

# Imported melioidosis in Japan: a review of cases

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**Abstract:** Fourteen cases of reported melioidosis in Japan were reviewed. The mean age was 52.4 years (33–69 years), and all patients were male. All of the presumed exposures originated in Southeast Asia. The most common underlying disease was diabetes mellitus, including those patients with impaired glucose tolerance (n=8). As for mode of onset, 13 patients had acute infections and one had chronic infection. Of these 14 patients, the most common infection site on admission was lung (n=8), followed by bone (n=5), skin (n=4), gastrointestinal abscess formation (n=3), urinary tract (n=3), aorta (n=2), mediastinal lymph node swelling (n=1), and central nervous system (n=1). Bacteremia was observed in nine patients, and *Burkholderia pseudomallei* isolates were mostly susceptible to ceftazidime and carbapenem. Overall mortality was 14.3%. Melioidosis is a rare infection in Japan, with all known cases to date having been imported from Southeast Asia. Diabetes was a common risk factor.

**Keywords:** melioidosis, *Burkholderia pseudomallei*, Japan, Southeast Asia

## Introduction

Melioidosis is a bacterial infection caused by the Gram-negative, facultative, environmental organism *Burkholderia pseudomallei*.<sup>1</sup> Clinical manifestations include a diverse pattern that can be acute such as pneumonia with severe sepsis (defined as symptoms present for less than 2 months) or chronic infection (defined as symptoms present for over 2 months), similar to tuberculosis. Therefore, melioidosis is referred to as the “great mimicker”.<sup>2</sup> With the expansion of commercial air traffic, international travel has become commonplace. As a result, travel-related infections are diagnosed in Japan. Therefore, cases of imported melioidosis from endemic regions have been reported recently. Because of the high fatality rate of melioidosis (14%–43%), it is essential that physicians are more aware of melioidosis. Currently, *B. pseudomallei* is considered to be absent in Japan, but Limmathurotsakul et al predict that Japan will have areas that would be suitable for *B. pseudomallei*, especially in the southern part of Japan, such as Okinawa and Kagoshima prefecture, due to similarity in the soil environment.<sup>3</sup> Our goal was to review and clarify a series of cases and the epidemiology related to clinical manifestations of imported melioidosis in Japan.

## Material and method

PubMed, Google, and Ichushi-Web (the Japanese Medical Database sponsored by the Japan Medical Abstracts Society) were searched for relevant articles from 1990 to 2017. The following keywords were used: melioidosis, *Burkholderia pseudomallei*, Japan, and case report. Case reports and reviews of case reports with full texts or

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abstracts available in English and Japanese were included. As a result, 14 cases were found. The data collected from medical articles are as follows: basic demographic characteristics (age, gender), underlying diseases, foreign travel history, mode of onset (acute or chronic with acute defined as symptoms lasting for less than 2 months before diagno-

sis and chronic defined as symptoms persisting for longer than 2 months), duration after exposure (<2 months, 2–6 months, >6 months, or unknown), chief complaints, clinical manifestations, septic shock status on admission, source of the *B. pseudomallei* isolates (blood, sputum, urine, skin/soft tissue, synovial fluid, cerebrospinal fluid, throat swab, and

**Table I** Summary of imported melioidosis cases in Japan

Case	Age	Gender	Travel status	Exposure region	Risk factors	Acute or chronic	Duration after exposure	Chief complaints	Clinical manifestations
1	41	Male	Business trip	Indonesia, Singapore	Diabetes, alcoholic liver dysfunction	Chronic	<2 months	Fever, loss of appetite	Liver abscess, spleen abscess
2	51	Male	Living in Malaysia	Malaysia	Diabetes, alcoholism	Acute	Unknown	Left knee pain	Lung abscess, osteomyelitis
3	58	Male	Travel	Thailand, Vietnam, Malaysia	Impaired glucose tolerance	Acute	<2 months	Fever	Mycotic aneurysm, pneumonia
4	69	Male	Travel	Myanmar	Diabetes	Acute	<2 months	Fever, dyspnea	Cellulitis, lung empyema
5	44	Male	Living in Thailand	Thailand	Gastric ulcer	Acute	<2 months	General fatigue, left knee pain	Lung abscess, osteomyelitis, subcutaneous abscess
6	34	Male	Immigrant from Vietnam	Vietnam	Diabetes	Acute	>6 months	Fever, left epigastric pain	Splenic abscess
7	65	Male	Travel	Thailand	Diabetes	Acute	<2 months	Fever, dysuria	Pneumonia, osteomyelitis, septic arthritis, prostate and kidney abscess
8	64	Male	Travel	Malaysia, Singapore, South China	Gastric ulcer	Acute	>2 months	Persistent low grade fever, weight loss	Prostatic abscess, renal abscess, mediastinal lymph node swelling
9	69	Male	Business trip	Vietnam	Diabetes	Acute	<2 months	Fever	Pneumonia, septic pulmonary embolism, subcutaneous abscess, spleen and kidney abscess
10	64	Male	Travel	Cambodia	Unknown	Acute	<2 months	Fever, cough	Mycotic aneurysm
11	61	Male	Travel	China, Malaysia, Singapore, Thailand	Diabetes, ureter cancer on chemotherapy	Acute	2–6 months	Fever	Bacteremia
12	33	Male	Residence in Malaysia	Malaysia	None	Acute	<2 months	Skin lesions in left femoral region	Subcutaneous abscess
13	41	Male	Immigrant from Philippines	Philippines	Unknown	Acute	<2 months	Fever, left leg pain,	Pneumonia, septic arthritis
14	40	Male	Business trip	Indonesia	Unknown	Acute	<2 months	Fever, chills, productive cough, dyspnea	Pneumonia, brain abscess

**Abbreviations:** S, susceptible; R, resistant; N/A, not available; TMP-SMX, trimethoprim-sulfamethoxazole.

pus), bacteremia or not, key therapeutic regimen, susceptibility to antibiotics (ceftazidime, imipenem), and outcome (cure, recurrence, death, and unknown). Recurrence was defined as a clinical feature of melioidosis in association with one or more cultures positive for *B. pseudomallei* in a patient with a history of one or more previous episodes. This study was approved by the St. Mary's Hospital Ethics Committee.

## Results

Table 1 shows the collected information on the 14 diagnosed melioidosis cases that have been reported in Japan.<sup>4-17</sup> The mean age was 52.4 years (33–69 years), and all of the patients were male. All of the estimated exposures were in Southeast Asia, including Malaysia (n=2), Thailand (n=2), Vietnam (n=2), Cambodia (n=1), Indonesia (n=1), Myanmar (n=1),

Shock on admission	Diagnosis	Bacteremia	HIV status	Key treatment	Ceftazidime	Imipenem	Outcome	Year	Reference
Absent	Blood culture, pus	Positive	Unknown	Imipenem Minomycin	N/A	N/A	Recurrence	1993	4
Absent	Blood culture, pus	Positive	Unknown	Panipenem Ceftazidime Minomycin, TMP-SMX, Tosufloxacin	S	S	Cure	1995	5
Absent	Blood culture	Positive	Unknown	Cefoperazone/ Sulbactam Imipenem Minomycin	N/A	S	Cure	1998	6
Absent	Pleural effusion, wound culture	Negative	Unknown	Panipenem Minomycin	N/A	S	Cure	1999	7
Absent	Blood culture, pus	Positive	Unknown	N/A	N/A	N/A	Unknown	2000	8
Absent	Pus	Negative	Negative	Meropenem Minomycin	S	S	Cure	2002	9
Absent	Blood culture, joint pus, urine	Positive	Unknown	Meropenem Minomycin	R	S	Recurrence	2007	10
Absent	Bronchoalveolar lavage	Unknown	Unknown	Meropenem Minocycline TMP-SMX	S	S	Cure	2007	11
Absent	Blood culture, pus	Positive	Unknown	Meropenem	S	S	Cure	2011	12
Absent	Pus	Unknown	Unknown	Imipenem Meropenem	S	S	Cure	2012	13
Absent	Blood culture	Positive	Unknown	N/A	S	S	Cure	2013	14
Absent	Pus	Unknown	Unknown	N/A	S	S	Unknown	2015	15
Present	Blood culture	Positive	Negative	Doripenem	S	S	Death	2015	16
Present	Blood culture, sputum culture	Positive	Negative	Meropenem Ceftazidime	S	S	Death	2017	17

Philippines (n=1), Indonesia and Singapore (n=1), Malaysia, Thailand, and Vietnam (n=1), Malaysia, Singapore, and South China (n=1), and China, Malaysia, Singapore and Thailand (n=1). Depending on the category of travel, the subjects were classified as tourists (n=6), expatriates (n=3), business travelers (3), and immigrants (n=2). The most common underlying disease was diabetes mellitus, including those patients with impaired glucose tolerance (n=8), followed by alcoholism (n=1), gastric ulcer (n=2), alcoholic liver dysfunction (n=1), ureter cancer (n=1), none (n=1), and unknown (n=3). As for the mode of onset, 13 patients had acute infections, and one had chronic infection. Cases 13 and 14 were in septic shock on admission, but the other cases were stable. Of these 14 patients, eight patients had lung involvement (five patients with pneumonia, two patients with lung abscesses, and one patient with empyema), five patients had bone involvement (two patients with osteomyelitis, one patient with septic arthritis, one patient with osteomyelitis and septic arthritis), four patients had cutaneous involvement (three patients with a subcutaneous abscess, one patient with cellulitis), three patients presented with gastrointestinal abscess formations (two patients with a spleen abscess, one patient with liver and spleen abscesses), three patients had urinary tract abscesses (two patients with kidney and prostate abscesses, one patient with a kidney abscess), two patients had a mycotic aneurysm, one patient had mediastinal lymph node swelling, and one patient had a brain abscess. Bacteremia was observed in nine patients, and *B. pseudomallei* isolates were mostly susceptible to ceftazidime and carbapenems except for case seven (resistant to ceftazidime; MIC  $\geq 16$ ). This patient did not have a history of treatment with ceftazidime. The overall mortality in the melioidosis patients was 14.3% (n=2), and the recurrence rate was 14.3% (n=2) during the follow-up.

## Discussion

In this study, all Japanese melioidosis cases were attributed to travel to Southeast Asia, with no evidence of *B. pseudomallei* acquisition within Japan, including southern regions with environmental suitability for this pathogen. The distribution of melioidosis is in the tropical region, mainly between the latitudes 20 degrees north and south, including Southeast Asia. Northeast Thailand, northern Australia, Singapore, and parts of Malaysia are currently recognized as highly endemic areas.<sup>18</sup> According to the reports for travel-related health problems in those returning to Japan, 65%–77.5% of the patients were returning after having traveled to melioidosis-endemic countries, especially Southeast Asia.<sup>19,20</sup> Although melioidosis is a rare disease in Japan, with no known autochthonous

cases reported to date, it is essential for physicians in Japan to be aware of possible infection in travelers returning from melioidosis-endemic countries, especially from Southeast Asia. This study found that the most common underlying disease was diabetes mellitus and impaired glucose tolerance. According to a previous report, the main risk factors for melioidosis are mainly diabetes mellitus, excessive alcohol use, thalassemia, chronic renal diseases, chronic lung diseases, and high soil and water exposure.<sup>21–23</sup> A previous report showed that the most common presenting feature of melioidosis was pneumonia (51%), followed by genitourinary infection (14%), skin infection (13%), bacteremia without any proven focus (11%), septic arthritis and/or osteomyelitis (4%), and neurological melioidosis (3%).<sup>24</sup> Similarly, 8/11 patients in our study had lung involvement and 5/11 patients had bone involvement. As for the mode of infection, 13 cases were acute, and one case was chronic. The incubation period from defined inoculating events was 1–21 days with an average of 9 days.<sup>25</sup> Physicians in non-endemic regions should be alert to a diagnosis of melioidosis for all patients who have a history of travel and residence in endemic areas including immigrants. In this study, carbapenem was the main therapeutic regimen. For intensive therapy, ceftazidime and carbapenem are the treatments of choice. A previous randomized comparative study in northeast Thailand showed that there was no difference between imipenem and ceftazidime in terms of survival advantage for patients with severe melioidosis but ceftazidime was significantly associated with treatment failure, relative to imipenem (ceftazidime group: 41%, imipenem group: 20%,  $p=0.025$ ).<sup>26</sup> An additional study suggested that meropenem may result in better outcomes, especially in severe cases of melioidosis. Meropenem is used rather than imipenem in Australia due to fewer neurogenic side effects.<sup>27</sup> Japanese doctors may choose carbapenem due to a lack of experience in management of patients with melioidosis. The fatality rate of human melioidosis is high: 43% in northeast Thailand and 14% in Australia.<sup>21,24</sup> In this study, the mortality rate was 14.3%. This result was similar to the outcome in Australia. In general, patients in developed countries have easier access to a hospital, and can receive a high level of intensive care in terms of modern equipment and adequate human resources, when compared to that of developing countries. Since treatment antibiotics were almost all the same, this may also explain the geographical difference in mortality. There are some limitations to this study. First, the data were extracted from the records of published articles on each patient. This study did not state the estimated assumed mode of transmission or the molecular analysis of the isolated strain that confirms

the actual source. So far, *B. pseudomallei* is considered to be absent in Japan. But there is the possibility that the causative bacteria may have been acquired in Japan. Another limitation was the inadequate follow-up duration. The actual recurrence rate may be higher than that in our results. Finally, this review is based on case reports with full texts or abstracts available in English and Japanese languages only.

## Conclusion

In conclusion, the epidemiological and clinical features of imported melioidosis cases in Japan were reviewed. It is important to keep in mind that melioidosis is a rare cause of imported infection, but can occur, especially in cases of bacteremia or lung involvement in patients with diabetes who are returning from Southeast Asia.

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## Disclosure

The author reports no conflicts of interest in this work.

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