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Short Report: Patterns of Organ Involvement in Recurrent Melioidosis

Direk Limmathurotsakul,* Wipada Chaowagul, Nicholas P. J. Day, and Sharon J. Peacock

Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; Medical Department, Sappasithiprasong Hospital, Ubon Ratchathani, Thailand; Center for Clinical Vaccinology and Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Churchill Hospital, Oxford, United Kingdom

Abstract. Recurrent melioidosis can be caused by two different mechanisms: relapse or re-infection. We examined the pattern of organ involvement in the first and second episodes in individual patients. Evaluation of 140 patients with recurrence showed that similar patterns of disease occurred during the first and second episode, independent of whether this was caused by relapse or re-infection.

Melioidosis is a community-acquired infection caused by the gram-negative bacillus *Burkholderia pseudomallei*. This organism is present in soil and water in areas where melioidosis is endemic, and infection is acquired by bacterial inoculation or inhalation. *B. pseudomallei* causes 20% of community-acquired septicemias in northeast Thailand[1] and is the most common cause of fatal community-acquired pneumonia in Darwin, Australia.[2] Clinical manifestations are extremely wide ranging, and pneumonia, hepatosplenic abscesses, septic arthritis, and skin and soft tissue infection commonly occur secondary to bacterial dissemination. Overall mortality is 50% in northeast Thailand and 19% in Australia.[3,4] The most important complication in survivors is recurrent infection, which occurs in 13% of Thai patients who survive the primary episode.[5] A comparison of the bacterial genotype of strain pairs isolated during primary and recurrent melioidosis in 141 patients showed that 92 patients (65%) had relapse (paired isolates had the same genotype), and 49 patients (35%) had re-infection with a new strain on their first recurrent episode.[6] Multifocal infection and bacteremia during the primary episode have been defined as specific risk factors for relapse, whereas no risk factors (other than re-exposure to a contaminated environment) have been defined for re-infection.[7] A previous study, comparing clinical manifestations between relapse and re-infection, identified several clinical predictors that differentiated re-infection from relapse, including duration of oral antimicrobial treatment received for the primary episode, the time interval between the primary episode and recurrence, season (rainy or dry season) when the recurrence occurred, and renal function at recurrence.[8] The aim of the study described here was to examine how the organ involvement in the second episode is related to the first episode in individual patients who had relapse and re-infection, respectively.

Study patients were adults (≥ 15 years) with culture-confirmed recurrent melioidosis who presented to Sappasithiprasong Hospital, Ubon Ratchathani, northeast Thailand, between June 1986 and September 2005. Follow-up was performed until February 2007. A total of 194 episodes of culture-confirmed recurrent melioidosis occurred in 170 patients during the 19-year study period, and 148 (76%) strains paired from the primary and recurrent episode were available for genotyping from 141 patients. Relapse and re-infection were defined on the basis of typing of isolates from the first and subsequent episode of infection using a combination of pulsed field gel electrophoresis (PFGE) and multilocus sequence typing (MLST), as described previously.[6,9] Isolates from the same patient that differed by one or more PFGE bands were examined using MLST. Isolates from the same patient with an identical PFGE banding pattern or variable banding pattern but identical MLST sequence type (ST) were classified as representing relapse, whereas those with a different ST were classified as representing re-infection. Six patients had recurrent infections more than once and, for the purposes of this study, only the 141 first episodes of recurrent melioidosis in each patient (92 relapse and 49 re-infection) were analyzed.

The approach taken was to define the body sites or organs involved during the first and second episode of melioidosis in each patient and determine whether the sites involved were more similar between the two episodes than would be expected by chance. The sites/organs considered were those most commonly defined during melioidosis, as follows: blood, lung, liver, spleen, skin or soft tissue, joint, or bone. Patients may have involvement of more than one organ during a single episode of infection, but each site was considered independently. The degree of agreement between each site/organ was expressed using the Kappa index and its P value. This describes the level of association, both positive and negative, beyond that caused by chance, as follows: 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, high. The McNemar test was used to compare the proportions of organ involvement for the first episode and recurrent episode. All P values were corrected using the Benjamini-Hochberg method for multiple comparisons.[10] All analyses were performed using the statistical software STATA/SE version 9.0 (StataCorp, College Station, TX).

Patients with relapse were found to have repeated presentation with pneumonia, liver abscess, splenic abscess, and skin or soft tissue infection (Table 1; Kappa values > 0.20 and P values < 0.05). For example, 35 patients had pneumonia during the primary episode, and 49% (17/35) of these had pneumonia at relapse. In contrast, only 18% (10/57) of patients who did not have pneumonia during the primary episode had pneumonia at relapse. This gives a Kappa value for pneumonia of 0.32 and a P value of 0.002. There was no difference in the proportion of patients with pneumonia on the primary versus the relapse episode (38% versus 29%; McNemar test, $P > 0.1$). We noted that the proportion of patients having splenic abscess was considerably lower during the relapse episode compared with the primary episode (15% versus 35%; McNemar test, $P = 0.004$), and this was of borderline significance in the case of liver abscess

*Address correspondence to Direk Limmathurotsakul, Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand. E-mail: direk@tropmedres.ac

TABLE 1
Similarity in clinical features at the first presentation with melioidosis (primary episode) and first relapse for 92 patients

Site or organ(s) infected during primary episode	Number of patients (% of 92 patients)	Site or organ(s) infected during relapse episode (%)	Kappa value* (*P* value)	McNemar test *P* value†
Bacteremia				
Yes	49 (53%)	27/49 (55%)	< 0.20	> 0.1
No	43 (47%)	16/43 (37%)		
Pneumonia				
Yes	35 (38%)	17/35 (49%)	0.32 (*P* = 0.002)	> 0.1
No	57 (62%)	10/57 (18%)		
Liver abscess				
Yes	28 (30%)	11/28 (39%)	0.34 (*P* = 0.002)	0.065
No	64 (70%)	6/64 (9%)		
Splenic abscess				
Yes	32 (35%)	9/32 (28%)	0.23 (*P* = 0.009)	0.004
No	60 (65%)	5/60 (8%)		
Skin or soft tissue				
Yes	27 (29%)	15/27 (56%)	0.30 (*P* = 0.004)	> 0.1
No	65 (71%)	16/65 (25%)		
Septic arthritis				
Yes	12 (13%)	2/12 (17%)	< 0.20	> 0.1
No	80 (87%)	11/80 (14%)		
Osteomyelitis				
Yes	3 (3%)	1/3 (33%)	—	—
No	89 (97%)	6/89 (7%)		

*Kappa test describes the level of association of repeated body site involvement beyond that caused by chance, as follows: 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, high.
†McNemar test was used to compare proportions of organ involvement between primary episode and relapse.

(18% versus 30%; McNemar test, $P = 0.065$). However, the proportion of patients who had repeated presentation with either abscess type was significantly higher than the proportion with liver or splenic abscess for the first time at relapse (Table 1). There were 15 patients who had repeated presentation of skin or soft tissue infection, 10 of whom had repeated infection at the previous site after apparent cure. The median interval between the primary episode and relapse in these 10 patients was 13 months, with a range of 8–70 months. This compared with eight patients who developed new foci of skin or soft tissue infection.

The analysis was repeated for the 49 patients with re-infection (Table 2). Repeated presentation was observed for pneumonia, liver abscess, and splenic abscess.

At the outset of this study, we predicted that patients with relapse would have a similar pattern of organ involvement during the first and second episodes of infection. This is because *B. pseudomallei* is presumed to form a quiescent nidus of infection after apparent cure, and persistence at the initial site(s) is supported by reports that *B. pseudomallei* forms granuloma in various organs *in vivo*.[11] Our study findings are consistent with this prediction but are challenged by the fact that patients with

TABLE 2
Similarity in clinical features at the first presentation with melioidosis (primary episode) and re-infection for 49 patients

Site or organ(s) infected during primary episode	Number of patients (% of 92 patients)	Site or organ(s) infected during relapse episode (%)	Kappa value* (*P* value)	McNemar test *P* value†
Bacteremia				
Yes	22 (45%)	15/22 (68%)	< 0.20	> 0.1
No	27 (55%)	13/27 (48%)		
Pneumonia				
Yes	23 (47%)	12/23 (52%)	0.33 (*P* = 0.016)	> 0.1
No	26 (53%)	5/26 (19%)		
Liver abscess				
Yes	11 (22%)	6/11 (55%)	0.50 (*P* = 0.001)	> 0.1
No	38 (78%)	3/38 (8%)		
Splenic abscess				
Yes	12 (24%)	5/12 (42%)	0.42 (*P* = 0.003)	> 0.1
No	37 (76%)	2/37 (5%)		
Skin or soft tissue				
Yes	9 (18%)	4/9 (44%)	< 0.20	> 0.1
No	40 (82%)	12/40 (30%)		
Arthritis				
Yes	5 (10%)	1/5 (20%)	< 0.20	> 0.1
No	44 (90%)	7/44 (16%)		
Osteomyelitis				
Yes	0 (0%)	0 (0%)	—	—
No	49 (100%)	1/49 (2%)		

*Kappa test describes the level of association of repeated presentation beyond that caused by chance, as follows: 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, high.
†McNemar test is used to compare proportions of organ involvement between first episode and recurrent episode.

re-infection also presented with similar organ involvement as in their primary episode. This cannot be explained by a predictable and characteristic pattern of organ involvement because, although the organs evaluated are preferential sites for infection, the clinical presentations within our patient group were highly variable. We propose that innate and/or acquired host factors must play a major role in determining the body sites involved during human infection. There may be a higher chance of bacterial seeding to previously damaged tissue, as observed for other bacterial infections such as those caused by *Staphylococcus aureus*. Alternatively, host genetic traits may increase the probability for specific organ involvement and disease manifestations. Although repeated presentation with pneumonia could relate to re-infection after inhalation, we consider that this is unlikely to account for repeated pneumonia because the most common route of infection in our population is probably inoculation. We conclude that repeated specific organ involvement was observed in both relapse and re-infection.

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Authors' addresses: Direk Limmathurotsakul, Mahidol–Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok, 10400, Thailand, E-mail: direk@tropmedres.ac. Wipada Chaowagul, Sappasithiprasong Hospital, Ubon Ratchathani Hospital, Ubon Ratchathani, Thailand, 34000, E-mail: vipada_1@yahoo.com. Nicholas P. J. Day and Sharon J. Peacock, Center for Clinical Vaccinology and Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Churchill Hospital, Oxford, OX3 7LJ, U.K., E-mails: nickd@tropmedres.ac and sharon@tropmedres.ac.

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