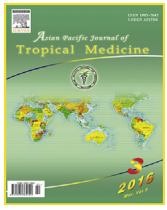
HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage: http://ees.elsevier.com/apjtm



Original research http://dx.doi.org/10.1016/j.apjtm.2016.01.034

Characteristics, clinical outcomes and factors influencing mortality of patients with melioidosis in southern Thailand: A 10-year retrospective study

Chaitong Churuangsuk[1], Sarunyou Chusri[1,2*], Thanaporn Hortiwakul[1], Boonsri Charernmak[1], Kachornsakdi Silpapojakul[1]

[1]*Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand*

[2]*Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand*

ARTICLE INFO

Article history:
Received 15 Dec 2015
Received in revised form 20 Dec 2015
Accepted 30 Dec 2015
Available online 11 Jan 2016

Keywords:
Melioidosis
Southern Thailand
Burkholderia pseudomallei

ABSTRACT

Objective: To study characteristics, clinical outcomes and factors influencing mortality of patients afflicted with melioidosis.

Methods: We retrospectively analyzed 134 patients, with a microbiologically-confirmed diagnosis of melioidosis, during the period from January 2002 to June 2011 at Songklanagarind Hospital, a tertiary care hospital in southern Thailand.

Results: The prevalence of melioidosis among admitted patients was 36.8 per 100 000 in patients. The median age was 49 years and they were predominantly male. The most common underlying disease was diabetes mellitus (47.01%). The majority of cases (50%) had localized infection. The rates of multifocal, bacteremic, and disseminated infections were 12.7%, 23.1%, and 14.2%, respectively. The lungs were the most common organ afflicted, resulting in infection (24.63%). Splenic abscess as well as liver abscess accounted for 20.90% and 19.40%, respectively. A total of one eighth of the patients had septic shock at presentation. The overall mortality rate was 8.96%. The factors influencing mortality were pneumonia, septic shock, a positive blood culture for *Burkholderia pseudomallei*, superimposing with nosocomial infection and inappropriate antibiotic administration.

Conclusions: Melioidosis is not uncommon in southern Thailand. The mortality of patients with pneumonia, bacteremia and septic shock is relatively high. Appropriate antibiotics, initially, will improve outcomes.

1. Introduction

Melioidosis, an infection caused by *Burkholderia pseudomallei* (*B. pseudomallei*), is an endemic in Southeast Asia and northern Australia [1]. The clinical manifestations vary from benign local skin and soft tissue infection to sepsis or septic shock [2]. In northeastern Thailand, melioidosis mostly accounts for the common cause of community-acquired septicemia [3]. The mortality rate remains high despite effective antibiotics regimens in the intensive phase of treatment [4]. For patients who had apparently been cured, recurrence occurred mostly within a year. This is another important problem [5]. Previous studies in northeastern Thailand defined several factors, which included age, underlying diseases of patients, the severity of clinical manifestations and antibiotic regimens; these factors influenced mortality and recurrence [4,5].

The incidence in the southern regions of Thailand were relatively low, compared to those in the northeastern regions [6]. In addition to the higher prevalence of *B. pseudomallei* in soil, higher rates of virulent biotype were prevalent in northeastern Thailand [7]. The aim of this study is to establish clinical characteristics, outcomes and factors influencing mortality of the patients with melioidosis in southern Thailand.

2. Materials and methods

2.1. Study design, study site, population and ethical consideration

This retrospective, cross-sectional study was conducted in Songklanagarind Hospital, an 800-bed university hospital in

*Corresponding author: Sarunyou Chusri, Division of Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
Tel: +66 74 451 483
Fax: +66 74 451 033
E-mail: sarunyouchusri@hotmail.com
Peer review under responsibility of Hainan Medical University.

Songkhla province, located in southern Thailand. All patients (>1 year old) of Songklanagarind Hospital who had a microbiologically-confirmed diagnosis during the periods from January 2002 to June 2011 were enrolled. Ethical permission was obtained from the research ethical committee of the Faculty of Medicine at the Prince of Songkla University.

2.2. Data collection

Demographic data, clinical manifestations together with treatment including antibiotic regimens were collected from the Hospital Information System, a computerized database system of Songklanagarind Hospital, and analyzed for the risk factors for mortality.

Focal infection was defined by 1 site of infection. Multifocal was defined by multiple sites of focal infection, without bacteremia. Bacteremia was defined by positive blood culture with, or without 1 site of focal infection, while disseminated melioidosis was defined by positive blood cultures with at least two, or more focal infections. Septic shock was described as the presence of hypotension without response to fluid replacement, and associated with hypoperfusion and organ dysfunction. Newly diagnosed diabetes mellitus cases were defined as patients who did not have any treatment including oral hypoglycemic agents, insulin and life style modifications.

Occupations, which were suspected risk factors for melioidosis, were classified into two groups according to the chances of exposure to *B. pseudomallei* from the soil and water. These were divided into high exposure and low exposure occupations. Death was defined by patients who died during initial therapy or during intensive therapy.

2.3. Data analysis and statistic

For descriptive statistics, median with inter-quartile range was used for non-normal distribution and continuous data, while frequency with percentage was used for categorical data. In terms of analytic statistics, for continuous variables, the Mann–Whitney *U* test was used, and for categorical variables, either the X^2 test with Yates' correction or Fisher's exact test was used. Logistic regression analysis was used to identify independent risk factors for mortality. A *P*-value of less than 0.05 was considered statistically significant difference. R program was used for analysis with package ‘commend’, ‘ICE’ and ‘epicalc’.

3. Results

During the 10-year study period (2002–2011), a total of 134 patients, with a microbiologically-confirmed diagnosis of melioidosis, were recruited. The prevalence of inpatients with melioidosis was 36.8 per 100 000 inpatients. The median age of affected patients was 49 years with the first and third quartile of 34 years and 58 years respectively. A total of 69.40% of the patients were men. In total, 29.10% of the patients were classified as high risk occupations for melioidosis.

The majority of cases were diagnosed throughout the year, rather than just during the rainy season. At least one underlying disease was documented in 99 (73.88%) of patients, and the most common predisposing condition was diabetes mellitus. Renal failure and abnormal hemoglobin disease were identified in 8 (5.97%) and 7 (5.22%) patients respectively. The majority of patients (89.55%) were treated with parenteral antibiotics as inpatients at Songklanagarind Hospital (Table 1).

A total of 95 (78.51%) patients had a fever prior to admission. Septic shock accounted for 12.40% of patients at initial diagnosis and 21.67% of the patients during hospitalization. A total of 20.83% of the patients required admission into the intensive care unit. A total of 15 patients (12.50%) were superimposed with nosocomial infection. In terms of distribution of infection, 50% of the patients had a localized infection. Multifocal infection, bacteremia, and disseminated infection were 12.69%, 23.13%, and 14.18% respectively.

Overall, there were 12 (8.96%) deaths during hospitalization. After successful treatment, no patient died from any other documented causes. A total of 2 patients died within 2 d, after admission, before laboratory confirmation of the causative organism. Median of time for defervescence was 8 d (Table 2). A total of thirty-three (24.63%) patients presented with community-acquired pneumonia, while only 13 of the 33 patients developed respiratory failure including acute respiratory distress syndrome. Splenic abscess and liver abscess presented in 28 (20.90%) and 26 (19.40%) patients respectively, in the primary diagnosis; however, drainage was required in only 5 patients in splenic abscess, and 2 patients underwent splenectomy. Only one patient with liver abscess underwent abscess drainage.

Similarly to visceral organ abscess, isolated superficial lymph node infection, along with intra-abdominal lymph node infection accounted for 9.70% and 2.24% of the patients respectively. In addition to this, less required aspiration. A total of twenty (14.93%) patients had rheumatologic manifestations involving joints (14 patients with septic arthritis), bones (7 patients with osteomyelitis), muscles (5 patients with muscle abscess) and 5 patients with a combination of the above. Patients, who had septic arthritis required intervention, including surgical drainage and simple aspiration. Genitourinary infection including prostatic abscesses (4.48%) and renal abscess (5.97%), along with parotid gland abscess (3.73%), were less common primary diagnoses (Table 3).

Amongst these patients, indirect hemagglutination antibody against *B. pseudomallei* test was performed in 8 (5.97%) patients, and the titer showed less than, or equal to 1:20 in 1 patient, 1:160 in 1 patient, 1:640 in 4 patients, 1:1 280 in 2 patients, and more than, or equal to 1:2 560 in 1 patient (data not shown).

On the univariate analysis, gender and age of the patients did not affect the mortality. The high exposure occupations, including rice farmers, gardeners and planters, were not related

Table 1
Demographic data of 134 patients with melioidosis.

Characteristics	No. of patients (%)
Sex: male	93 (69.40)
Age in years	49 (34, 58)
Occupation: high risk	39 (29.10)
Underlying diseases	
At least 1 underlying disease	99 (73.88)
Diabetes mellitus	63 (47.01)
Chronic kidney disease	8 (5.97)
Thalassemia	7 (5.22)
Malignancy	11 (8.21)
CMT/Steroid/Immunosuppressant	14 (10.45)
Outpatient cases	14 (10.45)
Inpatient cases	120 (89.55)

Table 2
Clinical data of 134 patients with melioidosis.

Characteristic	No. of patients (%)
Fever prior to admission	95 (78.51)
Septic shock prior to admission	15 (12.40)
Septic shock during admission	26 (21.67)
Intensive care unit admission	25 (20.83)
Superimposed with nosocomial infection	15 (12.50)
Distribution of infection	
Localized	67 (50.00)
Multifocal	17 (12.69)
Bacteremia	31 (23.13)
Disseminated infection	19 (14.18)
Death during intensive phase of treatment	12 (8.96)
Time for defervescence in days, median(IQR)	8 (4, 15)

with a higher mortality. The underlying conditions including diabetes mellitus, chronic kidney disease, thalassemia or hemoglobin diseases, malignancy and application of steroids or immunosuppressant, were not associated with a higher mortality rate. Septic shock prior to, and during admission was significantly associated with a higher mortality rate with an *OR* of 29.14 (7.02, 121.02), and 68.20 (8.20, 567.33) ($P < 0.001$), respectively. Bacteremia, disseminated infection and pulmonary involvement were also significantly related to a higher mortality. Intensive care unit admission was 100% mortality (Table 4).

On the other hand, the initial treatment with antibiotics, another than ceftazidime, or carbapenems, did raise the mortality. It was, however, emphasized that these antibiotics were replaced with ceftazidime and carbapenems a few days after the culture was reported. Patients who were initially treated with carbapenems did not show a lower mortality when compared with an initial treatment with ceftazidime.

4. Discussion

The prevalence and mortality of melioidosis among admitted patients in Songklanagarind Hospital was relatively low. The majority of cases had localized infection, with the lungs being the most commonly involved organ. The factors influencing mortality were pneumonia septic shock, positive blood culture for *B. pseudomallei*, superimposing with nosocomial infection and inappropriate antibiotic administration.

Although melioidosis was the most common cause of community-acquired septicemia, and an important pathogen, causing community-acquired pneumoniain in northeastern Thailand, the clinical data of this disease in southern Thailand is sparse [3]. The incidence of inpatients with melioidosis in this study (36.8:100000 inpatients) was similar to the reports from the central, eastern and northern parts of Thailand [6,8,9]. The incidence of this study was relatively low compared with the previous study in northeastern Thailand [6], along with those of the Northern Territory of Australia [10]. However, it was higher than those in Vietnam [11].

It is unfortunate that the data of melioidosis in 'land-linked' countries of Thailand including Loa PDR, Myanmar and Cambodia is scarce [12–14]. The previous study showed the paucity of cases of melioidosis occurring in the southern regions of Thailand. This could be explained by a lower prevalence of *B. pseudomallei* in soil, when compared with that in the northeastern region [6,15]. According to the arabinose assimilation property, one of the determinant indicating virulence, *B. pseudomallei* was differentiated into two (2) biotypes, including those with the ability to utilize arabinose (Ara^+) and those without the ability to utilize arabinose (Ara^-) [16]. The significantly higher ratio of Ara^- *B. pseudomallei* in environmental isolation from the northeastern region, than other regions, could influence the disease burden [7].

The median age of our study (49 years) was lower than the average ages of previous studies conducted in the northeastern, northern, and eastern parts of Thailand, whereas they were similar to the reports from the tropical northern parts of Australia, Malaysia, Singapore and northern Vietnam [3,8–11,17–19]. Similar to this knowledge, most cases were male, which could be because of the fact that males were more often than not involved in outdoor activities leading to exposure from the soil and surface water, more so than females [2,6].

The proportion of patients with high exposure occupations including rice farmers and fruit agriculturists was quite different from the reports of other regions in Thailand except those of the eastern part of Thailand [3,5,6,8,9]. An explanation of this could be that the low proportion of rice farmers amongst the agriculturists in the southern regions. Secondly, the low prevalence of *B. pseudomallei* in soil could not influence the burden of melioidosis in people exposed to high amounts of soil and water [6,20].

Diabetes mellitus was well established as an important risk factor for melioidosis [3,18,21]. The most likely mechanism for this predisposition was the impairment of neutrophil functions including chemotaxis, phagocytosis, and intracellular killing, whilst the inhibitory effect of insulin on the growth of *B. pseudomallei* was unacceptable [22]. As pursuant to this knowledge, half of all patients had diabetes mellitus and 29 (45.31%) patients were diagnosed during the first time of admission. Unlike the report from northeastern Thailand, there were only 6 patients who had hematologic disease including thalassemia disease, thalassemia traits, along with other hemoglobin diseases [21].

Fever was the most common presentation. Some patients had no specific organ involvement in so saying, specific organ involvement was sequentially identified in the following days after admission. This encouraged the physicians to conduct a complete physical examination on patients with fevers and with non-specific organ involvement. This finding supported the previous report, which ranged melioidosis as differential diagnosis of acute undifferentiated fever in Thailand [23]. Our study also filled in the lack of data of melioidosis, as the cause of fever of an unknown origin in the endemic area [24].

The incidence of patients with blood stream and disseminated infection were lower than the incidence from other regions of Thailand, and nearly all the incidence from the Northern Territory of Australia, Malaysia and Singapore [3,10,18]. Because the site of study was a referral center, the low proportion of bacteremic patients was suspected primarily from the prescription of antibiotics prior to referral of the patients to our hospital. The possible different virulence of *B. pseudomallei* isolated in southern Thailand needs to be investigated further.

This study demonstrated pulmonary involvement as the most common manifestation among bacteremic and non-bacteremic patients. Similar to the prospective study in Australia, pneumonic patients in this study were primarily diagnosed rather than after another primary diagnosis [10]. The differences from previous studies were that there were 12 patients with pleural involvement including pleural effusion and empyema thoracis among 33 patients with pulmonary involvement [25–27]. Multi-lobar involvement was

Table 3
Organ involvement of melioidosis.

Organ involvement	No. of patients (%)
Lung	33 (24.63)
- Reticular infiltration	6
- Patchy infiltration	12
- Cavity lesion	1
- Pleural effusion	12
- Lobar involvement	
Left upper lobe	1
Right upper lobe	4
Right middle lobe	2
- Multilobar involvement	11
- Respiratory failure	13
- Acute respiratory distress syndrome	2
Liver	26 (19.40)
- Require drainage	1
Spleen	28 (20.90)
- Require drainage	5
- Splenectomy	2
Bone and joints	20 (14.93)
- Osteomyelitis	7
- Muscle abscess	5
- Septic arthritis	14
Skin and soft tissue	25 (18.66)
Prostate gland	6 (4.48)
Kidney	8 (5.97)
Parotid gland	5 (3.73)
Intra-abdominal lymph node	3 (2.24)
Superficial lymph node	13 (9.70)

predominated rather than isolated lower lobar lesions which were described in the report from northern Australia, or confluent upper lobe lesions which were described in the report from northeastern Thailand [25–27]. There were no patients who had initial cavity lung lesion, whilst only 1 patient developed cavity lung lesions, these developed during admission.

As in the previous reports, the spleen is the most common source of visceral organ infection, followed by the liver and the genito-urinary organ [28]. Multiple abscesses, in our study, were more prevalent than isolated abscess, while isolated splenic abscess was commonest. These findings were similar to many reports, which demonstrated predominate splenic abscess among melioidotic patients [3,18,28,29]. Because the splenic infection was rare, the detection of isolated splenic abscess, or splenic abscess in various conditions, in these endemic areas was suggestive to melioidosis [28–30].

During the last decade, the overall fatality rate in the northern and eastern regions of Thailand was similar to those in the northeast of Thailand [8,9,6]. The death rate accounted for only 8.96%, which is relatively lower than the previous study, in several parts of Thailand, and even in Malaysia and Singapore which is located nearby. It is, however, similar to the last 5 years of reports from Darwin, Australia [8,10,6].

This finding raised the aspect that the regional strains of *B. pseudomallei* in the south of Thailand might have differences in pathogenicity and virulence [15]. In addition, the differences in host genetic and pathogen-host response, which were previously described, have to be studied further [31]. The high proportion of pulmonary involvement was significantly associated with a higher mortality rate, compared with patients without pulmonary involvement. Although the previous study demonstrated the explanation of the low mortality rate, in pneumonic melioidotic patients, was contributed to a low infecting load of *B. pseudomallei* from inhalation [31], this study showed almost all pneumonic patients had blood stream infections, which caused a higher infecting load than isolated inhalation. However, the predictor of severity, which was determined by individual genetic polymorphism, has to be studied further [32]. The delay in the administration of appropriate antibiotics against *B. pseudomallei*, which was well established as an important risk factor for the mortality, was also demonstrated in this study [3]. Similarly the treatment concept of other gram negative septicemia, along with the lack of effective bactericidal agents, contributed to the higher death rate [8]. We have demonstrated the incidence, manifestations and mortality of melioidosis in southern Thailand. Pneumonia, septic shock and bacteremia are risk factors for mortality in this study. An early diagnosis, coupled with appropriate antibiotics, during initial and maintenance phases, improve the outcome of the disease. Further investigation into molecular epidemiology, as well as specific host immune response of *B. pseudomallei* in the south of Thailand, is needed.

Table 4
Risk factors influencing mortality for 134 patients with melioidosis.

Risk factors	No. (%) of survivors n = 122	No. (%) of dead n = 12	*OR* (95%*CI*)	*P*-value
Sex: male	84 (68.9)	9 (75.0)	0.74 (0.19, 2.88)	0.660
Age in years, median(IQR)	48 (31, 58)	52 (49.2, 56.2)	1.03 (0.99, 1.07)	0.167
High exposure occupation	36 (30.3)	3 (25.0)	0.77 (0.20, 3.01)	0.705
DM	55 (45.1)	8 (66.7)	2.44 (0.70, 8.52)	0.163
Chronic kidney disease	8 (6.6)	0	—	—
Thalassemia	7 (5.7)	0	—	—
Malignancy	10 (8.2)	1 (8.3)	1.02 (0.12, 8.71)	0.987
CMT/Steroid/Immunosuppressant	12 (9.8)	2 (16.7)	1.83 (0.36, 9.37)	0.466
Septic shock prior to admission	7 (6.4)	8 (66.7)	29.14 (7.02, 121.02)	<0.001
Septic shock during admission	15 (13.9)	11 (91.7)	68.20 (8.20, 567.33)	<0.001
Intensive care unit admission	13 (12)	12 (100.0)	—	—
Superimposed with nosocomial infection	10 (9.3)	5 (41.7)	7.00 (1.87, 26.18)	0.004
Distribution of infection				
- Localized infection	67 (54.9)	0	—	—
- Multifocal infection	15 (12.3)	2 (16.7)	1.43 (0.28, 7.15)	0.666
- Bacteremia/disseminated infection	40 (32.8)	10 (83.3)	10.25 (2.14, 49.00)	0.004
Lung involvement	24 (19.7)	9 (75.0)	12.25 (3.08, 48.73)	<0.001
Appropriate antibiotics use	111 (91.0)	3 (37.5)	37.67 (7.29, 238.94)	<0.001

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Ramphal R. Infections due to *Pseudomonas* species and related organisms. In: Longo DL, Jameson JL, Kasper DL, Fauci AS, Hauser SL, Loscalzo J, editors. *Harrison's principles of internal medicine*. 18th ed. New York: McGraw-Hill; 2012, p 1273.

[2] McLeod C, Morris PS, Bauert PA, Kilburn CJ, Ward LM, Baird RW, et al. Clinical presentation and medical management of melioidosis in children: a 24-year prospective study in the Northern Territory of Australia and review of the literature. *Clin Infect Dis* 2015; **60**(1): 21-26.

[3] Bhengsri S, Lertiendumrong J, Baggett HC, Thamthitiwat S, Chierakul W, Tisayaticom K, et al. Economic burden of bacteremic melioidosis in eastern and northeastern, Thailand. *Am J Trop Med Hyg* 2013; **89**(2): 369-373.

[4] Currie BJ. Melioidosis: evolving concepts in epidemiology, pathogenesis, and treatment. *Semin Respir Crit Care Med* 2015; **36**(1): 111-125.

[5] Benoit TJ, Blaney DD, Gee JE, Elrod MG, Hoffmaster AR, Doker TJ, et al. Melioidosis cases and selected reports of occupational exposures to *Burkholderia pseudomallei* - United States, 2008–2013. *MMWR Surveill Summ* 2015; **64**(Suppl 5): 1-9.

[6] Limmathurotsakul D, Wongratanacheewin S, Teerawattanasook N, Wongsuvan G, Chaisuksant S, Chetchotisakd P, et al. Increasing incidence of human melioidosis in northeast Thailand. *Am J Trop Med Hyg* 2010; **82**(6): 1113-1117.

[7] Thaipadungpanit J, Chierakul W, Pattanaporkrattana W, Phoodaeng A, Wongsuvan G, Huntrakun V, et al. *Burkholderia pseudomallei* in water supplies, southern Thailand. *Emerg Infect Dis* 2014; **20**(11): 1947-1949.

[8] Limmathurotsakul D, Peacock SJ. Melioidosis: a clinical overview. *Br Med Bull* 2011; **99**(1): 125-139.

[9] Bhengsri S, Baggett HC, Jorakate P, Kaewpan A, Prapasiri P, Naorat S, et al. Incidence of bacteremic melioidosis in eastern and northeastern Thailand. *Am J Trop Med Hyg* 2011; **85**(1): 117-120.

[10] Currie BJ, Ward L, Cheng AC. The epidemiology and clinical spectrum of melioidosis: 540 cases from the 20 year Darwin prospective study. *PLoS Negl Trop Dis* 2010; **4**(11): e900.

[11] Kurata K, Nukui Y, Shimada H, Inoue Y, Yoshimura N, Horino A. A case of melioidosis occurring after a long-term stay in Vietnam that developed pulmonary cavitation and relapsed with multiple pulmonary nodules. *J Jpn Respir Soc* 2011; **49**(6): 443-448.

[12] Nasner-Posso KM, Cruz-Calderón S, Montúfar-Andrade FE, Dance DA, Rodriguez-Morales AJ. Human melioidosis reported by ProMED. *Int J Infect Dis* 2015; **35**: 103-106.

[13] Hotez PJ, Bottazzi ME, Strych U, Chang LY, Lim YA, Goodenow MM, et al. Neglected tropical diseases among the Association of Southeast Asian Nations (ASEAN): overview and update. *PLoS Negl Trop Dis* 2015; **9**(4): e0003575.

[14] Chheng K, Carter MJ, Emary K, Chanpheaktra N, Moore CE, Stoesser N, et al. A prospective study of the causes of febrile illness requiring hospitalization in children in Cambodia. *PLoS One* 2013; **8**(4): e60634.

[15] Sermswan RW, Royros P, Khakhum N, Wongratanacheewin S, Tuanyok A. Direct detection of *Burkholderia pseudomallei* and biological factors in soil. *Trans R Soc Trop Med Hyg* 2015; **109**(7): 462-468.

[16] Stone JK, DeShazer D, Brett PJ, Burtnick MN. Melioidosis: molecular aspects of pathogenesis. *Expert Rev Anti Infect Ther* 2014; **12**(12): 1487-1499.

[17] Musa HI, Hassan L, Shamsuddin ZH, Panchadcharam C, Zakaria Z, Abdul Aziz S, et al. Case-control investigation on the risk factors of melioidosis in small ruminant farms in Peninsular Malaysia. *J Appl Microbiol* 2015; **119**(2): 331-341.

[18] Fong SM, Wong KJ, Fukushima M, Yeo TW. Thalassemia major is a major risk factor for pediatric melioidosis in Kota Kinabalu, Sabah, Malaysia. *Clin Infect Dis* 2015; **60**(12): 1802-1807.

[19] Liu X, Pang L, Sim SH, Goh KT, Ravikumar S, Win MS, et al. Association of melioidosis incidence with rainfall and humidity, Singapore, 2003–2012. *Emerg Infect Dis* 2015; **21**(1): 159-162.

[20] Inglis T. VIth World Melioidosis Congress report: celebrating a century of research. *Future Microbiol* 2011; **6**(3): 263-264.

[21] Limmathurotsakul D, Kanoksil M, Wuthiekanun V, Kitphati R, deStavola B, Day NP, et al. Activities of daily living associated with acquisition of melioidosis in northeast Thailand: a matched case-control study. *PLoS Negl Trop Dis* 2013; **7**(2): e2072.

[22] Saengmuang P, Kewcharoenwong C, Tippayawat P, Nithichanon A, Buddhisa S, Lertmemongkolchai G. Effect of host factors on neutrophil functions in response to *Burkholderia pseudomallei* in healthy Thai subjects. *Jpn J Infect Dis* 2014; **67**(6): 436-440.

[23] Susilawati TN, McBride WJ. Acute undifferentiated fever in Asia: a review of the literature. *Southeast Asian J Trop Med Public Health* 2014; **45**(3): 719-726.

[24] Alves Galvão MG, Rocha Crispino Santos MA, Alves da Cunha AJ. Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age. *Cochrane Database Syst Rev* 2014; **2**: CD007880.

[25] Ko SF, Kung CT, Lee YW, Ng SH, Huang CC, Lee CH. Imaging spectrum of thoracic melioidosis. *J Thorac Imaging* 2013; **28**(3): W43-W48.

[26] Burivong W, Wu X, Saenkote W, Stern EJ. Thoracic radiologic manifestations of melioidosis. *Curr Probl Diagn Radiol* 2012; **41**(6): 199-209.

[27] Suntornsut P, Kasemsupat K, Silairatana S, Wongsuvan G, Jutrakul Y, Wuthiekanun V, et al. Prevalence of melioidosis in patients with suspected pulmonary tuberculosis and sputum smear negative for acid-fast bacilli in northeast Thailand. *Am J Trop Med Hyg* 2013; **89**(5): 983-985.

[28] Apisarnthanarak P, Thairatananon A, Muangsomboon K, Lu DS, Mundy LM, Apisarnthanarak A. Computed tomography characteristics of hepatic and splenic abscesses associated with melioidosis: a 7-year study. *J Med Imaging Radiat Oncol* 2011; **55**(2): 176-182.

[29] Sugi Subramaniam RV, Karthikeyan VS, Sistla SC, Ali SM, Sistla S, Vijayaraghavan N. Intra-abdominal melioidosis masquerading as a tubercular abdomen: report of a rare case and literature review. *Surg Infect (Larchmt)* 2013; **14**(3): 319-321.

[30] Guo RF, Wong FL, Perez ML. Splenic abscesses in a returning traveler. *Infect Dis Rep* 2015; **7**(1): 5791.

[31] Reynolds C, Goudet A, Jenjaroen K, Sumonwiriya M, Rinchai D, Musson J, et al. T cell immunity to the alkyl hydroperoxide reductase of *Burkholderia pseudomallei*: a correlate of disease outcome in acute melioidosis. *J Immunol* 2015; **194**(10): 4814-4824.

[32] Alam S, Amemiya K, Bernhards RC, Ulrich RG, Waag DM, Saikh KU. Characterization of cellular immune response and innate immune signaling in human and nonhuman primate primary mononuclear cells exposed to *Burkholderia mallei*. *Microb Pathog* 2015; **78**: 20-28.