Case Report

Respiratory Failure Associated with Human Metapneumovirus Infection: Case Report

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Acute respiratory tract infection is one of the top three causes of pediatric hospitalization, viral infection being the most common etiology. It has recently been discovered that human metapneumovirus (hMPV), a paramyxovirus is an important respiratory virus that plays major role of pediatric acute respiratory tract infection. The present report included two cases of hMPV infection in children presenting with progressive wheezing, hypoxia, and acute respiratory failure. The first patient was a 10-year-old girl with an underlying neurological disorder who developed severe respiratory problems due to hMPV infection. The other was a 6-month-old male infant who developed progressive dyspnea because of co-infection hMPV and *Streptococcus pneumoniae*. Consequently, hMPV should be investigated in children with severe respiratory failure with negative culture from common pathogens. Although both cases were admitted to the pediatric intensive care unit (PICU) owing to acute respiratory failure, only good supportive treatment was needed.

Keywords: Human metapneumovirus, Acute respiratory failure, Children

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Viruses are common pathogens of pneumonia in children. Human metapneumovirus (hMPV) is a member of the Paramyxovirus family that was first recognized in 2001[1-3]. The hMPV is one of the common pathogens accounted for respiratory tract infection among all age groups from children to adult. Clinical manifestations of hMPV infection are indistinguishable from RSV infection. Symptoms can range from mild self-limited illness to severe respiratory failure. Risk factors for severe hMPV infection are preterm, young age, and underlying pulmonary, cardiovascular, or neurological disorders[1,4]. In recent studies, hMPV infection experienced a significant increase in respiratory illness prevalence in many countries in Southeast Asian Nations and China, which have different clinical manifestations[5-10] (Table 1).

These case reports described the presentation of a 10-year-old girl with neurological disorder with severe respiratory problems from hMPV infection, and a 6-month-old male infant with progressive dyspnea caused by co-infection of hMPV and *Streptococcus pneumoniae*.

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Case Report

Case 1

A 10-year-old girl, known to have Angelman syndrome and epilepsy, presented with progressive dyspnea two hours prior to arrival. Her regular medications were valproic acid, clonazepam, and folic acid. She had a 3-day history of a high-grade fever and productive cough. She was diagnosed with acute tonsillitis and treated with amoxicillin-clavulenic acid and paracetamol. However, her symptoms got worse. She was brought back to the emergency department because of progressive dyspnea and productive cough.

On physical examination, her temperature was 38.8°C, respiratory rate was 36 breaths per minute, and heart rate was 135 beats per minute. Her oxygen saturation was 93% without oxygen supplementation, and 96% with 2 LPM oxygen supplementation. She had drowsiness, looked pale, and had periorbital petechiae. Chest auscultation showed bilateral crepitation and wheezing, which was predominated

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Table 1. Demographic data and clinical manifestation of hMPV-infected children in different countries in Southeast Asian Nations and China

Data	Thailand[5]	Thailand[6]	Cambodia[7]	Malaysia[8]	Singapore[9]	China[10]
No. of cases	6	12	65	167	21	103
Year	2002 to 2004	2001 to 2003	2007 to 2009	2010 to 2012	2005 to 2007	2013 to 2016
Age (months)	Mean 9.4 (5 to 18.5)	22.3±11.5*	≤5 years 80%		≤1 year 67%	≤5 years 95.1%
Sex	Male 50%	Male 75%	Male 54%			Male 55.4%
LOS (days)	Mean 3.2 (25 to 179)	6.8±3.6*		Mean 7.5		
History of passive smoker	100%					
Co-infection			18.5%			18.4%
Symptoms		Fever 37.7±0.5℃*		Fever 100%		Cough 100%
				Cough 98.8%		Abnormal breath sound 91.1%
				Rhinorrhea 92.8%		Fever 88.1%
				Wheezing 94%		Expectoration 77.2%
				Sore throat 84.4%		Coryza 50.5%
				Lethargy 97.6%		Wheezing 46.5%
				Shortness of breath 88.6%		GI illness 46.5%
Disease						
Acute bronchiolitis		42%	9.2%		Lower respiratory tract infection 52%	9.5%
Pneumonia		50%	58.5%			79.8%
Bronchitis			15.4%			
Chest X-ray		Perihilar 42%				
		Hyperinflation 16.7%				
		Patchy 25%				
		Interstitial 8.3%				
Investigation	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR

LOS=length of stay; RT-PCR=reverse transcription polymerase chain reaction; GI=gastrointestinal

* Mean±SD

on the left side.

The complete blood count showed hemoglobin (Hb) 12.5 g/dl, hematocrit (Hct) 36.7%, white blood cell (WBC) 2,500 cells/cm³ (54% polymorphonuclear cells, 42.5% mononuclear cells, 3.2% monocytes, 0.2% basophils, and 0.1% eosinophils) and platelets 74,000/mm³. The nasopharyngeal swabs for influenza type A/B and respiratory syncytial virus (RSV) screening test were negative. Cefotaxime (150 mg/kg/day), azithromycin (10 mg/kg/day), and oseltamivir were given.

Twenty-four hours later, she developed dyspnea and desaturation 92% to 93% despite 10 LPM of oxygen supplement via a non-rebreathing mask. She was transferred to pediatric intensive care unit (PICU) and a high-flow nasal cannula (HFNC) was initiated. However, her symptom did not improve. Two hours later, she was intubated while a team carried out a work-up for septic screening results. Her symptoms progressed to acute respiratory distress syndrome (ARDS) two hours later. At this point, she had unstable hemodynamics, so dopamine, adrenaline and norepinephrine were titrated. Because she was in respiratory failure and had unstable hemodynamics, meropenem (60 mg/kg/day) and vancomycin (40 mg/kg/day) were administered.

Repeat blood test results were as followed, complete blood count showed Hb 11.5 g/dl, Hct 35.6%, WBC 2,320 cells/cm³ (28.8% polymorphonuclear cells, 65.7% mononuclear cells, 0.6% monocytes, 0.9% basophils and 0.2% eosinophils) and platelets 68,000/mm³. Blood chemistry results were blood urea nitrogen (BUN) 4 mg/dl, creatinine 0.38 mg/dl, sodium 139 mmol/L, potassium 3.3 mmol/L, chloride 105 mmol/L, Total CO_2 18 mmol/L, calcium 8.3 mg/dl, phosphate 2.8 mg/dl, magnesium 1.59 mEq/L, procalcitonin 0.859 ng/ml, blood lactate 1.06 mmol/L, fibrinogen 216 mg/dl (150 to 400 mg/dl) and D-dimer

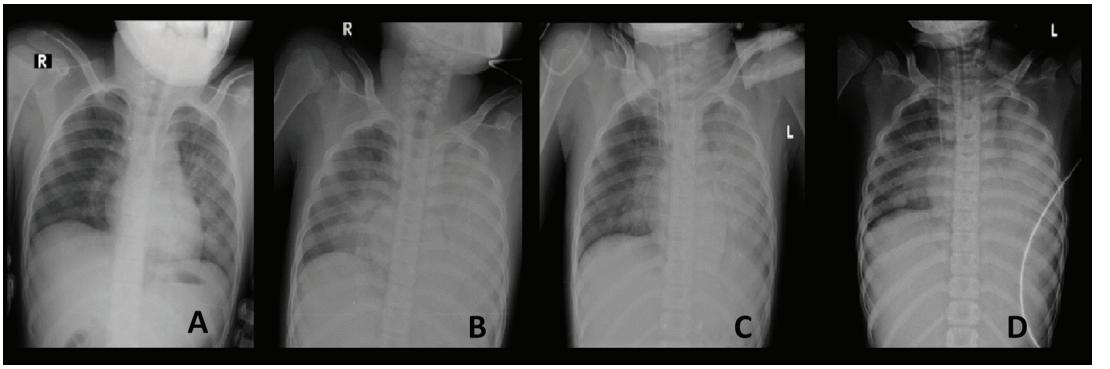

Figure 1. Chest radiograph of the patient (case 1). (A) In the first 24 hours after hospital admission. (B) Over the next 48 hours, portable chest radiograph showed haziness at total left lung and greater infiltration of the right lung. (C, D) After PICU admission, a high-setting mechanical ventilator was prescribed on the first and second day of PICU admission.

911 ng/ml (<500 ng/ml). Liver function test results were total protein 5.2 g/dl, albumin 2.9 g/dl, globulin 3.3 g/dl, alkaline phosphatase 80 U/L, cholesterol 125 mg/dl, aspartate aminotransferase (AST) 56 U/L, alanine aminotransferase (ALT) 18 U/L, total bilirubin (TB) 0.1 mg/dl, direct bilirubin (DB) 0.07 mg/dl. She had normal total creatinine kinase (CK) 306 U/L (91 to 391 U/L) and troponin T 9.2 pg/ml (<14 pg/ml), despite she had high pro B-type natriuretic peptide (pro-BNP) 662.9 pg/ml (10 to 140 pg/ml). The nasopharyngeal swabs for influenza and RSV were negative. Her chest radiographs are shown as Figure 1. An echocardiogram was requested and showed good left ventricular systolic function with left ventricular ejection fraction of 65% (while the patient was on 10 mcg/kg/minute dopamine). There was no pericardial effusion, but right and pleural effusion of 8 mm and 1 cm, respectively. Trivial tricuspid regurgitation and trivial mitral regurgitation were detected.

On the second day in PICU admission, her chest X-ray revealed no improvement. At 72 hours post admission the hemoculture and sputum culture results demonstrated no growth. Both dengue IgM and IgG were negative. Mycoplasma IgM was negative while IgG was positive. Three days later, the respiratory panel test from a polymerase chain reaction (PCR) from tracheal suction showed a positive result for hMPV but was negative for other pathogens. On the seventh day in PICU admission, the patient had stable vital signs and chest auscultation findings indicated better air entry, however, the highest setting of the ventilator was used. A trial of methylprednisolone 2 mg/kg/day was given for five days. The patient had transient improvement and the setting of ventilator could be reduced. The antibiotics were stopped after completion of a 14-day-course. The patient continued supportive treatment and rehabilitation. She stayed in the hospital for three weeks.

Case 2

A case of a 6-month-old male infant, with no previous medical history. He had a 2-day history of fever, cough, and nasal congestion. He was refusing solid food and taking minimal liquids. Six hours prior to admission, he had fever and progressive dyspnea. His temperature was 38.5°C, tachypnea at 60 breaths per minute, and had tachycardia at 170 beats per minute. His oxygen saturation was 90% without oxygen supplementation. Chest auscultation revealed fine crepitations and wheezing in both lungs. Chest radiograph indicated bilateral hyperinflation and perihilar infiltration. He was given an oxygen supplement of 3 LPM via cannula, normal saline challenge 10 ml per kg in 15 minutes, and intravenous cefotaxime 150 mg/kg/day. However, he still had dyspnea. He was transferred to PICU to receive respiratory support with a HFNC and close monitoring.

Complete blood count demonstrated Hb 11.8 g/dl, Hct 34.4%, WBC 16,460 cells/cm^3 (54.8% polymorphonuclear cells, 32.1% mononuclear cells, 8.6% monocytes, 0.2% basophils, and 1.3% eosinophils) and platelets 309,000/mm^3. The nasopharyngeal swabs for influenza type A/B and RSV screening test were negative. Cefotaxime (150 mg/kg/day) and azithromycin (10 mg/kg/day) were given. Blood chemistry results were BUN 8 mg/dl, creatinine 0.26 mg/dl, sodium 138 mmol/L, potassium 5.1 mmol/L, chloride 101 mmol/L and Total CO_2 18 mmol/L. Twenty-four hours later, the patient

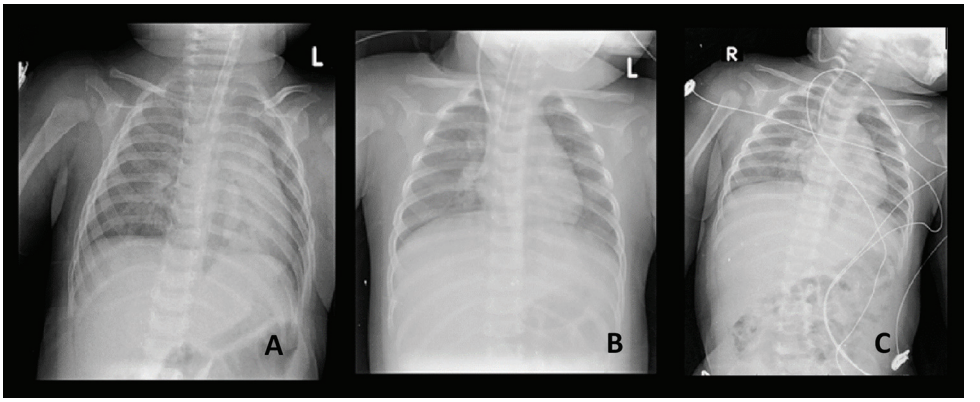

Figure 2. Chest radiograph of the patient (case 2). (A) Portable chest radiograph revealed perihilar infiltration of both lungs and left lower lung atelectasis after intubation. (B) 72 hours after PICU admission, portable chest radiograph showed decreasing infiltration and hyperinflation. (C) 5 days after PICU admission, the patient was extubated.

developed progressive dyspnea and desaturation, 88% to 90% despite having a HFNC flow of 14 LPM and FiO_2 0.6. Consequently, he required intubation and was put on mechanical ventilator support on a maximum setting at PC mode: PIP 20, PEEP 5, MAP 10, Ti 0.75, RR 20, and FiO_2 1.0. His chest radiographs after intubation are shown as Figure 2. Blood tests were repeated: complete blood count showed Hb 10.7 g/dl, Hct 33.7%, WBC 12,790 cells/cm^3 (39.1% polymorphonuclear cells, 52.2% mononuclear cells, 8.4% monocytes, 0.2% basophils, 0.1% eosinophils) and platelets 297,000/mm^3. Blood chemistry results were BUN 3 mg/dl, creatinine 0.25 mg/dl, sodium 136 mmol/L, potassium 3.7 mmol/L, chloride 104 mmol/L, Total CO_2 19 mmol/L, calcium 9.6 mg/dl, phosphate 4.5 mg/dl and magnesium 1.96 mEq/L. He had normal total CK 161 U/L (<190 U/L) and troponin T 4.0 pg/ml (<30 pg/ml), despite having a high pro-BNP 1,722 pg/ml (10 to 140 pg/ml). The nasopharyngeal swabs for influenza and RSV were negative. The sputum gram stain was found to have many polymorphonuclear cells without presence of organisms. Sputum PCR for virus and bacteria demonstrated positive for *Streptococcus pneumoniae* and hMPV, although the sputum culture for bacteria had no growth. A trial of methylprednisolone was given due to wheezing and difficulty of weaning from the ventilator. Three days later, the patient had improved both as regards his symptoms and chest radiograph. He could be weaned from the mechanical ventilator and was extubated after five days of PICU admission. The 10-day-course of antibiotics was completed. The patient continued supportive treatment and was weaned off oxygen. He stayed in the hospital for 10 days.

Discussion

In 2001, hMPV was discovered in the Netherlands and had been found in 4% to 16% of respiratory tract infected patients[1-3]. In Thailand, the prevalence of hMPV was shown ranging between 3.5% to 5.4% and 6.3% in young children and all age groups, respectively[5,6,11]. Most hMPV detection were found between August and November[5]. The hMPV is a member of the Paramyxovirus family, which is an enveloped RNA virus[4]. The hMPV infection is commonly found in the pediatric and elderly populations. It is particularly prevalent in young children less than two years old and in immunocompromised patients[1,4]. Risk factors of severe hMPV infection are preterm, young age, and underlying disease of pulmonary, and cardiovascular systems, and neurological disorders[1,4]. The hMPV leads to upper and lower respiratory tract diseases, which range from mild upper respiratory infection such as rhinorrhea to severe lower respiratory tract disease such as severe pneumonia[1,4,12]. The incubation period and shedding occur at between 3-9 days and 7-14 days, respectively[1,4]. The hMPV is transmitted by close contact with contaminated secretion or droplets[13]. The peak seasonal incidence is February to April. RSV, rhinovirus, PIV, adenovirus, coronavirus, and influenza virus can be a co-infection with hMPV infection[1,4,14,15]. Furthermore, some studies report that hMPV has a co-infection with bacterial pathogens such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*[1,4,15]. Several mechanisms of co-infection have been reported including when the respiratory epithelium is destroyed by the virus facilitating a secondary bacterial infection

or by the viral infection inducing increasing regulation of bacterial adhesion[16]. However, hMPV co-infection and other pathogens results in no difference in disease severity from infection with hMPV-alone[4,17].

In animal models, hMPV infection is associated with peribronchial inflammation with increasing infiltration by mononuclear cells and respiratory epithelial cell change[4]. In addition, the infection results in thickening of myofibroblasts around the airway epithelium and remains in the lung for several weeks in the same way as RSV[14]. The hMPV-infected-patients mostly present with rhinorrhea, coryza, and acute otitis media in upper respiratory tract infections. The hMPV-related-lower respiratory tract condition commonly presents with cough, wheezing, crepitation, and dyspnea[4]. In severe cases, patients have hypoxia and cyanosis that necessitates mechanical ventilatory support in ICU. Furthermore, hMPV infection may cause non-respiratory symptoms such as vomiting, diarrhea, rash, febrile seizure, and myocarditis[4,18]. Pro-BNP is a useful biomarker for heart failure, and troponin T is an indicator for diagnosis myocarditis[19-22]. The present report demonstrated that both patients have high pro-BNP level and low troponin T level. The high pro-BNP value may cause pneumonia accompanied by heart failure, which is unlikely from myocarditis, that is confirmed by low troponin T, especially less than 10 pg/ml[19-21,23]. The radiologic findings are perihilar infiltration, consolidation, atelectasis, and hyperinflation. Moreover, bronchopneumonic changes, lobar pneumonia, and effusion can be found in radiologic abnormalities[4]. The clinical symptoms, risk factors, and radiologic findings of hMPV infection are similar to RSV infection. The peak age of hMPV infection is usually associated with older infants, which differs from the age known to be associated with RSV infection.

The multiplex reverse transcriptase polymerase chain reaction (mRT-PCR), the gold standard for diagnosis, is used to confirm hMPV diagnosis. The mRT-PCR has greater efficacy in detection of the low viral load than does the cell culture. The sensitivity and specificity of cell culture are 68% and 99%, compared to 100% and 96%, respectively in the mRT-PCR method[1,4]. These case reports explain the importance of testing for infection with hMPV where there is severe respiratory distress. In addition, early diagnosis of hMPV enhances appropriate antibiotic use and infection control.

Currently, the treatment for hMPV infection is supportive treatment. Supplementation with oxygen or providing mechanical ventilatory support, if the patients have indications, may be needed in the case of severe lower respiratory tract infection. In addition, the appropriate antibiotics need to be prescribed for the patients who have a hMPV infection with a suspected secondary bacterial infection[1,4].

In conclusion, hMPV, an important respiratory pathogen, has various severity from mild illness to severe respiratory failure. The clinical symptoms of hMPV infection can progress to respiratory failure in both infant and older children, in term of either immunocompetent or immunocompromised hosts. Further research requires better clinical significance of both single hMPV infection and role of bacterial co-infection involving acute respiratory failure. Eventually, good supportive care is the primary treatment.

What is already known on this topic?

Severe ARDS and heart failure from hMPV infection are unusual clinical presentation in children, however, these lead to high morbidity and mortality. Moreover, severe respiratory failure in children from co-infection of hMPV and *Streptococcus pneumoniae* are also rare.

What this study adds?

This case reports describe the presentation of a girl who developed severe ARDS and heart failure from hMPV infection and an infant who developed severe respiratory failure due to co-infection between hMPV and *Streptococcus pneumoniae*. The hMPV should be investigated in children with severe respiratory failure with negative culture from common pathogens.

Acknowledgement

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Ethics approval and consent to participate

The authors' ethics committee waived the requirement of ethics approval because all medical and laboratory procedures are routinely carried out and do not affect decisions concerning treatment. The authors declare that the study was assessed and approved by the Institutional Ethics Committee No. PED-2561-05499. Patient/guardian consents were obtained for publication of the present case report.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Panda S, Mohakud NK, Pena L, Kumar S. Human metapneumovirus: review of an important respiratory pathogen. Int J Infect Dis 2014;25:45-52.
2. van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719-24.
3. Lu G, Li J, Xie Z, Liu C, Guo L, Vernet G, et al. Human metapneumovirus associated with community-acquired pneumonia in children in Beijing, China. J Med Virol 2013;85:138-43.
4. Schuster JE, Williams JV. Human metapneumovirus. Pediatr Rev 2013;34:558-65.
5. Teeratakulpisarn J, Ekalaksananan T, Pientong C, Limwattananon C. Human metapneumovirus and respiratory syncytial virus detection in young children with acute bronchiolitis. Asian Pac J Allergy Immunol 2007;25:139-45.
6. Samransamruajkit R, Thanasugarn W, Prapphal N, Theamboonlers A, Poovorawan Y. Human meta-pneumovirus in infants and young children in Thailand with lower respiratory tract infections; molecular characteristics and clinical presentations. J Infect 2006;52:254-63.
7. Arnott A, Vong S, Sek M, Naughtin M, Beaute J, Rith S, et al. Genetic variability of human metapneumovirus amongst an all ages population in Cambodia between 2007 and 2009. Infect Genet Evol 2013;15:43-52.
8. Vinomarlini G, Samuel L, Thayan R, Zainah S, Bhassu S. Incidence of human metapneumovirus in hospitalized patients admitted for respiratory illness in Malaysia. Int Res J Biological Sci 2014;3:51-7.
9. Loo LH, Tan BH, Ng LM, Tee NW, Lin RT, Sugrue RJ. Human metapneumovirus in children, Singapore. Emerg Infect Dis 2007;13:1396-8.
10. Zhang L, Liu W, Liu D, Chen D, Tan W, Qiu S, et al. Epidemiological and clinical features of human metapneumovirus in hospitalised paediatric patients with acute respiratory illness: a cross-sectional study in Southern China, from 2013 to 2016. BMJ Open 2018;8:e019308.
11. Horthongkham N, Athipanyasilp N, Sirijatuphat R, Assanasen S, Sutthent R. Prevalence and molecular characterization of human metapneumovirus in influenza a negative sample in Thailand. J Clin Lab Anal 2014;28:398-404.
12. Edwards KM, Zhu Y, Griffin MR, Weinberg GA, Hall CB, Szilagyi PG, et al. Burden of human metapneumovirus infection in young children. N Engl J Med 2013;368:633-43.
13. Kim S, Sung H, Im HJ, Hong SJ, Kim MN. Molecular epidemiological investigation of a nosocomial outbreak of human metapneumovirus infection in a pediatric hemato-oncology patient population. J Clin Microbiol 2009;47:1221-4.
14. Esposito S, Daleno C, Prunotto G, Scala A, Tagliabue C, Borzani I, et al. Impact of viral infections in children with community-acquired pneumonia: results of a study of 17 respiratory viruses. Influenza Other Respir Viruses 2013;7:18-26.
15. Lin PY, Lin TY, Huang YC, Tsao KC, Huang YL. Human metapneumovirus and community-acquired pneumonia in children. Chang Gung Med J 2005;28:683-8.
16. Ishizuka S, Yamaya M, Suzuki T, Takahashi H, Ida S, Sasaki T, et al. Effects of rhinovirus infection on the adherence of Streptococcus pneumoniae to cultured human airway epithelial cells. J Infect Dis 2003;188:1928-39.
17. Choi EH, Lee HJ, Kim SJ, Eun BW, Kim NH, Lee JA, et al. The association of newly identified respiratory viruses with lower respiratory tract infections in Korean children, 2000-2005. Clin Infect Dis 2006;43:585-92.
18. Kim HJ, Yoo GH, Kil HR. Clinical outcome of acute myocarditis in children according to treatment modalities. Korean J Pediatr 2010;53:745-52.
19. Felker GM, Petersen JW, Mark DB. Natriuretic peptides in the diagnosis and management of heart failure. CMAJ 2006;175:611-7.
20. McKie PM, Burnett JC Jr. NT-proBNP: The Gold Standard Biomarker in Heart Failure. J Am Coll Cardiol 2016;68:2437-9.
21. Eisenberg MA, Green-Hopkins I, Alexander ME, Chiang VW. Cardiac troponin T as a screening test for myocarditis in children. Pediatr Emerg Care 2012;28:1173-8.
22. Soongswang J, Durongpisitkul K, Nana A, Laohaprasittiporn D, Kangkagate C, Punlee K, et al. Cardiac troponin T: a marker in the diagnosis of acute myocarditis in children. Pediatr Cardiol 2005; 26:45-9.
23. Hu D, Liu Y, Tao H, Gao J. Clinical value of plasma B-type natriuretic peptide assay in pediatric pneumonia accompanied by heart failure. Exp Ther Med 2015;10:2175-9.