


## INSTRUCTIVE CASE

# Believing bocavirus: A rare cause of life-threatening acute respiratory distress syndrome requiring extracorporeal membrane oxygenation

Julie Huynh <sup>1,2</sup>, Krista Mos,<sup>3</sup> Alison Kesson,<sup>1,2,4</sup> Jonathan Egan<sup>2,3</sup> and Nitesh Singhal<sup>3</sup><sup>1</sup>Department of Infectious Diseases and Microbiology, <sup>2</sup>Paediatric Intensive Care Unit, The Children's Hospital at Westmead, <sup>3</sup>Discipline of Child and Adolescent Health, and <sup>4</sup>Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Sydney, New South Wales, Australia

## Case Report

A previously healthy 6-year-old girl presented to a regional hospital with a 24-h history of cough, lethargy and fever. On presentation to the emergency department, she was febrile (38.1°C) with mild subcostal recession and reduced air entry in the left lung base (respiratory rate 28/min, oxygen saturation 92% in room air). Chest radiograph revealed early left lower lobe consolidation (Fig. 1). She was admitted to the ward for benzylpenicillin (45 mg/kg/q6h intravenous injection (IVI)) and low-flow oxygen (1 L/min). Over an 8-h period, she had worsening respiratory distress, dramatic progression of chest radiograph appearances (Fig. 1) and required escalation to high-flow oxygen (2 L/kg) via nasal prongs. She was mechanically ventilated prior to transfer to a tertiary paediatric centre for the management of respiratory failure. Full blood count revealed haemoglobin 122 g/L, white cell count  $16.4 \times 10^9/L$ , platelet count  $230 \times 10^9/L$ , neutrophil count  $14.7 \times 10^9/L$ , lymphocyte count  $0.6 \times 10^9/L$ , C-reactive protein 46 mg/L, procalcitonin 1.6 ng/mL. Renal, liver functions and coagulation profile were all within normal ranges. Antimicrobial

therapy was broadened to clindamycin (10 mg/kg/q8h IVI), cefotaxime (50 mg/kg/q8h IVI) and azithromycin (10 mg/kg/q24h IVI). Upon arrival to our tertiary paediatric centre, she was haemodynamically stable, but in severe respiratory failure with an oxygenation index of 45. A diagnosis of acute respiratory distress syndrome (ARDS) was made. Respiratory support was escalated to high-frequency oscillatory ventilation and inhaled nitric oxide. A chest ultrasound demonstrated dense left-sided consolidation and a small pleural effusion. Oseltamivir (45 mg/q12h orally) was added, and trimethoprim-sulphamethoxazole (5/25 mg/kg/q6h IVI) for possible *Pneumocystis jirovecii* pneumonia in light of lymphopenia and respiratory failure.

Her childhood immunisations were up to date. There was no history of travel or contact with birds. She did not have a history of asthma or previous hospitalisations.

She then developed refractory hypoxia (arterial blood gas: pH 7.0, pCO<sub>2</sub> 104 mmol/L, SO<sub>2</sub> 83% (oxygen index 51)) and commenced on veno-venous extracorporeal membrane oxygenation (ECMO) via right jugulo-vena cava cannulation. A chest radiograph demonstrated worsening appearances with new right upper lobe densities (Fig. 1). A transthoracic echocardiogram showed a structurally normal heart, normal ventricular function, no vegetations and normal pulmonary artery pressures. Bronchoscopy and bronchoalveolar lavage (BAL) revealed normal airways, copious purulent endobronchial secretions with moderate polymorphonuclear cells and no bacterial or fungal growth but secretions from the left lingula lobe were positive for HBoV1-4 by polymerase chain reaction (PCR) with a cycle threshold (Ct) value of 13.38 (cutoff Ct value 36). Nasopharyngeal aspirate also demonstrated mono-detection of HBoV1-4. With the exception of HBoV1-4, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Bordetella pertussis/parapertussis*, adenovirus, enterovirus, coronaviruses NL63/229E/OC43, influenza A and B, human metapneumovirus, parainfluenza,<sup>1-4</sup> rhinoviruses and respiratory syncytial virus A and B were all negative. In both the nasopharyngeal aspirate (NPA) and BAL, only HBoV1-4 was detected on the full respiratory panel. *P. jirovecii* pneumonia PCR on BAL and *M. pneumoniae* IgM were negative and blood cultures sterile. Human immunodeficiency virus antibody was negative.

Over the course of 5 days, she remained in single organ failure, was weaned from ECMO support and decannulated on day 6. She made a rapid recovery, was extubated to high-flow oxygen via nasal prongs on day 9, discharged from intensive care unit (ICU) the following day and made a complete recovery with

### Key Points

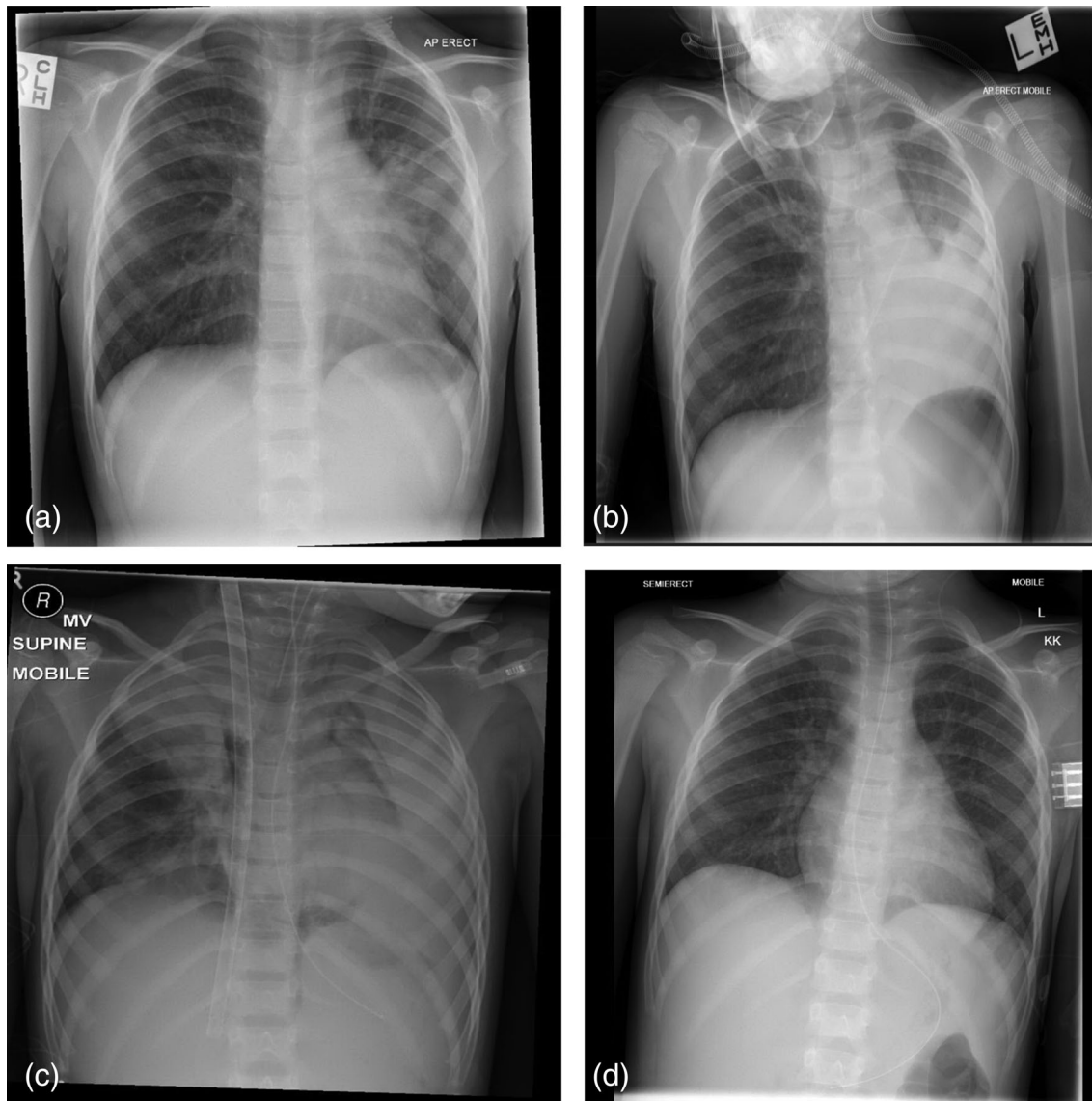
- 1 Human bocavirus-1, usually causes mild respiratory tract infections or is found in asymptomatic children. However, it can also be a rare cause of fulminant respiratory failure requiring emergent extra-corporeal membranous oxygenation.
- 2 Attributing lower respiratory tract infection to human bocavirus alone is difficult and requires more than one microbiological technique, for example DNA, RNA, antigen testing or serology.
- 3 Fulminant acute respiratory distress syndrome caused by human bocavirus-1 can be associated with viraemia and mono-detection on respiratory samples.

**Correspondence:** Dr Nitesh Singhal, Paediatric Intensive Care Unit, The Children's Hospital Westmead, Cnr Hawkesbury Road, Hainsworth Street, Sydney, NSW 2145, Australia. Fax: +61298451221; email: nitesh.singhal@health.nsw.gov.au

J Huynh and K Mos contributed equally to the manuscript and are both first authors.

Conflict of interest: None declared.

Accepted for publication 16 January 2020.



**Fig. 1** Serial chest radiographs of bocavirus pneumonia in a 6-year-old girl admitted with life-threatening acute respiratory distress syndrome. (a) Day 1 of illness (at presentation to the emergency department). (b) Eight hours after presentation; dense lingual consolidation/collapse and left lower lobe consolidation. (c) Day 2 of illness, post-extracorporeal membrane oxygenation cannulation, complete left sided consolidation with new right upper lobe pulmonary infiltrate. (d) Complete resolution of consolidation on day 10 of illness. Discharged the following day.

normal chest radiographic appearances (Fig. 1). She completed 10 days of cefotaxime and clindamycin. The lymphopaenia resolved prior to discharge and is presumed to be due to the viral illness. At the 6-week follow up, she remained in good health with normal growth and development. Unfortunately immune testing (lymphocyte subsets and immunoglobulins) were not done during convalescence. Further follow up for this was arranged with a local paediatrician.

HBoV1-4 PCR on blood taken prior to the institution of ECMO was positive (Ct value = 29.58) (Table 1). HBoV1-4 PCR on blood taken during convalescence (day 8) was negative (Ct value = 41.5). One week following our patient's admission,

her 4-year-old brother developed fevers, tachypnoea, wheeze and hypoxia. His chest radiograph showed bilateral alveolar opacities. NPA and blood PCR were positive for HBoV1-4 (Ct value = 22.28 and Ct value = 31.83), respectively. Only HBoV1-4 and not any other viral or bacterial target, was detected in all samples from the index case and sibling.

## Discussion

Human bocavirus (HBoV), a small non-enveloped DNA virus, belongs to the family *Parvoviridae* and was discovered in 2005 in NPAs of young children with acute respiratory tract infections

**Table 1** Bocavirus polymerase chain reaction testing in sibling pair admitted with respiratory illnesses

	Index case Ct value	Bocavirus result†	Sibling Ct value	Bocavirus result†
NPA	17.63 (day 2 of illness)	Positive	22.28 (day 2 of illness)	Positive
BAL	13.34 (day 3 of illness)	Positive	NP	—
Blood‡	29.58 (day 2 of illness)	Positive	31.83 (day 2 of illness)	Positive
	41.50 (day 8 illness)	Negative	Testing during recovery NP	

†Positive result deemed as Ct value less than 36 as per validated cutoff for respiratory samples. ‡Positive result deemed as Ct value less than 36 as per validated cutoff for respiratory samples. There are currently no cutoff Ct values for blood. BAL, bronchoalveolar lavage; CT, cycle threshold; NP, not performed; NPA, nasopharyngeal aspirate.

(RTIs).<sup>1</sup> Four different species of bocavirus (HBoV1-4) have been proposed with HBoV1 being associated with RTIs. Unlike most respiratory viruses occurring in childhood, there is no clear seasonality of HBoV infections.<sup>2</sup> It however remains controversial whether HBoV1, as a single pathogen, causes disease as it is found in asymptomatic individuals,<sup>3</sup> has prolonged shedding from the respiratory tract of up to 1 year following primary infection,<sup>4</sup> and is found as a co-pathogen in up to 75% of children with lower RTIs.<sup>2</sup> Co-detection with other viruses raises the question whether HBoV1 has an active or synergistic role in respiratory infections. Studies evaluating potential viral-viral interactions are lacking. Therefore, attributing disease to HBoV1 alone is difficult and requires fulfilling of several microbiological criteria. Evidence is now emerging that HBoV1 alone can be a rare cause of acute severe RTIs necessitating critical care management.<sup>5,6</sup>

The clinical manifestations of RTI caused by HBoV1 include cough, fever, dyspnoea, vomiting and rhinorrhoea.<sup>7</sup> Primary infection usually occurs in early childhood with seroprevalence reaching 90% in children by 3 years of age.<sup>8</sup> RTIs caused by HBoV1 are clinically indistinguishable from other common respiratory viruses in childhood. Children hospitalised with HBoV1 induced RTIs are often diagnosed with bronchiolitis, pneumonia or acute exacerbations of asthma.<sup>9,10</sup> Children admitted to ICU with HBoV1 are older than those admitted with RSV (median 24 vs. 2 months).<sup>11</sup> Although rare, it is notable that there are increasing reports of HBoV1 causing severe, life-threatening respiratory infections which require critical care support.<sup>5,6</sup> This included a previously reported case fatality in an 18 month-old child with chronic lung disease of prematurity.<sup>12</sup> To our knowledge, our case is only the second case describing the use of ECMO support for life-threatening RTI caused by HBoV and the first describing critical ARDS caused by HBoV.

HBoV1 infection induces inflammasome activation, caspase 1-induced cell death, interleukin and interferon (IF)- $\gamma$  production which have been implicated in the pathophysiology of ARDS.<sup>13</sup> In acute HBoV1 infections, C-reactive protein concentrations and white blood cell counts are usually within normal limits. Chest radiograph appearances in our case were unique as peribronchial, interstitial infiltrates and atelectasis are most commonly described.<sup>10</sup>

As multiple viruses are often detected in respiratory samples, diagnosing RTI due to HBoV1 requires multiple microbiological criteria. Current expert guidance recommends that HBoV1 infection should not be diagnosed on the basis of HBoV1 DNA detection from respiratory samples alone. Additional diagnostic

approaches include quantitative HBoV1 DNA analysis ( $>10^6$  copies/mL) of nasopharyngeal secretions, serology (IgM, low IgG avidity or a more than or equal to fourfold IgG titre rise) and/or HBoV1 antigen detection in nasopharyngeal secretions.<sup>14</sup> With advancements in diagnostic approaches, clinicians have been able to diagnose acute HBoV1 infection with greater confidence, which might explain the increasing reports of acute paediatric infections caused by HBoV1.

Primary HBoV1 infection could be distinguished from virus shedding by analysis of anti-HBoV1 antibodies.<sup>15</sup> HBoV1 serology is not yet available anywhere in Australia. In the absence of HBoV1 serological and antigen testing, DNA in blood could be used to diagnose HBoV1 RTI. The presence of HBoV1 viraemia is usually specific for acute HBoV1 infection.<sup>2</sup> Viraemia is rarely detected in controls, has a short duration and rarely lasts beyond the first week of acute illness.<sup>14</sup> We were able to demonstrate HBoV viraemia during the acute illness (day 2) which became undetectable during recovery (day 8). Significantly higher viral loads have been demonstrated in respiratory samples of children admitted to ICU with HBoV-induced RTI.<sup>2</sup> Our laboratory currently provides semi-quantitative HBoV 1–4 viral loads only. Low Cts clearly below the cut off (Ct value cutoff – 36) in all respiratory samples (Ct value 17.6 – NPA, Ct value 13.3 – BAL) and blood (Ct value – 29.6) would indicate significantly high viral loads. The lack of evidence for other viruses or bacteria on multiple respiratory samples (BAL, NPA) provided support for HBoV as the aetiology. Only one set of BAL washings were taken from the lingula lobe as the child was too unstable to extend the procedure longer than necessary and take samples from other lobes. In the absence of other positive results, mono-detection of HBoV1-4 from multiple respiratory samples separated in time and location, combined with PCR positivity in blood, we believe this to be strong evidence of true mono-infection with HBoV. It is notable, however, that existing reports of severe disease attributed to HBoV has been in children with underlying conditions or immunocompromised status and that the typical age of infection for HBoV primary infection is under 2 years of age. It is therefore highly unusual that a previously well 6-year girl develops HBoV infection of this magnitude. One hypothesis is the potential role of unique host–virus interactions in causing disease however this remains to be elucidated.

Transmission of HBoV1 occurs via respiratory secretions and secondary HBoV1 infection has occurred within families.<sup>16</sup> The younger sibling of our patient, who was a household contact developed fever, cough, wheeze and hypoxia 1 week after our index case. The sibling's disease was less severe requiring typical

supportive management (oxygen and bronchodilators) only. As in the index case we demonstrated HBoV 1–4 monodetection on NPA, however, viral loads were lower (Ct value 22.28 – NPA, Ct value 31.83 – blood). There is currently no specific antiviral treatment available for HBoV1 infections. A *post-hoc* analysis of a randomised controlled trial demonstrated that prednisolone was ineffective at reducing hospital admission stay in wheezing children with HBoV1 infection.<sup>17</sup> Supportive management for HBoV1 bronchiolitis or pneumonia have been the mainstay of treatment. This rare case report adds new knowledge that the extent of respiratory support in extreme cases of HBoV 1–4 induced ARDS may require consideration of veno-venous ECMO.

HBoV1 is emerging as a rare cause of life-threatening lower RTI in children. Clinicians should be aware of varying presentations and the techniques to diagnosing acute HBoV1 infection in children.

Verbal and written consent for publication was provided by the patient's parents.

## Acknowledgements

The authors would like to acknowledge all the intensive care nurses, allied health staff and doctors involved in the care of the patient, as well as Kin-Cheung Li, senior molecular scientist, Children's Hospital at Westmead, for assisting with microbiological diagnosis.

## References

- Allander T, Tammi MT, Eriksson M, Bjerkner A, Tiveljung-Lindell A, Andersson B. Cloning of a human parvovirus by molecular screening of respiratory tract samples. *Proc. Natl. Acad. Sci. USA* 2005; **102**: 12891–6.
- Christensen A, Nordbo SA, Krokstad S, Rognlien AG, Dollner H. Human bocavirus in children: Mono-detection, high viral load and viraemia are associated with respiratory tract infection. *J. Clin. Virol.* 2010; **49**: 158–62.
- Jartti T, Hedman K, Jartti L, Ruuskanen O, Allander T, Soderlund-Venermo M. Human bocavirus-the first 5 years. *Rev. Med. Virol.* 2012; **22**: 46–64.
- Martin ET, Kuypers J, McRoberts JP, Englund JA, Zerr DM. Human bocavirus 1 primary infection and shedding in infants. *J Infect Dis* 2015; **212**: 516–24.
- Edner N, Castillo-Rodas P, Falk L, Hedman K, Soderlund-Venermo M, Allander T. Life-threatening respiratory tract disease with human bocavirus-1 infection in a 4-year-old child. *J. Clin. Microbiol.* 2012; **50**: 531–2.
- Eskola V, Xu M, Soderlund-Venermo M. Severe lower respiratory tract infection caused by human bocavirus 1 in an infant. *Pediatr. Infect. Dis. J.* 2017; **36**: 1107–8.
- Moriyama Y, Hamada H, Okada M *et al.* Distinctive clinical features of human bocavirus in children younger than 2 years. *Eur. J. Pediatr.* 2010; **169**: 1087–92.
- Karalar L, Lindner J, Schimanski S, Kertai M, Segerer H, Modrow S. Prevalence and clinical aspects of human bocavirus infection in children. *Clin. Microbiol. Infect.* 2010; **16**: 633–9.
- Calvo C, Garcia-Garcia ML, Pozo F, Carballo D, Martinez-Monteserin E, Casas I. Infections and coinfections by respiratory human bocavirus during eight seasons in hospitalized children. *J. Med. Virol.* 2016; **88**: 2052–8.
- Allander T, Jartti T, Gupta S *et al.* Human bocavirus and acute wheezing in children. *Clin. Infect. Dis.* 2007; **44**: 904–10.
- Moesker FM, van Kampen JJ, van der Eijk AA *et al.* Human bocavirus infection as a cause of severe acute respiratory tract infection in children. *Clin. Microbiol. Infect.* 2015; **21**: 964.e1–8.
- Uršic T, Krivec U, Kalan G, Petrovec M. Fatal human bocavirus infection in an 18-month-old child with chronic lung disease of prematurity. *Pediatr. Infect. Dis. J.* 2015; **34**: 111–2.
- Chung JY, Han TH, Kim JS, Kim SW, Park CG, Hwang ES. Th1 and Th2 cytokine levels in nasopharyngeal aspirates from children with human bocavirus bronchiolitis. *J. Clin. Virol.* 2008; **43**: 223–5.
- Christensen A, Kesti O, Elenius V *et al.* Human bocaviruses and paediatric infections. *Lancet Child Adolesc. Health* 2019; **3**: 418–26.
- Söderlund-Venermo M, Lahtinen A, Jartti T *et al.* Clinical assessment and improved diagnosis of bocavirus-induced wheezing in children, Finland. *Emerg. Infect. Dis.* 2009; **15**: 1423–30.
- Jula A, Waris M, Kantola K *et al.* Primary and secondary human bocavirus 1 infections in a family, Finland. *Emerg. Infect. Dis.* 2013; **19**: 1328–31.
- Jartti T, Söderlund-Venermo M, Allander T, Vuorinen T, Hedman K, Ruuskanen O. No efficacy of prednisolone in acute wheezing associated with human bocavirus infection. *Pediatr. Infect. Dis. J.* 2011; **30**: 521–3.