



## CASE REPORT

# Reconstitution of Oseltamivir Capsules for Pediatric Use on a Long-Term Cruise: A Treatment Option

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Influenza is a concerning disease in terms of risk management for cruise passengers during a voyage. Currently, cruise passengers include children in addition to elderly people. Oral oseltamivir can be used to treat pediatric influenza. In addition, early antiviral treatment may reduce the spread of influenza on board. However, the capsule form of oseltamivir is not of the recommended dosage for children. In this report, we describe 2 siblings who acquired influenza during travel on a world cruise ship and were treated with decapsulated oseltamivir. The siblings' mother was instructed to decapsulate a 75 mg oseltamivir capsule, suspend the powder in 15 mL of water (5 mg·mL<sup>-1</sup>), stir well, and administer the required amount of medicine orally to each patient using a syringe. Both patients recovered successfully with no complications. The presented case suggests that suspending decapsulated oseltamivir in water and measuring the required amount with a syringe for orally administration to children with influenza can be a safe treatment strategy in resource-limited settings.

**Keywords:** influenza, travel medicine, suspensions, extreme environments, emergency medicine, pediatrics

## Introduction

Travel on cruise ships has been increasing all over the world, including long-term cruises. Although the majority of the population on cruises are elderly people,<sup>1</sup> cruise passengers may also include children.<sup>2,3</sup> Unexpected illnesses and injuries may occur on long-term cruises.<sup>4</sup> However, medical facilities vary widely among cruise ships.<sup>5</sup> In general, children require a more cautious medical approach than adults and require different dosage of medicines according to their body weight. Moreover, there are challenges in treating children in resource-limited settings involving limited availability of pediatric drugs.<sup>6</sup>

There are some reports of influenza outbreaks on cruise ships.<sup>2,7</sup> Patients with severe influenza requiring hospitalization and those with mortality related to cruise travel have also been documented.<sup>7-9</sup> For management of

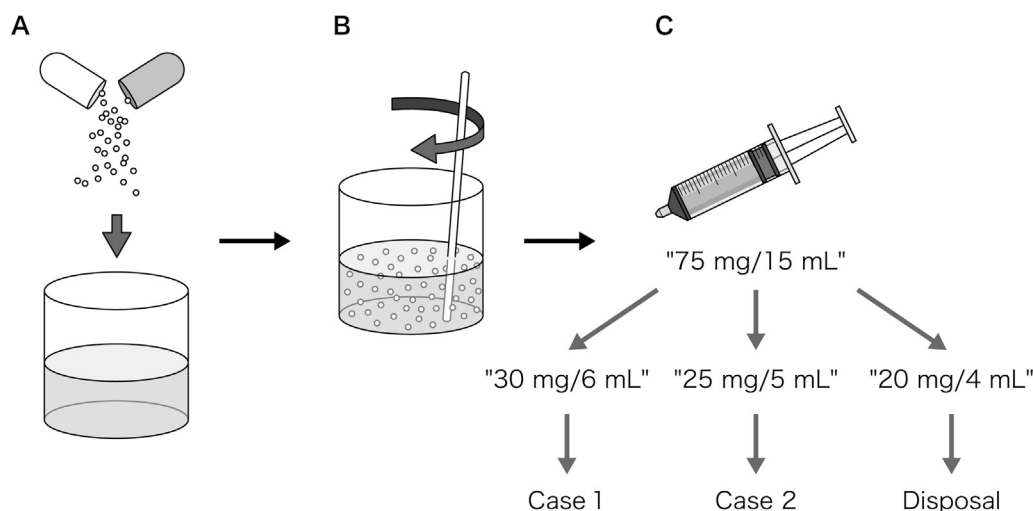
influenza-like illness on cruise ships, the Centers for Disease Control and Prevention recommends early antiviral treatment with neuraminidase inhibitors, such as oral oseltamivir, in patients with suspected or confirmed influenza who have severe illness or are at a high risk of complications. The guidance also states that specific management to reduce the spread of influenza includes the use of influenza antiviral medications in people with suspected or confirmed influenza.

In general pediatrics, selective use of oseltamivir is recommended in hospitalized patients with influenza; children with severe, complicated, or progressive illness attributable to influenza; and children with influenza of any severity at high risk of complications of influenza.<sup>10</sup> It also has been suggested that antiviral treatment may be considered in previously healthy children if treatment can be initiated within 48 h of illness onset, but so far, the effectiveness of antiviral treatment in children without complications has not been well established.<sup>10</sup> Although there is no direct evidence, oseltamivir use may be appropriate in preventing the spread of infection on board if a child is infected with influenza on a cruise ship. However, a detailed report describing the treatment of

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**Figure 1.** Method for suspending oseltamivir to administer the required dose to children. (A) Decapsulate 75 mg of oseltamivir and suspend in 15 mL of water ( $5 \text{ mg}\cdot\text{mL}^{-1}$ ) in a cup. (B) Stir the contents well to make a uniform liquid suspension with the medicine. (C) Administer 6 mL=30 mg to case 1 and 5 mL=25 mg to case 2 using a syringe; discard 4 mL.

pediatric influenza patients on cruise ships has not been published to date.

Herein, we describe 2 cases involving siblings who contracted influenza on a world cruise ship and were treated with decapsulated adult oseltamivir suspension to achieve pediatric dosing.

### Case Report

A previously healthy 5-y-old Japanese boy visited the on-board clinic due to high fever (case 1, body weight 15 kg). The patient had been on the 105-day world cruise ship, which departed from Japan, along with his mother and sister. On day 77, he developed cough, nasal discharge, and sore throat. He developed mild anorexia 2 d before this visit and developed fever and general weakness the night before the consultation. On admission, he presented with fever of  $38.4^{\circ}\text{C}$ , tachypnea, tachycardia, and pharyngeal redness. A rapid diagnostic antigen test showed that he was positive for influenza type A virus. Subsequently, his 2-y-old sister (case 2, body weight 12 kg) presented with coryza, cough, and pharyngeal redness. Although her temperature was recorded as  $37.1^{\circ}\text{C}$  and her condition was generally well, she was clinically diagnosed with influenza considering the close direct exposure to case 1. Neither sibling had been vaccinated against the seasonal influenza virus before boarding.

The vessel was estimated to be at sea for more than 10 d before the next scheduled port of call. Because of the limited treatment options for severe cases in the vessel

and to prevent further transmission to other passengers, we considered the administration of antiviral drugs. Although some pediatric drugs such as antibacterial medicine were available, oseltamivir dry syrup for children was unavailable at that time. Furthermore, there was no lactose powder or a scale to accurately weigh the powder. After obtaining informed consent for the off-label use of the medicine, the mother was instructed to follow the following procedure: decapsulate 75 mg of oseltamivir, suspend in 15 mL of water ( $5 \text{ mg}\cdot\text{mL}^{-1}$ ), stir well, administer 6 mL (30 mg) to case 1 and 5 mL (25 mg) to case 2, and discard 4 mL using a syringe (Figure 1). After confirming that the mother was able to perform this procedure, the medicine was administered to the siblings twice daily for 5 d. Both siblings could ingest the drug when the medicine was mixed with juice or miso soup. Case 1 became afebrile on the second day of cabin isolation. Case 2 remained afebrile throughout the course, and both patients recovered without any complication. Eventually, they completed their voyage. Concurrently, there were more than 30 influenza cases among >1200 passengers on board, and these patients were managed according to the guidelines for influenza-like illness management on cruise ships. These were the only 2 pediatric cases and were the third and fourth patients diagnosed with influenza during the epidemic.

### Discussion

We successfully administered oseltamivir capsules meant for adults to children in a creative manner in the

challenging resource-limited environment of a long-term cruise ship. Although medical facilities vary among cruise ships, resources are generally limited, and it is difficult to provide sufficient care for critically ill patients on board.<sup>11</sup> In addition, depending on the route of voyage, medical evacuation may take some time.<sup>12</sup> Owing to crowded and confined living spaces, respiratory tract and gastrointestinal infections are easily transmitted.<sup>2,13</sup> In addition to appropriate infection control, each patient, including pediatric patients, should be offered the best treatment with the available resources. Several pediatric drugs such as clarithromycin, amoxicillin/clavulanic acid, acyclovir, domperidone, acetaminophen, epinastine, and carbocysteine were available on the vessel, but no anti-influenza drugs were available. Oseltamivir for children currently is commercially available in dry powder and oral suspension formulations (Tamiflu oral suspension; Genentech, Inc., South San Francisco, CA). Although there has been no detailed information on individual patients, some studies have reported confirmed influenza in children on board.<sup>2,14</sup> Therefore, in the future, cruise management may have to consider including pediatric anti-influenza medicines as well.

Oseltamivir is highly dispersible and easily forms a water suspension. This allowed us to measure the required amount with a syringe after suspending the powder in water. A report has showed the chemical and microbial stability of an extemporaneous oral liquid formulation made from commercially available oseltamivir.<sup>15</sup> Furthermore, the Food and Drug Administration (FDA) has approved decapsulation, suspension, and administration of the required dosage of oseltamivir intended for adult use only in particular situations. This method of suspending drugs in water may not be appropriate in some situations, such as when tablets are suspended after grinding, because the nonuniformity of the particles after grinding makes it difficult or impossible to measure the required amount with a syringe. Furthermore, we must be cautious when modifying some medications, such as Aspirin protect (aspirin) and Teolong (theophylline), which should not be crushed or decapsulated because of the possibility of increased side effects.<sup>16</sup>

Although a method similar that used in our study has been approved by the FDA, no safety data existed on the medical package insert used in Japan regarding the domestic off-label use of capsulized oseltamivir. Moreover, we were not aware of the FDA-approved administration of oseltamivir. Therefore, we carefully instructed the mother on our procedure. In addition, we explained to her in advance and obtained consent regarding the possibility that the drug administration would not be effective or that adverse events could occur because some medications

cause increased adverse events when their mode of administration is changed.<sup>16</sup>

In a low-resource setting, such as that described in this report, it is sometimes necessary to determine the best treatment for the patient after careful consideration of the advantages and disadvantages of medication use. Timely administration of oseltamivir has been reported to decrease the duration of fever and the rate of acute otitis media as an influenza complication.<sup>17,18</sup> Although a review of 74 observational studies showed that oral oseltamivir may reduce mortality in high-risk populations compared with those receiving no treatment,<sup>19</sup> its effectiveness in reducing mortality in general has not been established.<sup>17</sup> Oseltamivir also may have vomiting as a side effect.<sup>10</sup> Therefore, nonselective administration of oseltamivir for all pediatric influenza patients is not recommended.<sup>10</sup> In our study, the patients might have recovered without medication because influenza is a self-limiting disease. However, although oseltamivir has not been reported to decrease household transmission,<sup>20</sup> in a crowded, low-income setting, oseltamivir treatment in index patients was reported to result in a small reduction in the rate of secondary influenza in households.<sup>21</sup> In a cruise setting, medical staff should not only take care of individual patients but also of all passengers to prevent potential outbreaks.

Preparation for and prevention of possible diseases and injuries are of utmost importance on a cruise. Medical staff on board cruise ships may be able to predict the medical requirements based on the travel period, area, seasons, passenger profiles, and epidemic diseases. It has been suggested that any traveler who wants to reduce the risk of influenza infection consider influenza vaccination, preferably at least 2 wk before departure.<sup>22</sup> In the future, influenza vaccination should be strongly recommended to passengers before boarding a cruise. Providing advice regarding postponing travel when passengers are sick and encouraging good respiratory hygiene and cough etiquette may also be important steps in reducing the spread of influenza.

Our report showed that suspending decapsulated oseltamivir in water and administering the required amount using a syringe to children with influenza can be a safe method and may decrease symptoms and transmission in resource-limited settings.

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contributing to the management of patients onboard and critically reviewing and revising the manuscript (LAD); contributing to patient management remotely and critically reviewing and revising the manuscript (KK, NM). Each author listed in the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

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