**Use of Intravenous Peramivir in a Critically Ill Toddler With Influenza A Infection and Cardiac Involvement**

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**Introduction**

Peramivir is the only intravenous (IV) formulation among the anti-influenza neuraminidase (NA) inhibitor compounds currently available. On December 19, 2014, the US Food and Drug Administration approved peramivir to treat influenza infection in adults. We report a pediatric case with influenza A myopericarditis with tamponade, where use of peramivir along with pericardial effusion drainage and steroid administration improved clinical status without any side effects of the medication. To our knowledge, this is the first case in the United States where peramivir was used for complicated influenza A infection in a pediatric case since the 2009 H1N1 pandemic.

**Case**

The patient was a 3-year-old previously healthy male who developed cough, congestion, and recurrent fevers with a maximum temperature spike of 102°F in the first week of January 2015. He was seen by his primary care physician 3 days prior to admission and was prescribed oral amoxicillin for possible streptococcal throat infection. During the next 2 days, the patient developed decreased oral intake with nonbloody, nonbilious vomiting and lethargy. He was brought to our hospital emergency department where he was found to be hypotensive (blood pressure: systolic/diastolic, 50-70/30-50 s mm Hg), tachycardic (to the 130-150 beats/min), and obtunded with waxing and waning mental status. Bedside heart ultrasound demonstrated a large pericardial effusion with tamponade, and he underwent emergent pericardial drainage and steroid administration improved clinical status without any side effects of the medication. To our knowledge, this is the first case in the United States where peramivir was used for complicated influenza A infection in a pediatric case since the 2009 H1N1 pandemic.

Infectious diseases service was consulted for assistance with diagnosis and management of the patient. On our examination of the patient in the intensive care unit, his temperature was 102.3°F and heart rate 168 beats/min. He was on conventional ventilator support (settings: rate = 20; PEEP: 5; PIP: 22; FiO2 : 40%; oxygen saturation: 97%), with blood pressures of 40-120/34-67 mm Hg. His weight was 15.7 kg (91st percentile). He was intubated and sedated. He had generalized edema, pupils round and reactive bilaterally, and no conjunctival injection or oral lesions. He had the full range of motion at the neck with no masses. Lungs were clear to auscultation bilaterally. His cardiovascular examination was remarkable for distant heart sounds with pericardial rub, increased capillary refill of 5 s with cold peripheral extremities, regular rate and rhythm, and no murmurs; the pericardial drain was in place with serous discharge. His abdomen was distended and firm.

His initial laboratory values were as follows: complete blood cell count of white blood cells (WBCs) of 13 × 10³/µL, with a differential of neutrophil 48%, bands 7%, lymphocytes 31%, and eosinophil 2.5%; platelet count of 148 × 10³/µL; and hemoglobin of 13 g/dL. His sedimentation rate was 9 mm/h and C-reactive protein <0.5 mg/dL. His blood urea nitrogen, serum creatinine, aspartate aminotransferase, alanine aminotransferase, and urine analysis were normal. B-type natripeptide was 102.9 pg/mL (normal <100 pg/mL).

Chest X-ray showed generous heart with perihilar atelectasis (Figure 1). Ultrasound of the abdomen showed no intussusception, normal appendix, and small pockets of free fluid in the right upper and lower quadrants, with upper quadrant-free fluid appearing complex, with gallbladder wall thickening. EKG showed normal

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sinus rhythm, low voltage QRS, and nonspecific T wave abnormality. Echocardiography of the heart showed moderate to large circumferential pericardial effusion, with greatest dimension along the diaphragmatic surface (~1.8 cm), right atrial wall collapse during end diastole, qualitatively normal right-ventricular size and systolic function, and qualitatively mild to moderate concentric left-ventricular hypertrophy.

His winter respiratory panel from nasal wash specimen was positive for influenza A, reverse transcription polymerase chain reaction (RT-PCR) positive (H3N2). The blood cultures were collected before starting antibiotics were negative. The pericardial fluid Gram stain showed many WBCs and moderate red blood cells but no organism; aerobic, anaerobic, and viral culture were negative. Molecular testing for bacterial, fungal, and viral pathogens on pericardial fluid were sent to University of Washington 2 days after initiation of oseltamivir and antibiotics and were negative for influenza A/B, respiratory syncytial virus, enterovirus/parechovirus, cytomegalovirus, parvovirus B19, adenovirus, and universal bacterial and fungal PCR. An aliquot of pericardial fluid and blood were also sent to the John Welsh Molecular Diagnostic Laboratory at Baylor College of Medicine for influenza PCR, which was negative. His purified protein derivative (PPD) test was negative.

Broad-spectrum IV antibiotics, vancomycin and cefotaxime, IV steroids, and oseltamivir via nasogastric tube were administered. Because of the patient’s persistent critical status and concern for poor absorption of oral oseltamivir, IV peramivir was administered at a dose of 10 mg/kg/dose every 24 hours for 5 days. Within 24 hours of IV peramivir administration, the patient recovered dramatically; he was extubated, and both epi-nephrine and norepinephrine drips were discontinued. Two days later, the pericardial drain was removed.

During recovery, the patient was noted to have truncal ataxia, possibly related to an influenza A induced encephalopathy, and he improved gradually over the following week. Follow-up echocardiography was normal. He was discharged home after 10 days of hospitalization. Figure 2 shows his clinical response and recovery. He and his family members received tetravalent influenza vaccine before discharge. He had a follow-up with the physical rehabilitation clinic a month later where he was found to be at his baseline function.

**Discussion**

Influenza is an orthomyxovirus, consisting of types A, B, and C, which are divided on the basis of the antigenicity of the surface proteins hemagglutinin (HA) and NA. Epidemic disease is caused by types A and B, and type C is associated with sporadic disease. There are 16 HA (H1-H16) and 9 NA (N1-N9) subtypes. The minor variations are called antigenic drifts and major variations antigenic shifts associated with influenza A only, leading to pandemics.

Cardiac manifestations of influenza are rare. Myocarditis or perimyocarditis with potentially fatal arrhythmias, atrioventricular block, and/or varying degrees of cardiogenic shock along with pericardial effusion and cardiac tamponade may occur. The prevalence of myocardial involvement in influenza infection ranges from 0% to 11%, depending on the diagnostic criteria used to define myocarditis. Our patient had severe pericardial effusion leading to tamponade, requiring urgent pericardiocentesis. There have been 3 similar cases reported in the past with significant pericardial effusion, and in 2 cases (Proby et al. and Mamas et al.), cardiac tamponade requiring pericardiocentesis was present. Bratincsak et al. reported 4 cases of fulminant myocarditis, including 1 fatal case, in their pediatric cohort of 80 patients during the H1N1 pandemic in 2009.

It is uncertain whether myocyte damage in the early phase of the myocarditic disease process is linked primarily to the influenza viral presence or immunomedi-ated damage. Human studies done on endomyocardial biopsies showed that infection of the myocardium with influenza A is associated with an increased expression of tumor necrosis factor (TNF)-α and its receptors TNFR1 and TNFRII in the myocardium. Moreover, an association between depressed myocardial function and elevated TNF-α mRNA and protein levels in the myocardium has been previously demonstrated in patients with myocarditis.
The diagnosis of influenza virus infection is best accomplished during the first 72 hours of illness. The rapid diagnostics tests such as EIA on the respiratory tract specimens have a sensitivity of 44% to 97% and specificity of 76% to 100%. Both RT-PCR and viral culture tests have higher sensitivity as well as specificity. In our case, RT-PCR from the nasal secretions was positive on the day of presentation, but all the other testing for presence of influenza virus on pericardial fluid and blood was negative when sent 48 to 72 hours after presentation. The lack of detection of influenza virus RNA in pericardial fluid suggests either a possible immunopathogenic process for myopericarditis or rapid clearance of the virus from internal bodily fluids.

The antivirals that are available for treatment or prophylaxis for influenza infections in pediatric patients are NA inhibitors (oseltamivir and zanamivir) and adamantanes (amantadine and rimantadine). Recently the US Food and Drug Administration approved peramivir, an IV NA inhibitor, to treat influenza virus infection in adults. In the 2009 H1N1 pandemic, it was administered to 41 patients, including 11 children, under the Emergency Investigational New Drug regulations for rapidly progressing respiratory failure. In most patients, the illness had progressed despite oseltamivir treatment, similar to the situation we described. Peramivir was administered for 1 to 14 days (median duration = 10 days). They reported 14-day, 28-day, and 56-day survival rates of 76.7%, 66.7%, and 59.0%, respectively. Peramivir was generally well tolerated in these patients, and 7 out of 11 children survived. The data encouraged us to use the medication in our patient, with successful results of drastic recovery of a critically ill patient within 24 hours. Moreover, the patient did not have any side effects related to the use of peramivir. A postmarketing safety and effectiveness study was conducted after IV peramivir was approved in October 2010 for use in the pediatric population in Japan. In 1254 children treated with IV peramivir, with half of the patients in the age group 1 to 7 years, safety and effectiveness of this medication were reported. Peramivir undergoes little metabolism in humans and is eliminated unchanged in the urine; drug clearance correlates with creatinine clearance.

In summary, a critically ill toddler with virologically confirmed influenza A H1N1 infection complicated with myopericarditis and cardiac tamponade was treated with IV peramivir and survived. We understand that a single case report cannot determine the efficacy of the medication in the pediatric age group, but it provides supporting evidence of safety of the medication. Also, we wanted to bring to light the availability of the medication and its

Figure 2. Clinical course of critically ill patient with fever and shock syndrome caused by influenza A and myopericarditis with cardiac tamponade, treated with oral oseltamivir followed by intravenous (IV) peramivir, showing clinical response and recovery.
Abbreviation: PCR, polymerase chain reaction.
potential benefit in a critically ill patient. Future studies are required in the United States to evaluate the effectiveness and safety of this medication in the pediatric population.

**Author Contributions**

Both the authors substantially contributed to conception, design, acquisition, analysis, or interpretation of data. MC drafted the manuscript. MC and GJH critically revised manuscript for important intellectual content and finally approved the manuscript.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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