

Severe Human Bocavirus–Associated Pneumonia in Adults at a Referral Hospital, Seoul, South Korea

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We report a case series of severe human bocavirus–associated pneumonia in adults in Seoul, South Korea. The virus accounted for 0.5% of all severe pneumonia cases. Structural lung disease and hematologic malignancy were common underlying diseases. Overall death rate was 54.5%. Higher death rates were associated with co-infection (83.3%) and immunocompromise (80.0%).

Human bocavirus (HBoV), a DNA virus in the *Parvoviridae* family, was first identified in 2005 (1). HBoV is distributed worldwide and has been found in 2%–33% of respiratory specimens, primarily from children with acute respiratory tract infection (2,3). In adults, HBoV is an uncommon cause of upper respiratory tract infection and pneumonia (4–6). It can also be associated with the acute exacerbation of chronic obstructive pulmonary disease (7). Recently, a few case reports have shown that HBoV can be associated with life-threatening pneumonia (8–12). However, severe HBoV-associated pneumonia has not been reported in a case series, and little is known about the characteristics of HBoV-associated pneumonia in critically ill adult patients. We investigated the incidence, clinical characteristics, and outcomes of severe HBoV-associated pneumonia in adults in Seoul, South Korea.

The Study

We conducted a prospective observational cohort study of severe pneumonia in adult patients admitted to the medical intensive-care unit (ICU) at a 2,700-bed referral hospital in Seoul, South Korea, during March

2010–February 2019 (13,14). We initially included all adult patients admitted to the ICU with a diagnosis of pneumonia but later excluded patients with non-severe pneumonia. We collected data on demographics, underlying diseases or conditions, immune status, seasonality, clinical manifestations, laboratory findings, pathogens, complications, treatment, and outcomes. This data collection was a routine part of the management and care of these patients at our hospital. Definitions and microbial evaluations are summarized in the Appendix (<https://wwwnc.cdc.gov/EID/article/27/1/20-2061-App1.pdf>). The Institutional Review Board of Asan Medical Center approved this study (approval no. 2010-0079) and waived informed-consent requirements.

During the study, 2,519 adult patients were admitted to the ICU with the diagnosis of severe pneumonia. After excluding 298 patients (83 community-acquired pneumonia [CAP] cases and 215 hospital-acquired pneumonia [HAP] cases) for whom multiplex respiratory virus PCR was not performed, 2,221 severe pneumonia patients (1,482 CAP cases and 739 HAP cases) were included. Among these 2,221 severe pneumonia patients, septic shock occurred in 1,306 (58.8%), and 2,141 (96.4%) required mechanical ventilation. Septic shock occurred in 80 patients (3.6%) who did not require mechanical ventilation.

Mean patient age was 65.8 years (range 16–97 years). Structural lung disease (26.9%) was the most common underlying disease in patients with CAP, and hematologic malignancy (25.4%) was the most common in patients with HAP (Appendix Table 1). One or more respiratory pathogens were identified in 1,510 patients (68.0%) (Appendix Table 2). Overall,

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888 (40.0%) patients had bacterial infections, 711 (32.0%) had viral infections, and 230 (10.4%) patients had bacterial–viral co-infection. A total of 787 viruses were identified in 711 patients. Two viruses were identified in 60 patients and 3 viruses in 8 patients. Influenza virus (8.6%) and rhinovirus (8.4%) were the most common viral pathogens for severe CAP, whereas parainfluenza virus and respiratory syncytial virus were the most common viral pathogens for severe HAP.

Eleven HBoV-associated severe pneumonia cases (0.5% [11/2,221]) were reported. Of those, HBoV accounted for 0.4% (6/1,482) of CAP cases and 0.7% (5/739) of HAP cases. Of the 711 virus-associated severe pneumonia cases, HBoV accounted for 1.2% (6/501) of CAP cases and 2.4% (5/210) of HAP cases. Appendix Table 3 summarizes the characteristics and outcomes of the 11 patients with HBoV-associated severe pneumonia, which included 6 patients with CAP and 5 patients with HAP. HBoV occurred in all 4 seasons but was more common during September–February (8 cases). Nine patients were men (81.8%); the median age was 69.0 years (range 36–81 years). All patients had ≥ 1 severe underlying diseases. Structural lung disease (5 patients) and hematologic malignancy (4 patients) were the most common underlying illnesses. Five patients (45.5%) were immunocompromised.

Viruses were detected by using nasopharyngeal aspirate or swab specimens. In 1 patient, the virus was detected in bronchoalveolar lavage fluid and nasopharyngeal samples. Co-infection was observed in 6 patients (54.5%). Eight patients underwent chest computed tomography. The most common radiologic findings were bilateral and multifocal consolidation and ground-glass opacity.

The median length of ICU stay was 9.0 days (range 1–74 days). Overall death rate was 54.5% (6/11). The death rate was 80.0% (4/5) for immunocompromised patients and 33.3% (2/6) for immunocompetent patients. Higher death rates were observed in cases of co-infection (83.3%, 5/6) than in cases of sole HBoV infection (20.0% [1/5]) ($p = 0.08$). All immunocompromised patients with co-infection died (3/3), whereas no immunocompetent patients without co-infection died (0/3).

Conclusions

Our study demonstrated that HBoV is an uncommon pathogen for adult patients with severe pneumonia requiring ICU admission. All episodes we investigated occurred in patients with serious underlying diseases, and co-infection was frequent. Overall death

rates were high and closely associated with immunocompromised state and presence of co-infection.

Information on severe HBoV-associated pneumonia in adults is limited. Five cases of severe HBoV-associated pneumonia have been reported to date (8–12), which included 3 cases from the same facility in Germany (9,10,12). Of the 5 patients, 3 had hematologic malignancy and 1 had cystic fibrosis. One of the patients was a 74-year-old immunocompetent man (10). He had an acute head injury and rib fracture, probably because of weakness from HBoV pneumonia, necessitating mechanical ventilation. In our study, patients with structural lung diseases, including chronic obstructive pulmonary disease and bronchiectasis, were predisposed to severe HBoV-associated pneumonia. Most of these patients were not immunocompromised and had CAP. Therefore, clinicians should consider HBoV as an uncommon pathogen of severe pneumonia in adults with structural lung disease.

Consistent with previous reports (4,5), we found a high rate of co-infection with other pathogens in patients with HBoV infection. HBoV has shown a prolonged persistence in the mucosa of the respiratory tract. Viral persistence contributes to the high frequency of coinfections with proper respiratory pathogens (15). This phenomenon might be associated with the underlying severe diseases. Of note, co-infection was closely related to higher overall death rates in our patients. Our series included 5 cases of sole HBoV infection, which was more common in CAP patients and associated with lower death rates. These findings indicated that HBoV itself has a lower virulence potential and rarely causes severe pneumonia, which is predominant in immunocompromised patients or patients with underlying structural lung disease. The higher incidence of severe HBoV-associated pneumonia in HAP patients compared with CAP patients (0.7% vs. 0.4%) might be explained by the higher proportion of immunocompromised patients in the HAP population.

Our study has some limitations. First, we excluded 298 patients (83 of 1,565 CAP patients [5.8%] and 215 of 954 HAP patients [22.5%]) for whom multiplex respiratory virus PCR was not performed. Because our study was observational, microbial evaluations and patient-management decisions were made by attending physicians, and multiplex respiratory virus PCR test was not used for all patients. Therefore, selection bias might have occurred, especially for HAP. Second, HBoV was mostly identified through nasopharyngeal specimens only and was frequently accompanied by copathogens. Therefore, we could

not evaluate in detail the virulence potential of sole HBoV infection. Finally, we did not conduct a genotypic study of HBoV, and the viral load therefore was not tested.

In summary, in this study, HBoV accounted for 0.5% of severe pneumonia cases in adults. HBoV-associated severe pneumonia could lead to high death rates. Underlying severe diseases and frequent co-infection seem to be responsible for poor outcomes.

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Appendix

Definitions

Pneumonia was defined as the presence of a new infiltration on a chest radiograph plus ≥ 1 of the following: fever (temperature $\geq 38^{\circ}\text{C}$) or hypothermia (temperature $< 35.0^{\circ}\text{C}$), new cough with or without sputum production, pleuritic chest pain, dyspnea, and altered breath sound on auscultation (1). Severe pneumonia was diagnosed when the patient required vasopressors for shock or mechanical ventilation for respiratory failure. The respiratory pathogens identified from specimens collected ≤ 72 hours after the diagnosis of pneumonia were considered pneumonia pathogens. Hospital-acquired pneumonia (HAP) was defined as pneumonia that occurred ≥ 48 hours after admission and did not appear to be incubating at the time of admission (2). Otherwise, the pneumonia was categorized as community-acquired pneumonia (CAP). An immunocompromised state was defined as one of the following conditions: (i) daily receipt of immunosuppressants, including corticosteroids; (ii) human immunodeficiency virus infection; (iii) receipt of solid organ or hematopoietic stem cell transplantation; (iv) receipt of chemotherapy for underlying malignancy in the previous 6 months; and (v) presence of underlying immune deficiency disorder (3).

Microbial Evaluations

The microbial evaluations were determined by the attending physicians, taking into consideration the patient's immune status, clinical course, acquisition site, and radiographic features. The microbial evaluations included the following: 1) bacteria: 3 sets of blood cultures; sputum or endotracheal aspirates, or BAL fluid Gram staining and culture; PCR for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* using an AmpliSens *M.*

pneumoniae/*C. pneumoniae*-FRT PCR kit and AmpliSens *L. pneumophila*-FRT PCR kit (InterLabService Ltd, <https://www.interlabservice.ru/en/>); urinary antigen test using the BinaxNOW kit for *Streptococcus pneumoniae* and *L. pneumophila* serogroup 1 (Abbott, <https://www.abbott.com/>); 2) viruses: nasopharyngeal aspirates or BAL fluid multiplex reverse transcription PCR assay using the Anyplex II RV 16 Detection kit or Allplex Respiratory Panel 1, 2, 3 (Seegene Inc., <http://www.seegene.com/>); BAL fluid shell vial culture for influenza virus, respiratory syncytial virus, parainfluenza virus, adenovirus, and cytomegalovirus (Diagnostic Hybrids, Inc., <https://www.quidel.com/>); 3) mycobacteria: sputum or endotracheal aspirates, or BAL fluid Ziehl-Neelsen staining; combination of solid media culture (Ogawa medium, Korean Institute of Tuberculosis, Seoul, South Korea) and liquid media culture using a BACTEC 960 Mycobacterial Growth Indicator Tube (BD, <https://www.bd.com/en-us>); identification of *Mycobacterium tuberculosis* and nontuberculous mycobacteria (NTM) by PCR using AdvanSure TB/NTM real-time PCR (LG Chem Life Sciences, <https://www.lgchem.com/main/index>); NTM identification using GenoType mycobacterium CM/AS (Hain Lifescience GmbH, <https://www.hain-lifescience.de/en/>); 4) fungi: sputum or endotracheal aspirates, or BAL fluid fungus staining and culture; serum or BAL fluid *Aspergillus* galactomannan antigen assay using a Platelia *Aspergillus* Antigen Kit (Bio-Rad, <https://www.bio-rad.com/>); direct fluorescence assay using Light Diagnostics *Pneumocystis carinii* DFA Kit (Millipore Sigma, <https://www.emdmillipore.com/US/en>) or real-time PCR assay using an AmpliSens *Pneumocystis jirovecii* (carinii)-FRT PCR kit (InterLabService Ltd, <https://www.interlabservice.ru/en/>).

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Appendix Table 1. Demographics and underlying diseases/conditions of 2,221 patients with severe pneumonia*

Identified virus(es)	No. (%)		
	Total (n = 2,221)	CAP† (n = 1,482)	HAP (n = 739)
Demographics			
Male sex	1,583 (71.3)	1,056 (71.3)	527 (71.3)
Median age (range), year	68.0 (16–97)	69.0 (16–97)	65.0 (16–97)
Underlying diseases or conditions‡			
Diabetes mellitus	551 (24.8)	378 (25.5)	173 (23.4)
Structural lung disease	542 (24.4)	398 (26.9)	144 (19.5)
Chronic obstructive pulmonary disease	254 (11.4)	190 (12.8)	64 (8.7)
Interstitial lung disease	165 (7.4)	118 (8.0)	47 (6.4)
Tuberculosis-destroyed lung	61 (2.7)	42 (2.8)	19 (2.6)
Bronchiectasis	63 (2.8)	48 (3.2)	15 (2.0)
Pneumoconiosis	9 (0.4)	7 (0.5)	2 (0.3)
Bronchiolitis obliterans	7 (0.3)	4 (0.3)	3 (0.4)
Solid cancer	484 (21.8)	317 (21.4)	167 (22.6)
Hematologic malignancy	337 (15.2)	149 (10.1)	188 (25.4)
Congestive heart failure	101 (4.5)	69 (4.7)	32 (4.3)
Chronic renal failure	91 (4.1)	67 (4.5)	24 (3.2)
End-stage renal disease	90 (4.1)	58 (3.9)	32 (4.3)
Immunocompromised state	1,029 (46.3)	632 (42.6)	397 (53.7)

*Data are presented as the number (percentage) of patients. CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia.

†Included 946 patients with healthcare-associated community-onset pneumonia.

‡Some patients had ≥1 underlying diseases or conditions.

Appendix Table 2. Identity of pathogens in 2,221 adult patients with severe pneumonia*

Identified organism	No. (%)		
	Total (n = 2,221)	CAP† (n = 1,482)	HAP (n = 739)
None	711 (32.0)	483 (32.6)	228 (30.9)
Bacteria			
<i>S. pneumoniae</i>	126 (5.7)	114 (7.7)	12 (1.6)
<i>S. aureus</i>	197 (8.9)	112 (7.6)	85 (11.5)
Methicillin-susceptible	58 (2.6)	51 (3.4)	7 (0.9)
Methicillin-resistant	139 (6.3)	61(4.1)	78 (10.6)
<i>L. pneumophila</i>	34 (1.5)	30 (2.0)	4 (0.5)
<i>H. influenzae</i>	14 (0.6)	13 (0.9)	1 (0.1)
<i>M. catarrhalis</i>	13 (0.6)	12 (0.8)	1 (0.1)
<i>C. striatum</i>	13 (0.6)	3 (0.2)	10 (1.4)
<i>S. pyogenes</i>	6 (0.3)	5 (0.3)	1 (0.1)
<i>Nocardia</i> species	3 (0.1)	3 (0.2)	0
<i>S. constellatus</i>	3 (0.1)	2 (0.1)	1 (0.1)
Group G streptococcus	2 (0.1)	2 (0.1)	0
<i>S. agalactiae</i>	2 (0.1)	2 (0.1)	0
<i>S. anginosus</i>	1 (0)	0	1 (0.1)
<i>R. mucilaginosus</i>	1 (0)	1 (0.1)	0
Enteric Gram-negative bacilli			
<i>K. pneumoniae</i>	270 (12.2)	196 (13.2)	74 (10.0)
<i>K. pneumoniae</i>	166 (7.5)	119 (8.0)	47 (6.4)
<i>E. coli</i>	64 (2.9)	50 (3.4)	14 (1.9)
<i>E. cloacae</i>	16 (0.7)	11 (0.7)	5 (0.7)
<i>K. aerogenes</i>	10 (0.5)	8 (0.5)	2 (0.3)
<i>S. marcescens</i>	8 (0.4)	7 (0.5)	1 (0.1)
<i>C. freundii</i>	6 (0.3)	3 (0.2)	3 (0.4)
<i>K. oxytoca</i>	3 (0.1)	1 (0.1)	2 (0.3)
<i>K. ozaenae</i>	2 (0.1)	2 (0.1)	0
<i>M. morgani</i>	2 (0.1)	2 (0.1)	0
<i>P. mirabilis</i>	2 (0.1)	1 (0.1)	1 (0.1)
<i>P. stuartii</i>	2 (0.1)	2 (0.1)	0
Non-enteric Gram-negative bacilli			
<i>P. aeruginosa</i>	284 (12.8)	135 (9.1)	149 (20.2)
<i>P. aeruginosa</i>	126 (5.7)	86 (5.8)	40 (5.4)
<i>A. baumannii</i>	125 (5.6)	41 (2.8)	84 (11.4)
<i>S. maltophilia</i>	29 (1.3)	5 (0.3)	24 (3.2)
<i>A. xylosoxidans</i>	5 (0.2)	3 (0.2)	2 (0.3)
<i>P. fluorescens</i>	1 (0.1)	1 (0.1)	1 (0.1)

Identified organism	No. (%)		
	Total (n = 2,221)	CAP† (n = 1,482)	HAP (n = 739)
<i>A. lwoffii</i>	1 (0.1)	1 (0.1)	1 (0.1)
<i>C. indologenes</i>	1 (0)	0	1 (0.1)
Atypical pathogen	24 (1.1)	23 (1.6)	1 (0.1)
<i>M. pneumoniae</i>	11 (0.5)	11 (0.7)	0
<i>O. tsutsugamushi</i>	9 (0.4)	9 (0.6)	0
<i>C. pneumoniae</i>	6 (0.3)	5 (0.3)	1 (0.1)
Virus	711 (32.0)	501 (33.8)	210 (28.4)
Rhinovirus	165 (7.4)	125 (8.4)	40 (5.4)
Influenza virus	165 (7.4)	127 (8.6)	38 (5.1)
Influenza A	133 (6.0)	103 (7.0)	30 (4.1)
Influenza B	32 (1.4)	24 (1.6)	8 (1.1)
Parainfluenza virus	121 (5.4)	71 (4.8)	50 (6.8)
Type 3	73 (3.3)	33 (2.2)	40 (5.4)
Type 1	24 (1.1)	18 (1.2)	6 (0.8)
Type 4	20 (0.9)	15 (1.0)	5 (0.7)
Type 2	5 (0.2)	5 (0.3)	0
Respiratory syncytial virus	100 (4.5)	54 (3.6)	46 (6.2)
Respiratory syncytial virus A	55 (2.5)	28 (1.9)	27 (3.7)
Respiratory syncytial virus B	46 (2.1)	27 (1.8)	19 (2.6)
Human coronavirus	85 (3.8)	64 (4.3)	21 (2.8)
229E/NL63	43 (1.9)	33 (2.2)	10 (1.4)
OC43/HKU1	43 (1.9)	31 (2.1)	12 (1.6)
Human metapneumovirus	57 (2.6)	50 (3.4)	7 (0.9)
Cytomegalovirus	34 (1.5)	20 (1.3)	14 (1.9)
Adenovirus	27 (1.2)	15 (1.0)	12 (1.6)
Herpes simplex virus 1	14 (0.6)	9 (0.6)	5 (0.7)
Bocavirus	11 (0.5)	6 (0.4)	5 (0.7)
Enterovirus	6 (0.3)	4 (0.3)	2 (0.3)
Mycobacterium	52 (2.3)	46 (3.1)	6 (0.8)
<i>M. tuberculosis</i>	39 (1.8)	34 (2.3)	5 (0.7)
Non-tuberculous mycobacterium	13 (0.6)	12 (0.8)	1 (0.1)
<i>M. intracellulare</i>	7 (0.3)	6 (0.4)	1 (0.1)
<i>M. avium</i>	1 (0)	1 (0.1)	0
<i>M. peregrinum</i>	1 (0)	1 (0.1)	0
Unspecified	3 (0.1)	3 (0.2)	0
Fungus	210 (9.5)	123 (8.3)	87 (11.8)
<i>Aspergillus</i> species	128 (5.8)	66 (4.5)	62 (8.4)
<i>Pneumocystis jirovecii</i>	83 (3.7)	58 (3.9)	25 (3.4)
<i>Rhizopus</i> species	3 (0.1)	1 (0.1)	2 (0.3)
<i>Cunninghamella</i> species	3 (0.1)	1 (0.1)	2 (0.3)
<i>Trichosporon asahii</i>	2 (0.1)	1 (0.1)	1 (0.1)
<i>Candida tropicalis</i>	1 (0)	0	1 (0.1)
<i>Penicillium</i> species	1 (0)	1 (0.1)	0

*Data are presented as the number (percentage) of patients. CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia.

†Included 946 patients with healthcare-associated community-onset pneumonia.

Appendix Table 3. Characteristics of 11 patients with severe bocavirus-associated pneumonia admitted between March 2010 and February 2019*

Patient no.	Category of pneumonia	Year/month	Age/sex	Underlying disease or condition	Immunocompromised state†	PCR-positive specimen	Copathogen‡	CT findings	Outcome (cause of death)
1	CAP	2014/Feb	79/male	COPD, heart failure	No	NP, BAL fluid	None	Diffuse and bilateral GGO with consolidation	Alive
2	CAP	2015/Jan	63/male	Diabetes mellitus, cerebrovascular attack	No	NP	<i>E. coli</i>	Multifocal patchy GGO with consolidation	Died on hospital day 19 (central-line associated <i>A. baumannii</i> bacteremia)
3	CAP	2015/Apr	75/male	Bronchiectasis	No	NP	None	Multifocal patchy consolidation	Alive
4	CAP	2015/Sep	74/male	COPD	No	NP	None	Consolidation and bronchial wall thickening on right upper lobe	Alive
5	CAP	2015/Nov	69/male	Ischemic heart failure	No	NP	<i>M. pneumoniae</i>	Diffuse and bilateral GGO with consolidation	Alive
6	CAP	2015/Dec	80/male	Idiopathic pulmonary fibrosis on steroids	Yes	NP	None	Multifocal patchy GGO with consolidation	Died on hospital day 44 (<i>P. aeruginosa</i> ventilator-associated pneumonia)
7	HAP	2011/May	54/female	Acute lymphocytic leukemia	Yes	NP	<i>A. baumannii</i> + parainfluenza virus type 3	Chest x-ray: Multifocal patchy consolidation and increased interstitial marking in both lungs	Died on ICU day 2 (refractory shock)
8	HAP	2011/Jun	63/female	Primary central nervous system lymphoma	Yes	NP	None	Multifocal patchy consolidation and interstitial thickening	Alive
9	HAP	2012/Sep	51/male	Acute myeloid leukemia	Yes	NP	Parainfluenza virus type 4	Chest x-ray: Ill-defined consolidation and GGO in left lower lung zone	Died on ICU day 10 (refractory shock)
10	HAP	2017/Nov	81/male	Tuberculosis-destroyed lung	No	NP	MRSA + rhinovirus	Chest x-ray: multifocal patchy GGO and consolidation	Died on ICU day 72 (intracranial hemorrhage)
11	HAP	2019/Jan	36/male	Acute lymphoid leukemia	Yes	NP	Influenza A	Chest x-ray: Multifocal patchy consolidation and increased interstitial marking in both lungs	Died on ICU day 9

*BAL, bronchoalveolar lavage; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CT, computed tomography; GGO, ground-glass opacity; HAP, hospital-acquired pneumonia; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; NP, nasopharyngeal swab or aspirate; PCR, polymerase chain reaction.

†Defined as one of the following conditions: (i) daily receipt of immunosuppressants, including corticosteroids; (ii) human immunodeficiency virus infection; (iii) receipt of solid organ or hematopoietic stem cell transplantation; (iv) receipt of chemotherapy for underlying malignancy in the previous 6 mo; and (v) presence of underlying immune deficiency disorder.

‡Respiratory pathogen(s) identified from specimens collected ≤ 72 hours after diagnosis of pneumonia.