

# A review of four cases of COVID-19 medically evacuated by ambulance jet from Asian countries to Japan: Importance of strict infection control measures against multidrug-resistant organisms

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**Abstract:** International medical evacuation, which is an option to receive better medical care for travelers with emergencies staying in low- and middle-income countries, has been more challenging during the coronavirus disease 2019 (COVID-19) pandemic. We herein discuss our experience with four Japanese patients with COVID-19 who required medical evacuation from Asian countries during the pandemic. Of these, none of the patients had received a COVID-19 vaccine; three patients needed oxygen therapy on admission to our hospital; and one patient died due to respiratory failure on day 50 after hospitalization. It was observed that multidrug-resistant organisms were colonized in two patients after obtaining culture results based on active surveillance. Strict infection control measures against multidrug-resistant organisms should be implemented during the care of patients with COVID-19 who require medical evacuation from high-risk countries. Further, it is important to communicate timely updates regarding the patient's condition with travel assistance agencies as the patient's condition may rapidly change during the course of arranging the evacuation.

**Keywords:** COVID-19, medical evacuation, multidrug-resistant organisms

An outbreak of coronavirus disease 2019 (COVID-19), which was first reported in Wuhan, China in December 2019, rapidly spread worldwide. The World Health Organization declared the COVID-19 outbreak as a pandemic on March 11, 2020 (1). As of December 12, 2021, a total of 268,934,575 COVID-19 cases, including 5,297,850 casualties have been reported across the globe (2). The pandemic has laid a heavy burden on medical facilities in many countries, and appropriate access to medical care has been often limited. Especially in low- and middle-income countries, receiving appropriate medical care has been difficult due to the lack of medical resources during the COVID-19 pandemic (3).

For overseas workers, medical evacuation is an option to receive better medical care in cases where appropriate medical care may not be available in their region of residence. For example, the evacuation of individuals infected with Ebola virus from West Africa to developed countries in Europe and the USA was associated with significantly improved mortality (4). However, international medical evacuation during the COVID-19 pandemic has been associated with more challenges because other countries, including the patient's home country, have also been affected by the pandemic, which continues to significantly restrict the availability of

air ambulance flights, number of countries that accept these services, and availability of medical facilities that can receive these patients (5). Several studies reported collective medical evacuation including that of critical patients with COVID-19 conducted by army forces (6-8); however, few studies to date have provided detailed reports of the clinical characteristics of patients with COVID-19 medically evacuated from abroad. We herein describe the characteristics of Japanese patients with COVID-19 who were evacuated from abroad and discuss important lessons learned regarding infection control and arrangement for the medical evacuation of patients with COVID-19 during the pandemic.

Between January 2020 and October 2021, four hospitalized patients with COVID-19 required medical evacuation and were transferred to Japanese Red Cross Narita Hospital, a large tertiary teaching hospital with 714 beds located at a 20-minute drive from Narita International Airport in Chiba, Japan. Medical evacuation was arranged by the same medical travel assistance company for all the patients; the patients were transported by an air ambulance jet with the assistance of medical doctors and nurses. Clinical data of all the patients were retrospectively obtained from electronic medical records. Screening cultures for active

surveillance were performed according to the hospital protocol, which required evaluation of patients who were hospitalized abroad or who received invasive medical procedure abroad within the last three months. Samples were collected for cultures from stool, sputum, urine, and wounds, if available, using selective media. Vancomycin-resistant enterococci were screened using CHROMagar™ VRE medium (CHROMagar, Paris, France). Extended-spectrum beta-lactamase-producing *Enterobacteriaceae* and carbapenemase-producing *Enterobacteriaceae* were screened using CHROMagar™ ESBL agar (CHROMagar) and CHROMagar™ mSuper CARBAagar (CHROMagar). Carbapenemase genes were identified using the Xpert Carba-R cartridge and the GeneXpert system (Cepheid, CA, USA). Sputum, urine, and wound samples were also cultured using non-selective medium, and the identification and susceptibility of microorganisms were confirmed as usual. The study was approved by the Ethics Committee of the Japanese Red Cross Narita Hospital under the condition that the confidentiality of all personal data be maintained (approval no, JRCNH-749-01). The requirement for individual consent was waived given the retrospective, observational nature of the study.

Table 1 summarizes the characteristics of the patients. All the patients arrived in the hospital either late at night or early in the morning. The median patient age was 49.5 (range, 49-63), all patients were male and had been staying in the destination country for business purposes, and none of the patients had received a COVID-19 vaccine. Three of the four patients were infected in Indonesia, whereas the remaining patient was infected in Nepal. All patients were admitted to local hospitals. The median duration between symptomatic onset and local hospital admission was 3 (range 2-4) days. Three patients received high-dose oxygen therapy. The treatment for COVID-19 varied among the patients and included favipiravir and remdesivir in 3 and 1 patient, respectively. Antimicrobial therapy was provided to all patients. The median length of stay in the local hospital was 12.5 (range 4-15) days.

Three of the four patients needed oxygen therapy on admission to our hospital. Multidrug-resistant bacteria were present in the screening cultures of two patients. Carbapenem-resistant *Escherichia coli* was cultured from the stool and later confirmed as New Delhi metallo-beta-lactamase-producing *E. coli* in one patient. Additionally, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* were cultured from the sputum of the same patient. AmpC beta-lactamase overproducing *Enterobacter cloacae* complex was cultured from the stool in another patient. In patients with multidrug-resistant organisms, strict contact precautions were continued until discharge. Three patients recovered without sequelae. In the remaining patient, the respiratory condition worsened and was complicated with ventilator-associated pneumonia and

COVID-19-associated pulmonary aspergillosis. Despite invasive ventilatory management and veno-venous extracorporeal membrane oxygenation, the patient died due to respiratory failure on hospital day 50.

As reflected in these four cases, strict infection control measures for multidrug-resistant organisms should be implemented during the care of patients who require medical evacuation from high-risk countries. Travel to South or Southeast Asia and history of medical practices (e.g., hospitalization, antibiotic administration, invasive treatment including surgery, device placement) at the destination country are considered as major risk factors for colonization of multidrug-resistant organisms (9,10). Additionally, 10% of patients who were hospitalized abroad and exhibited multidrug-resistant bacteria were reported to subsequently develop symptomatic multidrug-resistant infections (9) and an outbreak of multidrug-resistant organisms originating from a traveler who was previously hospitalized abroad was reported in a Japanese hospital (11). All four patients reported herein were hospitalized in the destination country before evacuation and received antimicrobial treatment. We implemented strict contact precautions, performed active surveillance according to the institutional protocol, and determined that two patients were colonized with multidrug-resistant organisms. Transmission to other patients in the COVID-19 ward was not observed. Our experience suggests that strict infection control including contact isolation and active surveillance should be considered during planning for the admission of patients who require medical evacuation from abroad.

Vaccination for COVID-19 is important even for international travelers. Vaccination has been proven to significantly reduce the rate of infection and the severity of COVID-19 (12,13). None of the four patients in the current report were vaccinated against COVID-19. The Centers for Disease Control and Prevention recommends that all international travelers complete the COVID-19 vaccine series prior to travel (14). Vaccination against COVID-19 is necessary for international travelers because adequate medical care might be inaccessible during the COVID-19 pandemic.

Close communication to share updated information about the clinical condition of patients with the medical travel assistance company is key for successful medical evacuation. The patient's condition may rapidly change during the arrangement for evacuation. In fact, the respiratory status in two of the four patients significantly changed before transportation to our hospital. Hypoxia worsened in one patient and improved in another patient after the first contact between the medical travel assistance company and our hospital for the arrangement of evacuation.

We also faced an ethical dilemma in terms of bed capacity. During the surge in the number of local COVID-19 cases, our hospital was nearly full or

**Table 1. Clinical details of four patients with coronavirus disease 2019 who required medical evacuation**

Items	Case 1	Case 2	Case 3	Case 4
Date of evacuation	December 2020	June 2021	July 2021	July 2021
Duration between initial contact and evacuation (days)	5	5	2	2
Time of admission	8:35	22:07	21:24	20:37
Patient demographics and background				
Age (year), sex	49, male	63, male	50, male	49, male
Comorbidities	Diabetes mellitus	Hypertension	Abdominal aortic aneurysm	Hypertension Diabetes mellitus
COVID-19 vaccination history	None	None	None	None
Purpose of international travel	Business	Business	Business	Business
Country	Indonesia	Nepal	Indonesia	Indonesia
Duration of stay in the destination country	3 months	6 months	Unknown	Unknown
Clinical condition and treatment before evacuation				
Duration from the onset of symptoms and admission to local hospital (days)	3	2	3	4
Oxygen therapy	High-flow nasal cannula	Oxygen mask (max 15 L/min)	None	Oxygen mask (max 6 L/min)
Treatment for COVID-19	Favipiravir Remdesivir Methylprednisolone Enoxaparin Ivermectin	Dexamethasone Methylprednisolone Enoxaparin Ivermectin	Favipiravir (discontinued for two days due to drug shortage)	Favipiravir Dexamethasone Heparin
Antimicrobial use	Tozilizumab Azithromycin	Ceftriaxone Meropenem	Ceftriaxone	Cefoperazone/sulbactam Levofloxacin
Length of hospital stay in local hospital (days)	13	15	4	12
Clinical condition and treatment after evacuation				
Respiratory status on admission	SpO <sub>2</sub> , 97% at 3L/min O <sub>2</sub>	SpO <sub>2</sub> , 90% at 15L/min O <sub>2</sub>	SpO <sub>2</sub> , 92% at room air	SpO <sub>2</sub> , 97% at 6 L/min O <sub>2</sub>
Culture results based on active surveillance to detect multi-drug resistant organisms	No specific organism in sputum, stool, and urine	<i>Escherichia coli</i> (NDM-CPE) from stool <i>Pseudomonas aeruginosa</i> and <i>Stenotrophomonas maltophilia</i> from sputum No specific organism in urine	<i>Enterobacter cloacae</i> (AmpC beta-lactamase overproducing) in stool No specific organism detected in urine and sputum	No specific organism in stool and urine
Oxygen therapy	Nasal cannula (max 3L/min)	Veno-venous ECMO	None	Oxygen mask (6 L/min)
Treatment for COVID-19	Dexamethasone Heparin	Baricitinib Methylprednisolone CAPA, VAP due to <i>S. maltophilia</i> , CRBSI due to <i>E. coli</i> (ESBL)	None	None
Major complications	None	None	None	None
Length of hospital stay (day)	6	49	7	6
Outcome	Survived	Died	Survived	Survived

CAPA, coronavirus disease 2019-associated pulmonary aspergillosis; COVID-19, coronavirus disease 2019; CRBSI, catheter-related blood stream infection; ECMO, extracorporeal membrane oxygenation; ESBL, extended-spectrum beta -lactamase; NDM-CRE, New Delhi metallo-beta-lactamase-producing carbapenem-resistant *Enterobacteriaceae*; VAP, ventilator-associated pneumonia.

overcrowded. Providing a bed to a patient requiring medical evacuation would prevent the admission of a local patient with COVID-19. Thus, we prioritized the patients who resided in or around Chiba. In all four cases, the medical travel assistance company directly contacted the hospital to determine the availability of a space for the patient. In ideal circumstances, a comprehensive bed control system is expected to provide beds both for local patients and those who require medical evacuation from abroad.

In conclusion, our experience with four patients with COVID-19 who required medical evacuation from Asian countries during the pandemic illustrates the need for implementation of strict infection control measures against multidrug-resistant organisms. Further, it is important to communicate timely updates regarding the patient's condition with travel assistance agencies during the arrangement of medical evacuation.

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