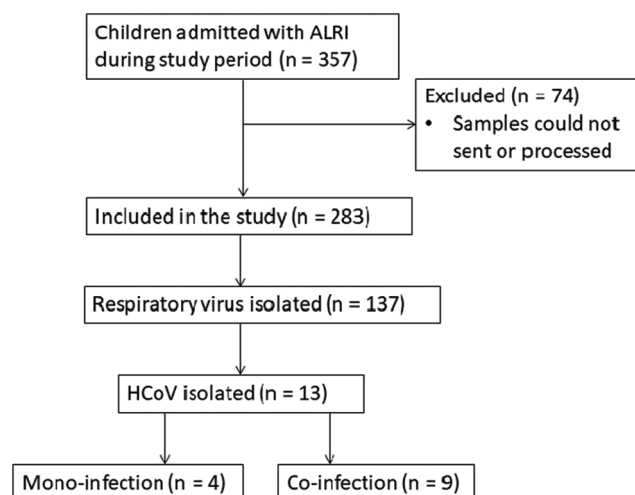


Figure 1: Flow of study participants

Table 1: Clinical, laboratory and radiological features of children with human coronaviruses acute lower respiratory infection

Viruses isolated	Age	Sex	Hospital stay (d)	Chief complaints	CXR	Comorbidity	Treatment given
HCoV-HKU1	2 years	Male	5	Cough and fast breathing	Normal	Interstitial lung disease	Intravenous ceftriaxone
HCoV-HKU1	3 months	Male	4	Cold and cough	Bilateral hyperinflation	-	Supportive (oxygen, nebulization)
HCoV-OC43	4 years	Female	2	Fever and cough	Bilateral hyperinflation	-	Syrup amoxicillin
HCoV-OC43 and PIV3	2 years	Female	5	Cold, noisy breathing	Normal	-	Supportive and nebulization
HCoV-NL63 and RV	9 months	Female	4	Fever and noisy breathing	Patchy infiltrates	Tracheobronchomalacia	Supportive (oxygen, nebulization)
HCoV-OC43 and RV	6 y	Male	4	Cough and cold	Normal	-	Symptomatic
HCoV-NL63 and RV	6 years	Female	2	Breathing difficulty	Right paracardiac infiltrate	Mild asthma	Supportive and nebulization
HCoV-NL63 and RSV	4 months	Male	7	Cough, fever, and fast breathing	Bilateral hyperinflation with infiltrates	Gastroesophageal reflux disease	Intravenous ceftriaxone
HCoV-NL63 and RSV	6 months	Male	2	Cold, noisy breathing	Normal	-	Supportive and nebulization
HCoV-OC43 and RSV	2 years	Female	1	Cough and fever	Perihilar infiltrates	-	Syrup cefpodoxime
HCoV-OC43, and RSV	4 years	Male	9	Fast breathing and hypoxemia (SpO2 <80%)	Patchy opacities with bilateral hyperinflation	Cystic fibrosis	Intravenous piperacillin/tazobactam and amikacin
HCoV-HKU1	2 months	Male	7	Cold and fast breathing	Bilateral infiltrates, right > left	-	Intravenous ceftriaxone
HCoV-OC43, PIV3, and RV	2.5 years	Male	4	Cough, cold, and fast breathing	Perihilar infiltrates	-	Syrup cefpodoxime

RV: Rhinovirus, RSV: Respiratory syncytial virus, PIV: Parainfluenza virus, CXR: Chest X-ray, HCoV: Human coronaviruses

the study and a high attrition rate (in 21% of children, samples could not be sent for viral isolation).

CONCLUSIONS

Nonzoonotic HCoV is an uncommon but increasingly recognized cause of ALRI in hospitalized children from the eastern part of India. No severe illness was found in children with underlying comorbidities, and there was no mortality. This study underscores the importance of nonzoonotic HCoV in causation of childhood ALRI, necessitating the establishment of a surveillance system in India.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: A systematic analysis for the global burden of disease study 2016. *Lancet Infect Dis* 2018;18:1191-210.
- Das RR, Singh M, Naik SS. Vitamin D as an adjunct to antibiotics for the treatment of acute childhood pneumonia. *Cochrane Database Syst Rev* 2018;7:CD011597.
- Shi T, McLean K, Campbell H, Nair H. Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta-analysis. *J Glob Health* 2015;5: 010408.
- Mishra P, Nayak L, Das RR, Dwibedi B, Singh A. Viral agents causing acute respiratory infections in children under five: A study from Eastern India. *Int J Pediatr* 2016;2016:7235482.
- Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: An overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. *Pediatr Infect Dis J* 2020;39:355-68.
- Suresha PG, Akhil C, Anjali A, Giselle DR, Revti B, Arunkumar G. Human coronaviruses in severe acute respiratory infection (SARI) cases in southwest India. *J Med Virol* 2016;88:163-5.
- World Health Organization (WHO). Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities: Evidence Summaries; 2014. Available from: https://www.who.int/maternal_child_adolescent/documents/child-pneumonia-treatment/en/. [Last accessed on 2020 May 26].
- Malhotra B, Swamy MA, Janardhan Reddy PV, Gupta ML. Viruses causing severe acute respiratory infections (SARI) in children ≤5 years of age at a tertiary care hospital in Rajasthan, India. *Indian J Med Res* 2016;144:877-85.
- Zeng ZQ, Chen DH, Tan WP, Qiu SY, Xu D, Liang HX, *et al.* Epidemiology and clinical characteristics of human coronaviruses OC43, 229E, NL63, and HKU1: A study of hospitalized children with acute respiratory tract infection in Guangzhou, China. *Eur J Clin Microbiol Infect Dis* 2018;37:363-9.
- Kuypers J, Martin ET, Heugel J, Wright N, Morrow R, Englund JA. Clinical disease in children associated with newly described coronavirus subtypes. *Pediatrics* 2007;119:e70-6.