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REVIEW

A review of melioidosis cases imported into Europe

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Abstract

Melioidosis is a tropical bacterial infection, rarely encountered, and poorly known by clinicians. In non-endemic areas, a misdiagnosis can lead to a fatal outcome. This study aims to identify the main characteristics of imported and diagnosed melioidosis cases in Europe to increase clinician's awareness of this diagnosis. A literature review of imported and diagnosed human melioidosis cases in Europe was performed. PubMed and Web of Science search engines were used for retrieving articles from 2000 to November 2018. Seventy-seven cases of imported melioidosis into Europe described in the literature were identified. More than half of the cases were acquired in Thailand (53%) by men (73%). Patients were usually exposed to *Burkholderia pseudomallei* during a holiday stay (58%) of less than 1 month (23%) and were hospitalized during the month following their return to Europe (58%). Among travelers, melioidosis is less often associated with risk factor (16%), diabetes being the most frequently comorbidity related (19%). The clinical presentation was multifaceted, pneumonia being the most common symptom (52%), followed by cardiovascular form (45%) and skin and soft tissues damages (35%). The diagnosis was obtained by culture (92%), often supplemented by morphological, biochemical, and molecular identification (23%). Misdiagnoses were common (21%). Over half of the patients received a complete and adapted treatment (56%). Mortality is lower for returning traveler (6%). Imported melioidosis cases into Europe have their own characteristics. This possibility should be considered in patients with pneumonia, fever, and/or abscess returning from endemic areas even years after.

Keywords Melioidosis · Pneumonia · Travel medicine · Case reports

Introduction

Melioidosis is a tropical bacterial infection, caused by a bacillus *Burkholderia pseudomallei*, formerly known as *Pseudomonas pseudomallei*, *Malleomyces pseudomallei*, or *Bacillus whitmori*. Each year, there are nearly 165,000 cases worldwide and 54% are estimated to be fatal [1]. The mortality burden is similar to that of measles [2]. Melioidosis is endemic in Southeast Asia, Northern Australia, India, and China. This disease sporadically occurs in tropical areas between the 20th of northern and southern parallels [3]. Melioidosis is extremely rare in the temperate zone: they are essentially imported cases by travelers or immigrants [4]. But global warming and mass international travel in Asia can increase the incidence in non-endemic areas [2].

Pseudomonas pseudomallei is an environmental Gram-negative bacterium found in soil and surface water, especially during the rainy season. Community-acquired infections in human results from exposure through wounded skin, inhalation, or ingestion. Nosocomial infections have been rarely

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reported [5]. Melioidosis is not considered to be a contagious infection and human-to-human transmission is very rare [3, 5].

This emerging disease is pleomorphic and opportunistic because it can affect various organs and displays different clinical presentations from chronic disease to sepsis and death. Nevertheless, the leading form of melioidosis is pulmonary disease, as this pathogenic agent is unknown in non-endemic areas and it can be easily mistaken for other diseases, such as community-acquired pneumonia or tuberculosis. So, it is often referred to as "the Great Mimicker" [4] and remains underdiagnosed. The first diagnosis is based on biochemical tests and morphology identification of bacterium. Molecular biology is also essential to limit the risk of confusion but takes longer to obtain. However, early diagnosis and treatment are crucial to reduce mortality, which may reach up to 87% without treatment [6]. Currently, no vaccine is available and *Pseudomonas pseudomallei* is widely resistant to several antibiotics, such as gentamicin, colistin, and rifampicin. The bacterium is most often susceptible to ceftazidime, meropenem, and amoxicillin–clavulanate.

In most European countries, melioidosis is not a nationally notifiable disease, making it difficult to ensure epidemiological surveillance. However, *Pseudomonas pseudomallei* is a selected agent according to the US federal law and belongs to Tier 1 agent list of the Centers for Diseases Control and Prevention (CDC). In France, the possession of this organism is subject to the regulation on highly pathogenic microorganisms and toxins (MOT) and must be handled in a biosafety level 3 laboratory. All these rules and regulations are explained by the high pathogenicity of the bacteria and by its possible use as bioterrorism agent [7–9].

Melioidosis has the potential to become a real public health problem, considering its rising incidence, misdiagnosis, therapeutic difficulties, high mortality, and induced biological risk [2, 7, 10]. So, we decided to conduct a systematic review of melioidosis cases imported and diagnosed in human in Europe since 2000 to increase clinicians' awareness of its diagnosis.

Materials and methods

Background definitions

The search method employed in this systematic review was to identify and select case reports of imported melioidosis in humans in Europe. Information on clinical characteristics, exposure history, comorbidities, management, and outcome were abstracted.

Data sources and searches

We searched MEDLINE/PubMed (National Library of Medicine—https://www.ncbi.nlm.nih.gov/pubmed) and Web of Science (Thomson Reuters Scientific—https://www.webofknowledge.com/) to identify all published case reports of melioidosis imported in humans into Europe. The literature search included English-, German-, and French-language articles and publications in other languages if informative abstracts in the English language were available.

Search terms were selected to detect case reports published about imported melioidosis applying exclusion criteria. The following terms combinations were applied: "melioidosis" OR "*Burkholderia pseudomallei*" OR "*Pseudomonas pseudomallei*" OR "*Malleomyces pseudomallei*" OR "Withmore bacillus" in human. The Boolean operators were varied according to the rules of each specific database. Searches were conducted using the final limit dates of January 1, 2000 and November 15, 2018.

Study selection

The review was performed in two main stages, as described by Matos [11]. Eligibility criteria were predetermined by the authors (Table 1). In the first step, they independently reviewed the titles and abstracts yielded by this comprehensive search and subsequently selected articles based on the predetermined inclusion criteria. Any reservations on eligibility for inclusion were resolved by discussion between reviewers. After removal of duplicates, the authors read each selected full text and eliminated articles fitting the exclusion criteria. During this second stage, the references of relevant articles were examined to identify additional cases not found in computerized databases.

Data extraction process

The data collected from all included studies are as follows: year and country of diagnosis or publication, basic demographic characteristics (age, gender, ethnicity, and socio-professional category), underlying diseases, foreign travel history (type, country, and duration (< 1 month, 1–6 months, > 6 months [4], or unknown)), route of exposure, manifestations and care in endemic area, time between arrival in Europe and hospitalization (< 1 month, 1–6 months, > 6 months [4], or unknown), clinical manifestations (included fever, pulmonary symptoms, weightless [12],, abscess and localization, bacteremia), source of the *B. pseudomallei* isolates, method used (phenotype, molecular biology, spectrometry), complementary examinations, researched pathogen agents and misdiagnosis, treatments and duration, observed adverse effects, resistance to recommended antibiotics, length of follow-up, and outcome (cure, recurrence, death, and unknown). Morphological and biochemical identification (VITEK 1 and 2, API 20 NE (bioMérieux, Marcy l'Etoile, France)) are grouped under the name of the phenotype. Molecular biology includes sequencing of 16SrRNA, PCR (polymerase chain

Table 1 Inclusion and exclusion criteria

	Parameter	Inclusion	Exclusion
1	Language	German, English, French, other languages if informative abstracts in English language were available	Any other language without informative abstract in English
2	Type of study	Clinical characteristics, exposure history, comorbid conditions, management, and outcome	Exclusively in vitro articles that focus only on biological parameters
3	Type of publication	Original manuscript, conference abstracts, thesis	Reviews, book chapters, table of contents, personal opinions, indexes, letters
4	Search terms	-	Merely citing keywords in text
5	Localization	Diagnosed and imported melioidosis in Europe	Diagnosed cases of all other geographic regions Nosocomial infections

reaction), and real-time PCR. Spectrometry names mass spectrometry, with or not MALDI-TOF (matrix-assisted laser desorption ionization—time of flight). 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.

Treatment consists of an initial intensive phase by intravenous followed by the oral maintenance eradication phase to prevent relapse (Table 2). We have referred to current recommended practices at the time of publication. Before 2014, we took the recommendation of the French Agency for the Medical Safety of Health Products [13] and international literature as guidelines [12, 14–16]. Eradication phase recommendations vary from country to country, except for trimethoprim–sulfamethoxazole, always prescribed. Since 2014, international recommendations have changed [4, 6, 14, 84, 85]. Duration depends on the clinical condition of the patient and monotherapy of trimethoprim–sulfamethoxazole without intensive phase may be enough in some localized and minor cutaneous infections. Doses are not being taken into account despite their importance because the majority of publications did not report them.

All graphics and figures have been generated with Excel and Powerpoint (Microsoft). A library of all relevant references was built using Zotero software (www.zotero.org) for bibliographic management.

Results

The database search identified 633 records. After the first evaluation phase (title/abstract), 577 records were excluded. Fourteen repeated files were discarded, leading to 56 citations. To the remaining articles, 14 publications were added from the reference lists of the identified studies (which had not been found in the initial search). Phase 2 was therefore conducted with a total of 70 articles. After the full-text reading, three articles were excluded because of their localization outside Europe. A final total of 67 records were included in this review, describing 77 different cases of melioidosis [17–83]. This process is illustrated by a flow diagram in Fig. 1.

Epidemiology

The majority of cases were described in 2005 after the 2004 Indian Ocean tsunami [57, 59, 60, 64] and in 2010, with the release of a set of five cases in Denmark [48] (Fig. 2).

The demographic and epidemiologic characteristics of the 77 cases are presented in Table 3. The mean age was 46 ± 17 years, with a median of 47 [11–90] years. The sex ratio of male/female was 2.7. Ethnicity was identified in only 30% of cases, with a majority of Caucasian and Asian origins. Socio-professional category was specified in only 4 cases (frame worker [32], psychiatry instructor [47], basketball trainer [54], student [25]).

Travelers were coming back from four different continents: 86% from Asia (66 cases), 9% from Africa (7 cases), 5% from America (4 cases), and 3% from Oceania (2 cases). Three patients traveled through several continents (Southeast Asia and Africa or America or Oceania). Thailand was by far the leading single country where travelers acquired the infection, with 41 cases (53%), followed by Vietnam and Cambodia, each with 7 cases (9%). Melioidosis was essentially reported in Western Europe in 68% of cases. This infection was most often acquired during holidays of less than 1 month abroad and probably caused by percutaneous inoculation. Patients were taken care of within 1 month after returns to Europe.

The development of melioidosis could be facilitated by risk factors (exposure and comorbidity), described in Table 4. Twenty-seven patients were exposed to several exposure risk factors (from two to six). The most common was skin injury and/or insect bites, which led to suspect contamination by percutaneous inoculation. Fifteen patients had multiple comorbidities (from two to four), especially an age over 45 years, diabetes and chronic lung diseases or smoking tobacco or cannabis.

Table 2 Treatment recommendations of melioidosis before and since 2014, with *IV*, intravenous and *PO*, per os

	Before 2014 [12–16]		Since 2014 [4, 14, 17]	
Phases	Intensive (IV)	Eradication (PO)	Intensive (IV)	Eradication (PO)
Antibiotics	First-line therapy: carbapenem or ceftazidime Second-line therapy: piperacillin–tazobactam Severe infections: adding doxycycline or trimethoprim–sulfamethoxazole	Simple, double, or triple therapy: trimethoprim–sulfamethoxazole (ever), doxycycline, chloramphenicol, or amoxicillin–clavulanic acid	Ceftazidime or meropenem Severe infections**: trimethoprim–sulfamethoxazole	First-line therapy: trimethoprim–sulfamethoxazole Second-line therapy: amoxicillin–clavulanic acid or doxycycline
Duration	20 weeks from 2–3 to 12–24 weeks (France, [13]) 10 days (intensive phase), followed by 8–20 weeks* (eradication phase) (endemic areas, [12, 14, 16])		10–14 days Severe infections***: 4–8 months	At least 3 months Severe infection****: 6 months
Patients	[18–68]		[17, 69–83]	

*At least 12 weeks, except for acute suppurative parotitis [12]

*Neurological melioidosis, osteomyelitis, septic arthritis, skin and soft tissue infections, or genitourinary infection, including prostatic abscess, persistent bacteremia, or intensive care transfers

**Complicated pneumonia, deep-seated infection, including prostatic abscess, neurological melioidosis, or septic arthritis

***Neurological infection or osteomyelitis

Travelers who died from melioidosis were only men returning from holidays abroad, mainly from Southeast Asia (80% of cases) and were hospitalized within 1 month after. In 60% of cases, they were diabetics and over age 45. During their holidays, 80% of them were exposed to at least one risk factor, varying from one patient to another.

Clinical presentations

The clinical characteristics of the imported cases are detailed in Table 5. Most travelers were symptom-free during their trip and only 11 patients received an empiric antibiotic therapy in an endemic area.

The most common clinical presentation was pneumonia followed by cardiovascular involvement, cutaneous and soft tissue infections. Several presentations were associated in 44 patients. More than half of the patients presented fever, pulmonary symptoms, and/or abscess. They were localized on the skin, soft tissue, and lungs. Several sites were identified in 14 patients (Supplementary Table 1). Four mycotic aneurysms have been described. Bacteremia occurred in nearly half of patients.

Three of five patients who died developed symptoms during their trip and two of them received an empiric antibiotic therapy. Four patients had a fever. Bacteremia and pneumonia occurred in all of them, four with an abscess and one with a gastrointestinal presentation.

Diagnosis

Melioidosis diagnostic is most often based on blood samples and abscess material cultured. Blood cultures were informative in 38 patients (49%) (Table 6; Supplementary Table 2). Bacillus was mostly identified thanks to its morphological, biochemical, and molecular characteristics. Medical imaging completed 79% of these results and biopsy, 26% (Supplementary Table 3). CT scan was informative in 33 cases (43%), radiography in 25 cases (32%), and ultrasound in 13 cases (17%). Another germ was suspected and investigated among 35% of travelers (27 cases), primarily *Mycobacterium tuberculosis* (14 cases). Wrong bacteria have been identified in ten travelers, including *B. cepacia* (4 cases) and *B. thailandensis* (4 cases) with biochemical and spectrometric methods. Nineteen misdiagnoses were made (25%), generally pneumonia or urinary infection.

Travelers who died from melioidosis were diagnosed using blood culture, morphologic and biochemical test identification, and/or molecular biology. *Salmonella* was suspected and investigated in two of these patients (Table 6).

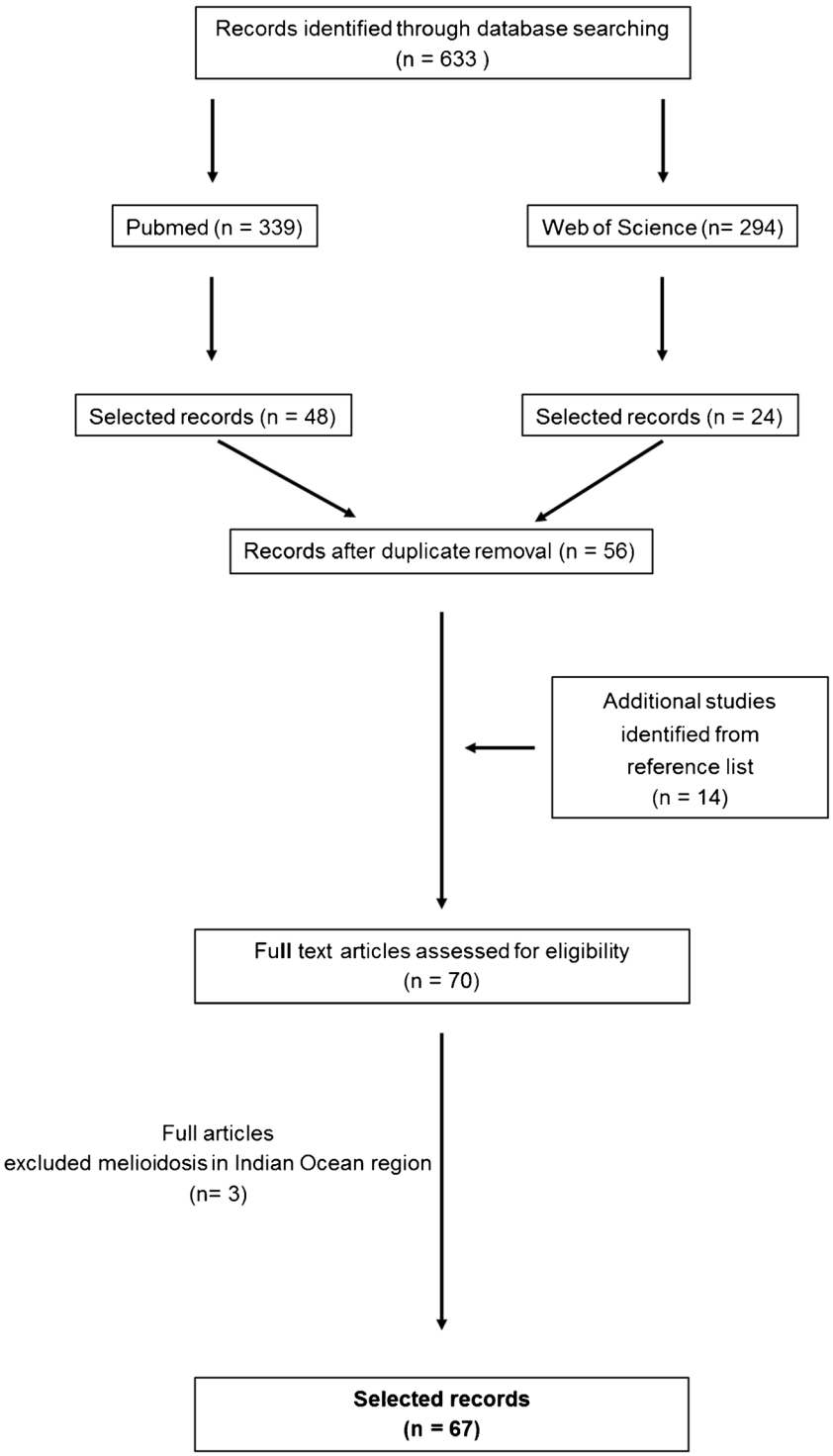

Fig 1 Flow diagram of study selection adapted from Matos [11]

Treatment

Before the identification of *Pseudomonas pseudomallei*, 48 patients (62%) were treated with an empiric antibiotic therapy including all patients who died. Twenty-four surgical drainages were carried out (31%). Three (4%) have received a local treatment and one (1%), a vascular filling. Nine patients (12%) were not treated.

Forty-three patients (56%) received a comprehensive and consistent with guidelines treatment (Table 2). Intensive antibiotic treatment and duration were appropriate to 79% and 82% of travelers, respectively (Table 7). Thirty-six patients

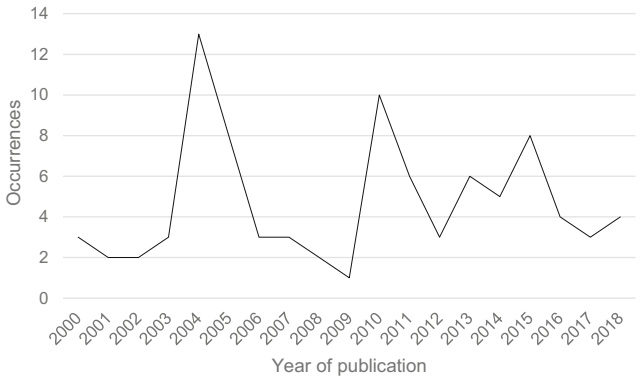

Fig. 2 Number of melioidosis cases imported into Europe, per publication year, from 2000 to 2018

received ceftazidime (47%), 23 meropenem (30%), and 3 piperacillin–tazobactam (4%) (Supplementary Table 4d). Treatment was given from 1 day to 5 months; the duration was too short in only 3 cases.

Regarding maintenance treatment, more than 70% of travelers were treated by an appropriate antibiotic for a sufficiently long period. Trimethoprim–sulfamethoxazole was used in 50 patients (65%), as monotherapy in 40% of them. Doxycycline was administered in 34 patients (44%), as monotherapy in 3 patients. Fourteen patients (18%) received amoxicillin–clavulanic acid, as monotherapy in 3 patients too. Adverse effects on 10 of the 71 treated patients (14%) were reported, including trimethoprim–sulfamethoxazole (7 cases), ceftazidime (2 cases), amoxicillin–clavulanic acid (1 case), and doxycycline (1 case). Only 14 antibiotic resistances were documented in 13 patients [22, 24, 32, 47, 48, 63, 66, 70, 72, 76, 79, 83], involving trimethoprim–sulfamethoxazole (8 cases, 10%), amoxicillin–clavulanic acid (4 cases, 5%), doxycycline (1 case, 1%), and meropenem (1 case, 1%).

Thirty patients were followed up post-treatment during on average 1 year and 4 ± 10 months, from 0 to 3 years. Sixty-five travelers were cured (84%). Among these, three had shown sequelae and one after first relapse. Three patients (4%) relapsed including one with antibiotic resistant and five have died (6%). No information was available for five travelers (6%).

Most deceased patients received adequate acute treatment. But the death occurred quickly and only one patient was treated by maintenance treatment. (Supplementary Table 4).

Discussion

Epidemiology

All patients included in the study traveled in an endemic area, mainly in Southeast Asia [1, 4]. Thailand is the leading risk country. Indeed, it represents a very popular touristic destination with 35.4 million travelers in 2017. Only three cases were

Table 3 Epidemiologic characteristics of 77 cases of melioidosis in travelers reported in the literature

	Cases *N* (% of total)	Deceased *N* (% per category)
Total	77	5
Age		
< 18 years	3 (4)	–
18–45 years	34 (44)	2 (6)
46–74 years	38 (49)	3 (8)
≥ 75 years	2 (3)	–
Gender		
Male	56 (73)	5 (9)
Female	21 (27)	–
Ethnicity		
Africa	1 (1)	–
Afro-Caribbean	1 (1)	–
Caribbean	1 (1)	–
Caucasian	10 (13)	–
Southeast Asia	7 (9)	–
Sub-Saharan Africa	3 (4)	–
Unknown	54 (71)	5 (9)
Type of trip		
Business	4 (5)	–
Family and relatives	10 (13)	–
Indigenous	2 (3)	–
Tourism	45 (58)	5 (11)
Unknown	16 (21)	–
Country of diagnosis		
Austria	2 (3)	1 (50)
Belgium	3 (4)	–
Denmark	9 (11)	1 (11)
Finland	4 (5)	–
France	17 (22)	–
Germany	13 (17)	–
Holland	4 (5)	1 (25)
Italia	4 (5)	–
Norway	3 (4)	–
Portugal	1 (1)	–
Slovenia	1 (1)	–
Spain	2 (3)	–
Sweden	2 (3)	–
Switzerland	3 (4)	1 (33)
United Kingdom	9 (12)	1 (11)
Exposure area(s)*		
Africa	7 (9)	–
Caribbean	3 (4)	1 (33)
China	1 (1)	–
India	1 (1)	–
Oceania	2 (3)	
South America	1 (1)	1 (100)
Southeast Asia	65 (84)	4 (5)

Table 3 (continued)

	Cases *N* (% of total)	Deceased *N* (% per category)
Total	77	5
Unknown	1 (1)	–
Exposure duration		
< 1 month	18 (23)	3 (17)
1 to 6 months	9 (12)	–
> 6 months	12 (16)	–
Unknown	38 (49)	2 (5)
Route of exposure		
Percutaneous inoculation	28 (36)	3 (11)
Percutaneous inoculation/ingestion	6 (8)	1 (17)
Inhalation	6 (8)	–
Ingestion	–	–
Unknown	37 (48)	1 (3)
Time between arrival in Europe and hospitalization		
< 1 month	37 (48)	5 (14)
1–6 months	17 (22)	–
> 6 months	11 (14)	–
Unknown	12 (16)	–

*Some patients traveled to several risk areas

reported in central and eastern Europe. This discrepancy with western and northern Europe could be explained by a higher proportion of low-income households, international tourism less often and more difficult access to molecular biology. There is no indigenous case in Europe but the situation might change in the years to come due to global warming and the increase in people mobility, like in the USA [86, 87].

In our study, melioidosis was usually diagnosed shortly after returning to Europe, which also corresponds to our review of the scientific literature which describes an incubation period of 1 to 21 days [3, 4, 88]. However, latent infections are possible several years after exposure [4]. The shorter the incubation period is, the more severe the infection could be [4]: the five deceased patients in our study were all hospitalized within 1 month after returning to Europe. For three of them, symptoms appeared during their trip. Our data are similar to those found in the literature of imported cases: melioidosis is most common in man in his fifties (Table 8). Indeed, being aged more than 45 years old is a risk factor known for this infection [4]. However, the average age tends to decline probably because travel is becoming more and more popular among young people for holidays and work.

Exposure factors correspond to those found in the literature, including skin lesion, rainy seasons, natural disasters, and traveling in the rural and dusty area [4].

In contrast to indigenous melioidosis and imported cases in Japan [4, 89], only 44% of travelers had at least one comorbidity (Table 8) with no clear explanation. Part of this difference could be explained by the organization and efficiency of the health care system that previously recorded it. In most country, where *Pseudomonas pseudomallei* is endemic, underreporting is highly plausible and unavailability of capacitated laboratories for diagnosis is conceivable. We might assume that naive people, such as travelers, may be more vulnerable than indigenous people, even to have genetic factors limited disease as the result of selection pressure [90]. Consistent with the literature, the major comorbidity excluding age remains diabetes [85]. Chronic lung disease and smoking are more common in our study than it is usually described [22, 88]. Other comorbidities rank in the same order as in the previous studies [22, 88, 89]. Thalassemia is often mentioned as a risk factor [4], but a single case of melioidosis infection in such a patient was reported in Europe since 2000. Indeed, this blood disorder is most common in tropical and subtropical areas where the melioidosis is endemic. In Europe, the Mediterranean Basin is the only region that still reports thalassemia cases [91, 92].

Clinical presentations

The absence of symptoms in the endemic area could be explained by an incubation period to 21 days, with a median of 9 days [4], and by the high frequency of short stays.

Among travelers, the pulmonary presentation is most often occurred, followed by cardiovascular damages and skin and soft tissue infections, on the same level as indigenous cases [4]. Only the results of Dan et al. are halved from similar studies, which could be explained by a lack of initial data (Table 8) [88]. Bacteremia has been reported in 43% of cases, which is in accordance with worldwide data (Table 8) [4]. The spectrum of clinical signs is due to opportunistic and adaptable *Pseudomonas pseudomallei* characteristics. The clinical presentation depends on the mode of contamination and the infected tissue [4]. In contrast to that described in indigenous people, weightless is not related to highest mortality among European travelers. Only one of the five deceased patients has lost weight [4].

Melioidosis clinical picture is not specific. This diagnosis should be considered for a patient with pneumonia, fever, or abscess returning form endemic area, even several years after. In this case, it is important to encourage patient to remember his trip and potential risk situations, if melioidosis diagnosis is not excluded.

Diagnosis

Melioidosis is a diagnostic challenge. Biological signs are not relevant. Medical imaging helps only to localize the infected site. Detection rate is low and European practitioners have a lack of experience [93]. The non-specificity of symptoms

Table 4 Risk factors of 77 cases of melioidosis in travelers reported in the literature

Risk factors	Patients *N* (% of total)	Deceased *N* (% per category)
Exposure		
Skin lesion, insect bites	23 (30)	2 (9)
Natural disaster (flood, hurricane, tsunami, etc.)	12 (16)	1 (8)
Rural and/or dusty areas	12 (16)	3 (25)
Rainy season	9 (12)	–
Moist soils (rice fields, river, muddy soils, etc.)	6 (8)	1 (17)
Resident, frequent trips	6 (8)	–
Surface/non-potable/stagnant water, nautical sport, freshwater bathing	6 (8)	3 (50)
Walking barefoot	2 (3)	–
Comorbidity*		
Diabetes	15 (19)	3 (20)
Chronic lung diseases, smoking, cannabis (with 1 detoxed)	15 (19)	–
Cirrhosis, hepatic disease, alcoholism (with 2 detoxed)	11 (14)	–
Immunosuppression	6 (8)	–
Chronic kidney disease	4 (5)	1 (25)
Cancer	3 (4)	–
Thalassemia	1 (1)	–
Recent fracture	1 (1)	–
Patients aged 45 or older	41 (53)	3 (7)
With at least one risk factor		
With at least one exposure factor	46 (60)	4 (9)
With at least one comorbidity increased melioidosis development	34 (44)	3 (9)
No risk factor		
Exposure factor	1 (1)	–
Comorbidity increased melioidosis development	32 (42)	2 (6)
Unknown		
Exposure factor	30 (39)	1 (3)
Comorbidity increased melioidosis development	11 (14)	–

Some patients have been exposed to several exposure factors and/or several comorbidities

*Other comorbidities: atrial fibrillation, stable angina, arterial hypertension, peripheral arterial disease, dyslipidemia, obesity, diverticulitis, gastritis, appendectomy, asymptomatic lithiasis, acanthosis nigricans, dengue, hypothyroid, treated Graves' disease, ophthalmic tuberculosis, benign prostatic hyperplasia

enhances misdiagnosis in travelers and in indigenous patients. *M. tuberculosis* is the leading pathogen sought, because of pulmonary symptoms, which usually occurred and are very suggestive of tuberculosis disease. Melioidosis is often referred to as "the Great Mimicker" [4, 93]. In our study, other pathogens have been sought for 26 patients (34%) because practitioners may have had no idea of diagnosis.

The culture of the bacterium is the mainly diagnostic method in our study (92%), as suggested in recommendations [4]. As this pathogen must be handled in biosafety level 3, this raises biosafety issues in laboratories where routine analyses are performed in biosafety level 2. Furthermore, *Pseudomonas pseudomallei* could be easily identified as a contaminant or confused with other bacteria, even with biochemical and spectrometric methods [4], which can lead to delayed diagnosis. This is problematic both for the patient because it delays its treatment but also for those around him due to the risk of nosocomial infections in certain circumstances [4, 5, 86]. Several techniques must be used to exclude melioidosis. Bacteremia is usually observed, and this is why blood cultures are the most informative samples. They are positive in 50 to 75% of patients in the literature [4, 94] and in near 50% in our study. Repeated samples and selective media may be used when there is a melioidosis suspicion. Due to the low growth of *Pseudomonas pseudomallei* an incubation time, up to 6 days may be required. In order to limit the infection consequences, germ can be rapidly detected by immunofluorescence, as this technic is very specific but not very sensitive [4]. However, this method was not used in our study. Among the diagnostic, arsenal molecular biology is the

Table 5 Clinical presentations of 77 cases of melioidosis in travelers reported in the literature

	Total		Bacteremia status			
			Bacteremia		No bacteremia	
	Patients *N* (% of total)	Deceased *N* (% per category)	Patients *N* (% per category)	Deceased *N* (% per category)	Patients *N* (% per category)	Deceased *N* (% per category)
In endemic area						
Symptomatic	24 (31)	3 (13)	12 (50)	3 (100)	12 (50)	–
Treatment*						
Antibiotics	11 (14)	2 (18)	6 (55)	2 (100)	5 (45)	–
Local	7 (9)	–	2 (29)	–	5 (71)	–
Symptomatic	3 (4)	–	3 (100)	–	–	–
None	12 (16)	1 (8)	2 (17)	1 (100)	10 (83)	–
Unknown	48 (62)	2 (4)	22 (46)	2 (100)	26 (54)	–
In Europe						
Clinical presentations** [4]						
Cardiovascular	35 (45)	3 (9)	32 (91)	3 (100)	3 (9)	–
Cutaneous, soft tissue	27 (35)	–	8 (30)	–	19 (70)	–
Gastrointestinal	13 (8)	1 (8)	8 (62)	1 (100)	5 (38)	–
Neurological	5 (6)	–	2 (40)	–	3 (60)	–
Osteoarticular	14 (18)	–	4 (29)	–	10 (71)	–
Pulmonary	40 (52)	5 (13)	21 (53)	5 (100)	19 (47)	–
Genitourinary	7 (9)	–	5 (71)	–	2 (29)	–
Many	44 (57)	3 (7)	30 (68)	3 (100)	14 (32)	–
Symptoms						
Fever	52 (68)	4 (8)	30 (58)	4 (100)	22 (42)	–
Weight loss	9 (13)	1 (11)	4 (44)	1 (100)	5 (56)	–
Pulmonary symptoms	39 (51)	5 (13)	25 (64)	5 (100)	14 (36)	–
Lesion	14 (18)	–	3 (21)	–	11 (79)	–
Abscess	46 (60)	4 (9)	20 (43)	4 (100)	26 (61)	–
Total	77	5	33 (43)	5 (100)	44 (57)	–

*Some patients have received several treatments in endemic areas

**Some patients have had different clinical presentations

Cardiovascular: aneurism mycotic, pericarditis, bacteremia

Cutaneous, soft tissue: cutaneous ulcer, cutaneous abscess, soft tissue abscess, neck abscess, lymphadenitis

Gastrointestinal: hepatic abscess, splenic abscess, para-intestinal mass

Neurological: cerebral abscess

Osteoarticular: osteomyelitis, myalgia, muscular abscess, bone damage, pyomyositis, bursitis

Pulmonary: pneumonia, pulmonary abscess, pleural abscess

Genitourinary: acute pyelonephritis, kidney abscess, prostatic abscess

most precise but is limited to research and reference centers. There are several instances [27, 30, 37, 38, 51, 59, 72] where these techniques avoided misdiagnosis [4]. Melioidosis may be confirmed or orientated by resistance profile. Indeed, most of *Pseudomonas pseudomallei* are resistant to colistin (or polymyxin) and to gentamicin but sensitive to amoxicillin–clavulanic acid. It is quite unusual and provides some good criteria to distinguish it, notably, from *Pseudomonas aeruginosa*.

In our study, antibodies were identified in 9% of travelers. But serology is not a recommended technique especially in early diagnostic, because *Pseudomonas pseudomallei* do not always cause melioidosis [4].

Medical imaging is widely used. It identifies the infection site and helps to find other localizations. Indeed, 57% of patients have had multiform melioidosis and 13% have developed abscesses on several sites, like in Hadano et al. and Saïdani et al. reports. [22, 89].

Table 6 Diagnosis of 77 cases of melioidosis in travelers reported in the literature

	Patients *N* (% of total)	Deceased *N* (% per category)
Total	77	5
Informative samples*		
Blood	38 (49)	5 (13)
Abscess material	28 (36)	1 (4)
Cutaneous swab	8 (10)	–
Sputum	8 (10)	–
Biopsy	7 (9)	–
Cerebral	2 (3)	–
Cutaneous	2 (3)	–
Bone	1 (1)	–
Vascular	2 (3)	–
Bronchoalveolar lavage fluid	7 (9)	1 (14)
Urine	4 (6)	–
Marrow	1 (1)	–
Cerebrospinal fluid	1 (1)	–
Pericardial fluid	1 (1)	–
Pleural fluid	1 (1)	–
Unknown	4 (5)	–
Method used**		
Culture	71 (92)	5 (7)
Molecular biology	37 (48)	3 (8)
Phenotype	29 (38)	3 (10)
Spectrometry	11 (14)	1 (9)
Serology	7 (9)	–
Selective media	6 (8)	–
Chromatography	1 (1)	–
Unknown	2 (3)	–
Other pathogens sought***		
Bacteria	22 (29)	3 (14)
Mycobacterium tuberculosis	14 (18)	–
Pseudomonas spp.	6 (8)	1 (17)
Salmonella spp.	3 (5)	2 (50)
Legionella	3 (4)	–
Brucella spp.	2 (3)	–
Staphylococcus aureus	2 (3)	–
Other (chlamydia, Yersinia spp., *Borrelia*, *Klebsiella* spp., *Pasteurella* spp., Rickettsia)	2 (3)	1 (50)
Virus	11 (14)	1 (9)
HIV	8 (10)	–
CMV	2 (3)	1 (50)
EBV	2 (3)	1 (50)
Hepatitis virus	2 (3)	1 (50)
Other (chikungunya, dengue fever, leptospirosis, retrovirus, parvovirus)	2 (3)	1 (50)
Parasites	5 (6)	1 (20)
Malaria	5 (6)	1 (20)
Schistosoma	1 (1)	–
Fungal infection	2 (3)	–
Unknown	51 (66)	2 (5)
Misdiagnosis		
Identification of another germ	11 (16)	1 (9)
Pneumonia	5 (7)	1 (20)
Urinary infection or sepsis	5 (6)	–
Tuberculosis (abscess, pulmonary)	3 (4)	–
Staphylococcus aureus	2 (3)	–
Diverticulitis with abscess	1 (1)	–
Typhoid fever	1 (1)	1 (100)
Gastroenteritis	1 (1)	–
Glioma or abscess	1 (1)	–
Unknown	54 (79)	3 (6)

*Several samples have been informative for some patients

**Several methods have been used for some patients

***Several pathogens have been sought for some patients

The diagnosis of melioidosis is very complex and involves different techniques. As a consequence, many cases would be undiagnosed or identified after a longer period of time.

Treatment

Melioidosis is a therapeutic emergency, because of fatal consequences [4]. Empiric antibiotic therapy is most often started before germ identification. Antibiotic is usually not relevant or dose delivery was insufficient, as was observed in our study. Even if this treatment may be sufficient for the least serious infections, the risk of relapse is increased.

Surgical drainage is required for treating prostatic, muscular and large hepatic abscesses, and septic arthritis [4, 12]. This choice is questionable for treating disseminated abscesses, which most often disappear with antibiotic therapy alone [4].

After the diagnostic, in most of the cases (56%), treatment regimen and duration followed the current recommendations, including for deceased patients. Doses were not verified because they were not mentioned in most case reports (Tables 2 and 7).

Numerous side effects were reported with trimethoprim–sulfamethoxazole used for a long time, in up to 40% of patients [4]. In our study, only 14% of them had adverse effects with no clear explanation of this discrepancy. But evaluation and signaling of the side effects are subjective and may differ across countries. Furthermore, the long-term effects of a 3-month antimicrobial treatment are quite unpredictable but have to be taken into account when initiating the therapy [95, 96]. These consequences are not mentioned in our cases,

Table 7 Treatments of 77 cases of melioidosis in travelers reported in the literature

	Patients *N* (% of total)	Deceased *N* (% per category)
Total	77	5
Intensive treatment		
Antibiotic choice		
Appropriate	61 (79)	3 (5)
Inappropriate	5 (7)	–
Unknown	4 (5)	–
None	7 (9)	2 (29)
Duration		
Appropriate to guidelines	52 (67)	1 (2)
Shorter duration	4 (5)	–
Unknown	12 (16)	–
None	7 (9)	2 (29)
Inapplicable	2 (3)	2 (100)
Maintenance treatment		
Antibiotic choice		
Appropriate	63 (82)	1 (2)
Inappropriate	3 (4)	–
Unknown	4 (5)	–
None	6 (8)	3 (50)
Inapplicable	1 (1)	1 (100)
Duration		
Appropriate to guidelines	56 (73)	1 (4)
Shorter duration	4 (5)	–
Unknown	10 (13)	–
None	6 (8)	3 (50)
Inapplicable	1 (1)	1 (100)

but it may be informative to complete future articles with long-term monitoring data.

There are more resistant strains when doxycycline or amoxicillin–clavulanic acid is used. Many resistant levels were reported according to the areas. Our rate (17%) is higher than in Malaysia (10%) [97] and in Thailand (13.2%) [98, 99]. It is nearly seven times higher than those related in Australia (2.5%) [100]. These results are consistent with the countries where our patients were contaminated. Resistances are responsible for relapse despite adequate initial treatment [17].

Relapse rate (4%) is low but follow-up remains short. One can assume that the real rate could be higher that this announced; besides, more often than not, relapse can be attributed to reinfection in endemic areas [101]. Melioidosis therapy is long and compliance is essential. At the end of the eradication treatment, it is hard to follow-up patients despite the inherent risk of relapse. That is why the warning signs of a relapse and measures to take should be explained to the patient.

Mortality rate (6%) is slightly lower than those reported in the literature (10–50%) (Table 8) [17]. This discrepancy is likely the result of differences in the quality of patient management and limited access to care in numerous endemic countries [4, 88]. A previous study also found a higher mortality rate that could be explained by numerous bacteremia, many concomitants diseases, such as diabetes, and a limited number of cases [17].

Moreover, no vaccine is available but several are currently in development. Significant progress has been made in subunit-based glycoconjugate vaccines, hence the high expectations for potentials candidates in the UK and in the USA in the years to come [102]. At this time, avoiding contact with

Table 8 Main clinical and epidemiological characteristics compared between our study in travelers and review of melioidosis, which are diagnosed in non-endemic areas

	Our study	Saïdani et al. [17]	Dan [88]	Hadano [89]
Geographical area	Europe	World	World	Japan
N	77	82	72	14
Age (years)	46	50.9	49.6	52.4
Male *N* (%)	56 (73)	66 (80.5)	55 (76)	14 (100)
Age ≤ 18 years *N* (%)	3 (4)	4 (4.8)	5 (7)	–
Clinical presentation *N* (%)				
Pulmonary	40 (52)	41 (50)	17 (24)	8 (57.1)
Cutaneous, soft tissue	27 (35)	23 (28)	9 (12.5)	5 (37.7)
Gastrointestinal	13 (8)	14 (17.1)	Unknown	3 (21.4)
Bacteremia *N* (%)	33 (43)	42 (51.2)	Unknown	9 (62.3)
Deceased *N* (%)	5 (6)	12 (14.6)	12 (17)	2 (14.3)
Comorbidities *N* (%)				
Diabetes	15 (19)	31 (37.8)	15 (21)	8 (57.1)
Chronic hepatic disease, alcoholism	11 (14)	15 (18.3)	5 (7)	2 (14.3)
Chronic lung disease, smoking	15 (19)	6 (7.3)	8 (11)	–
Immunosuppression	6 (8)	4 (4.9)	–	–
None	32 (42)	25 (30.5)	Unknown	1 (7.1)

contaminated water and soil in the endemic area is the best way of preventing melioidosis [1, 4]. Travelers should drink only bottled water, eat cooked food, or cleaned with clear water and wear closed-toe shoes, especially in a rural and dusty area and during the rainy season. In the case of contact or skin lesion, it is imperative to wash immediately with clear water and soap. All wounds should be protected and kept clean until healing [103]. If high-risk exposure occurs, especially patient's relatives, post-exposure prophylaxis is to assess on a case-by-case. It consists of oral trimethoprim–sulfamethoxazole for 10–21 days. Doxycycline or amoxicillin–clavulanic acid can be administrated as a second-line treatment [4, 13].

From the imported cases of melioidosis diagnosed in Europe between 2000 and 2018, a typical patient would be a diabetic man over 45 years, with chronic lung disease or active smoking. He would return from short holidays in Southeast Asia, where he probably had been contaminated by percutaneous inoculation after a skin lesion. He would consult an emergency department within 1 month after his return to Europe. He would have a fever, pulmonary symptoms, or abscesses. The latter would be localized in the skin, soft tissue, or lung. Melioidosis would be a pulmonary or cutaneous presentation. Diagnosis would be based on a blood sample or abscess material cultured. The bacterium would be identified thanks to its morphological, biochemical, and molecular characteristics limit the confusion with other germs. Medical imaging would complete the diagnosis. The misdiagnosis that should be avoided is tuberculosis disease. An empiric antibiotic therapy would be prescribed before bacterium isolation. The intensive and eradication treatment and their duration would be consistent with the recommendations. No adverse effect and no resistance would be reported. Patient would be cured and followed up during just over 1 year.

In the years to come, these situations are likely to become more and more frequent due to the rise in international traveling and the growing risk of natural disasters in endemic areas. The best hope may be the vaccine candidates currently in development, expected to be available in a few years.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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