Cutaneous Melioidosis in the Tropical Top End of Australia: A Prospective Study and Review of the Literature

Katherine B. Gibney,1 Allen C. Cheng,1,2 and Bart J. Currie1,2

1Infectious Diseases Unit and Northern Territory Clinical School, Royal Darwin Hospital, and 2Tropical and Emerging Infectious Diseases Division, Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, Australia

Background.  
Burkholderia pseudomallei is endemic in northern Australia, and melioidosis is a common cause of sepsis in the region.

Methods.  
We summarized the cutaneous manifestations of melioidosis from a prospective cohort of 486 patients with culture-confirmed melioidosis in northern Australia, and we compared those who had primary skin melioidosis with those who had other forms of melioidosis.

Results.  
Primary skin melioidosis occurred in 58 patients (12%). Secondary skin melioidosis—multiple pustules from hematogenous spread—was present in 10 patients (2%). Patients with primary skin melioidosis were more likely to have chronic presentations (duration, ≥2 months). On multivariate analysis, patients with primary cutaneous melioidosis were more likely to be children aged ≤15 years (adjusted odds ratio, 8.50; 95% confidence interval [CI], 3.24–22.28) and to have a history of occupational exposure to B. pseudomallei (adjusted odds ratio, 3.12; 95% CI, 1.56–6.25) but were less likely to have typical risk factors—including diabetes (adjusted odds ratio, 0.26; 95% CI, 0.12–0.56), excessive alcohol intake (adjusted odds ratio, 0.45; 95% CI, 0.22–0.90), and chronic lung disease (adjusted odds ratio, 0.26; 95% CI, 0.10–0.67). Of those patients with primary skin melioidosis, 1 patient was bacteremic and none had severe sepsis or died from melioidosis. Four (7%) of the 58 patients presenting with primary skin melioidosis had disseminated melioidosis, and 1 (2%) experienced a relapse of melioidosis. Nine patients (16%) were cured with a regimen of oral antibiotics alone, and 1 recovered with no therapy.

Conclusion.  
In our cohort, patients with primary skin melioidosis were younger, had fewer underlying medical conditions, and had better outcomes than did those with other forms of melioidosis. There may be a role for exclusive oral antibiotic therapy for some cases of primary skin melioidosis.

Burkholderia pseudomallei, the cause of melioidosis, is endemic in northern Australia and Southeast Asia. The clinical manifestations of melioidosis range from localized infection to overwhelming sepsis and death. Pneumonia is the most common presentation of melioidosis, and at the Royal Darwin Hospital in northern Australia, B. pseudomallei has been the most common cause of community-acquired bacteraemic pneumonia [1, 2]. Melioidosis is responsible for 20% of cases of community-acquired sepsis in northeastern Thailand [3]. The mortality rate associated with melioidosis is high and varies between countries; it is ~50% among affected adults in northeastern Thailand and ~19% in northern Australia. Severe septicemic melioidosis has reported mortality rates of 90% and 86% in northeastern Thailand and northern Australia, respectively [4–6].

Skin and soft-tissue infection comprise 13%–24% of clinical presentations with melioidosis in published case series [1]. Primary skin melioidosis is often localized and less severe than other forms of melioidosis—in northern Australia, there were no cases of bacteremia or death among the 32 patients seen over a 10-year period who had primary skin melioidosis [5]. On the other hand, primary skin melioidosis has been reported to be associated with necrotizing fasciitis, sepsis, and internal organ abscesses in Southeast Asia [3, 7–9]. Other cutaneous manifestations of melioidosis that...
have been described include polyarteritis nodosa [10], extensive skin pustules associated with sepsis [11], and extensive ec- thyma-like lesions associated with disseminated melioidosis [12].

The most significant risk factor for melioidosis is diabetes, which has been reported in 37%-60% of patients with me- lioidosis [1]. In northern Australia, diabetes, excessive alcohol intake (current average daily use of >60 g of alcohol for men and >40 g of alcohol for women), chronic renal disease, and chronic lung disease were all independent risk factors for me- lioidosis, and men, indigenous Australians, and people aged ≥45 years were over-represented in the group with melioidosis [13]. In addition, thalassemia and occupational exposure to soil and water (e.g., rice farming) have been demonstrated to be independent risk factors for melioidosis in Thailand [14].

PATIENTS AND METHODS

This study included all patients with culture-confirmed me- lioidosis in the tropical “Top End” of Northern Territory, Aus- tralia, from 1 October 1989 through 31 July 2007. The Top End comprises an area of 516,945 km² and had a population of ∼160,000 in 2005, ∼25% of whom were indigenous Australians [15]. Data were collected prospectively as part of the Darwin Prospective Melioidosis Study, and the methods of collection and results of the first 10 years of this study have been reported elsewhere [5].

Variables of interest included age, sex, ethnicity (indigenous Australian Aboriginal or other), and duration of symptoms before presentation (≥2 months was defined to be chronic melioidosis in the Darwin study). Time of presentation was categorized as dry season (16 May through 15 November) or wet season. Age was categorized as child (age, ≤15 years) or adult. Risk factors were defined as follows: diabetes (docu- mented diagnosis either before or at hospital admission for me- lioidosis), chronic renal disease (creatinine level, >150 µmol/ L measured before the episode of melioidosis, or if creatinine level not previously documented, measured after recovery from melioidosis), excessive alcohol intake, chronic lung disease (documented diagnosis of chronic obstructive pulmonary air- ways disease), and no risk factor (none of these 4 risk factors and no “other” risk factor—i.e., malignancy, immunosuppres- sive therapy, cardiac failure, or cirrhosis). Information was col- lected about potential exposure to B. pseudomallei in the course of the patient’s occupation and/or recreational activities (some patients had both potential exposures). Admission laboratory results were the first tests collected during the hospital stay, performed as many as 48 h after admission. These results were categorized as follows: positive melioidosis serological test re- sults (indirect hemagglutination titer, ≥1:40), leukocytosis (WBC count, >11.0 × 10⁹ cells/L), neutrophilia (neutrophil count, >7.5 × 10⁹ cells/L), lymphopenia (lymphocyte count, <1.5 × 10⁹ cells/L), and hypoalbuminemia (serum albumin level, <35 g cells/L).

We considered primary skin melioidosis on the basis of clinical presentation; patients whose major presenting symptom was skin infection were considered to have primary skin me- lioidosis, whereas those with a clinical presentation suggestive of an infection at another site or evident systemic sepsis were categorized as having “other melioidosis.” Those with other melioidosis who had incidental skin manifestations in the form of multiple skin pustules were considered to have secondary skin melioidosis; all tested skin lesions were culture positive for B. pseudomallei and were presumed to be a result of hematog- enous spread. Septic shock was defined as hypotension that was not responsive to fluid replacement, combined with hypoper- fusion abnormalities that resulted in end organ dysfunction [16]. Death due to infection with B. pseudomallei could occur during hospital admission or after discharge from the hospital, if the patient experienced recrudescence or relapse of melioidosis.

The group with primary skin melioidosis was compared with the group with other melioidosis by univariate analysis, to generate an OR, and by multivariate analysis, to generate an adjusted OR (aOR). Univariate analysis was performed for the following variables: demographic characteristics, risk factors, presentation, laboratory results at the time of presentation, and outcomes. Three multivariate models were created (demo- graphic characteristics, risk factors, and laboratory results at the time of presentation), and backward stepwise logistic regres- sion was performed for each model. Age ≤15 years and sex were included in each of the 3 multivariate models. For the continuous variables, age was compared between the 2 groups with use of Student’s t test, whereas the results of WBC count, neutrophil count, lymphocyte count, and serum albu- min level (which were not normally distributed) were compared using the nonparametric Kruskal-Wallis test for difference.

Data were collected prospectively and were stored using Or- acle software, version 8.0.4 (Oracle). Statistical analysis was performed using Intercooled Stata, version 9.0 (Stata). Ap- proval for this study was obtained from the Human Research Ethics Committee of the Menzies School of Health Research and from the Northern Territory Department of Health and Community Services.

RESULTS

During October 1989 through July 2007, 486 people from the Top End of Australia’s Northern Territory had culture-con- firmed melioidosis. Primary skin melioidosis occurred in 58 patients (12%). Other presentations included 249 patients (51%) with a primary diagnosis of pneumonia, 71 (15%) with primary genitourinary infection, 67 (14%) with systemic sepsis without an evident focus, 14 (3%) with soft-tissue infection,
13 (3%) with neurological melioidosis, and 9 (2%) with bone and/or joint infection. The large majority of patients with primary skin melioidosis had single lesions that were nonspecific in nature, with size varying from several millimeters to several centimeters. The most common presentation was with an ulcer, with or without a purulent exudate. Other appearances included single pustules, boils, crusted erythematous lesions, and dry asymmetric erythematous flat lesions. Cellulitis was rare. The location of the primary skin lesion(s) was documented for 49 patients, as follows: leg (21 patients), foot (8), arm (7), hand (5), face (2), neck (2), multiple sites (2), groin (1), and buttock (1). Secondary skin melioidosis in the form of multiple pustules occurred in 10 (2%) of 428 patients with other melioidosis: 5 with a primary diagnosis of pneumonia and 5 with primary sepsis, of whom 9 (90%) had documented bacteremia. In addition, cutaneous disease was occasionally seen as an extension of underlying infection, such as chronic melioidosis osteomyelitis or lymphadenitis. Some examples of primary and secondary skin melioidosis are shown in figure 1.

Patients were divided into 2 groups, according to their primary melioidosis diagnosis (primary skin or other). Compared with those with other melioidosis, patients with primary skin melioidosis were younger (mean age, 37.2 vs. 48.5 years; \(P < .001\)), were more likely to present with chronic melioidosis (OR, 6.35; 95% CI, 3.38–11.93), and were more likely to present during the dry season (OR, 2.27; 95% CI, 1.22—4.24). On multivariate analysis, primary skin melioidosis was found to be less common among men (aOR, 0.50; 95% CI, 0.26–0.97) and indigenous Australians (aOR, 0.43; 95% CI, 0.22–0.82). People reporting potential occupational exposure to \textit{B. pseudomallei} were more likely to present with primary skin melioidosis (aOR, 3.12; 95% CI, 1.56–6.25); however, there was no detected difference among those reporting potential recreational exposure (table 1). On univariate analysis, the melio-
Table 1. Patient demographic characteristics, presentation, and outcomes, by primary melioidosis diagnosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary melioidosis diagnosis, no. or proportion (%) of patients</th>
<th>Univariate analysis</th>
<th>Multivariate analysis&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skin (n = 58)</td>
<td>Other (n = 428)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Demographic characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤15 years</td>
<td>9 (16)</td>
<td>12 (3)</td>
<td>6.37 (2.55–15.87)</td>
</tr>
<tr>
<td>Male sex</td>
<td>38 (66)</td>
<td>303 (71)</td>
<td>0.78 (0.44–1.40)</td>
</tr>
<tr>
<td>Indigenous Australian</td>
<td>18 (31)</td>
<td>229 (54)</td>
<td>0.39 (0.22–0.70)</td>
</tr>
<tr>
<td>Urban residence</td>
<td>44 (76)</td>
<td>278 (65)</td>
<td>1.70 (0.90–3.19)</td>
</tr>
<tr>
<td>Occupational exposure</td>
<td>19 (33)</td>
<td>65 (15)</td>
<td>2.72 (1.48–5.00)</td>
</tr>
<tr>
<td>Recreational exposure</td>
<td>47 (81)</td>
<td>321 (75)</td>
<td>1.42 (0.71–2.85)</td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic melioidosis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22 (38)</td>
<td>36 (8)</td>
<td>6.35 (3.38–11.93)</td>
</tr>
<tr>
<td>During dry season&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17 (29)</td>
<td>66 (15)</td>
<td>2.27 (1.22–4.24)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay &gt;2 weeks&lt;sup&gt;d&lt;/sup&gt;</td>
<td>16/51 (31)</td>
<td>257/346 (74)</td>
<td>0.16 (0.08–0.30)</td>
</tr>
<tr>
<td>Bacteremia&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 (2)</td>
<td>261 (61)</td>
<td>0.01 (0.00–0.08)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>0 (0)</td>
<td>109 (25)</td>
<td>0.00 (0.00–0.19)</td>
</tr>
<tr>
<td>Death&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0 (0)</td>
<td>73 (17)</td>
<td>0.00 (0.00–0.32)</td>
</tr>
</tbody>
</table>

**NOTE.** aOR, adjusted OR; NS, not significant (P>.05).
<sup>a</sup> Included all variables in the “Demographic characteristic” section, performed using backward stepwise logistic regression.
<sup>b</sup> Symptoms duration, ≥2 months at time of presentation.
<sup>c</sup> Presentation between 16 May and 15 November.
<sup>d</sup> Patients who died were excluded from the analysis (n = 73). Data are missing for 7 patients in the primary skin melioidosis group and for 9 in the other melioidosis group.
<sup>e</sup> Eight patients who did not have blood cultures performed are included in the nonbacteremic group.
<sup>f</sup> Related to infection with *Burkholderia pseudomallei*.

Table 2. Comparison of risk factors for melioidosis, by primary melioidosis diagnosis.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Primary melioidosis diagnosis, no. (%) of patients</th>
<th>Univariate analysis</th>
<th>Multivariate analysis&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>Skin (n = 58)</td>
<td>Other (n = 428)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (16)</td>
<td>182 (43)</td>
<td>0.25 (0.12–0.52)</td>
</tr>
<tr>
<td>Excessive alcohol intake</td>
<td>12 (21)</td>
<td>181 (42)</td>
<td>0.35 (0.18–0.69)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>5 (9)</td>
<td>122 (29)</td>
<td>0.24 (0.09–0.60)</td>
</tr>
<tr>
<td>Chronic renal impairment</td>
<td>2 (3)</td>
<td>57 (13)</td>
<td>0.23 (0.06–0.98)</td>
</tr>
</tbody>
</table>

**NOTE.** aOR, adjusted OR; NS, not significant (P>.05).
<sup>a</sup> Included all variables shown in the table, as well as age ≤15 years and male sex, and was performed using backward stepwise logistic regression.
phocyte count \( (2.2 \times 10^9 \text{ vs. } 1.0 \times 10^9 \text{ cells/µL; } P < .001) \), and higher median serum albumin level \( (41.5 \times 10^6 \text{ vs. } 34.0 \times 10^6 \text{ cells/µL; } P < .001) \). Primary skin melioidosis was associated with positive serological test results for melioidosis \((\text{OR}, 2.48; 95\% \text{ CI}, 1.28–4.78)\) on univariate analysis. In the multivariate model, leukocytosis \((\text{aOR}, 0.13; 95\% \text{ CI}, 0.05–0.35)\), lymphopenia \((\text{aOR}, 0.30; 95\% \text{ CI}, 0.13–0.67)\), and hypoalbuminemia \((\text{aOR}, 0.13; 95\% \text{ CI}, 0.04–0.39)\) were all less common among patients in the primary skin melioidosis group (table 3).

The majority of patients (54 [93%] of 58) who presented with primary skin melioidosis had localized disease; however, 4 patients (7%; all adults) had primary skin melioidosis with evidence of disseminated disease. One patient (2%) with primary skin melioidosis was bacteremic, compared with 261 patients (61%) with other melioidosis \((P < .001)\). This patient received a diagnosis of type 2 diabetes at the time of melioidosis diagnosis and had secondary abscesses in her liver and lungs. One man with diabetes had splenic abscesses, and another man, with no risk factors for melioidosis, had secondary abscesses of the liver and spleen. Culture of a sputum sample of another patient was positive for \( B. pseudomallei \), despite a normal chest radiograph; this patient had the risk factors of diabetes, excessive alcohol intake, and chronic lung disease. Two of these 4 patients presented with chronic melioidosis. The skin lesions in these 4 patients with primary skin melioidosis plus disseminated disease were not overtly different from those of the 54 patients with localized primary skin melioidosis.

There were no episodes of septic shock and no deaths due to melioidosis in the group with primary skin melioidosis, compared with 25% and 17%, respectively, in the other group (for each analysis, \( P < .001 \)). Those with primary skin melioidosis were less likely to be hospitalized for >2 weeks \((\text{OR}, 0.16; 95\% \text{ CI}, 0.08–0.30)\) (table 1). Among those with primary skin melioidosis, there were no episodes of melioidosis recrudescence and only 1 episode of relapse—that is, septic arthritis 610 months after the initial presentation of a patient who was poorly compliant with the eradication phase of therapy (oral doxycycline).

The majority of patients (48 [83%] of 58) received both intravenous and oral antibiotics for their primary skin melioidosis. Nine patients (16%) with primary skin melioidosis received only oral antibiotics, and a 9-year-old girl received no antibiotic therapy (the lesion had healed by the time the diagnosis was confirmed). This girl’s serological test result was positive (indirect hemagglutination titer, 1:80 at diagnosis and 1:160 one month after diagnosis). Of those patients who received no intravenous antibiotics, 6 had no risk factors for melioidosis, 1 was diabetic, 2 consumed excessive amounts of alcohol, and 1 had chronic lung disease. All patients had a good outcome, and none experienced recrudescence or relapse of their melioidosis.

### DISCUSSION

Melioidosis is a severe infection that causes significant morbidity and mortality in northern Australia and Southeast Asia. Primary skin melioidosis at presentation accounted for 12% of our cases involving melioidosis, which is in keeping with the proportion of skin and soft-tissue melioidosis in other case series [1]. Patients with primary skin melioidosis were younger, had fewer risk factors for melioidosis, were more well at the time of presentation (assessed using the surrogate marker of laboratory results), and had better outcomes than those with other forms of melioidosis. They were also more likely than other patients with melioidosis to have chronic infection and, therefore, sometimes presented during the dry season.

Acquisition of melioidosis has been reported to occur through inoculation and inhalation and, much less commonly,
through ingestion, nosocomial, laboratory, sexual, and vertical transmission [6]. Periods of heavy rainfall have been associated with an increased number of cases of melioidosis, a greater proportion of presentations with pneumonia, and a higher mortality from melioidosis, presumably attributable to a shift toward inhalation of B. pseudomallei [17]. Although inhalation of B. pseudomallei is thought to cause more-severe disease, it is likely that inoculation of B. pseudomallei through the skin is the most common mode of acquisition [1]. Interestingly, an inoculating event was documented in only 25% of cases in northern Australia, with a mean incubation period of 9 days (range, 1–21 days) [18]. In our study, it is presumed that primary skin melioidosis occurred at the site of inoculation in the 58 affected people, with the infection remaining localized in all but 4 of these cases. A small number (10 [2%] of 428) of those with other melioidosis had multiple skin lesions as a result of hematogenous spread. Although it is assumed that infection was acquired by inoculation in most patients with other melioidosis, there was no residual evidence of cutaneous infection in the vast majority of these patients.

In addition, we reported 1 child with primary skin melioidosis (associated with an increasing indirect hemagglutination titer) who recovered with no treatment. It is possible that self-resolving cutaneous melioidosis accounts for some of the subclinical disease detected by seroprevalence surveys in endemic regions. Thus, it is likely that inoculation of B. pseudomallei through the skin can result in 3 outcomes: (1) subclinical disease (with or without seroconversion) or latent infection, (2) primary skin melioidosis at the site of inoculation (usually localized, with occasional dissemination), or (3) melioidosis involving other organ systems, presumably from early bacteremic spread from the inoculation but usually without concomitant infection at the site of inoculation. The factors determining which of these outcomes occurs after inoculation have not been fully elucidated; however, host factors, size of the inoculum, and differential virulence of bacteria are likely to play a role [1, 17]. Likewise, the risks and determinants of reactivation of melioidosis from a latent focus are not clear; however, reactivation that presents as cutaneous melioidosis has been reported after a latency period of 62 years in a World War II veteran [19].

In our study, children were more likely than adults to present with primary skin melioidosis. Previous studies have indicated that children with melioidosis are more likely to have localized disease, with a range of 46%–60% in Southeast Asia [8, 20, 21]. Even after adjustment for age, many of the risk factors for melioidosis—diabetes, excessive alcohol intake, and chronic lung disease—were less common in our study among those with primary skin melioidosis. The only measured risk factor that was not different between the 2 groups (i.e., those with primary skin or other melioidosis) was chronic renal failure, possibly because of the small number of patients. It has been observed elsewhere that patients who have melioidosis without typical risk factors had a lower risk of death (risk ratio, 0.08; 95% CI, 0.01–0.58) [5]. Patients with primary skin melioidosis in our study were much more likely to have no melioidosis risk factors, and this group had much better outcomes, with no episodes of septic shock or death due to melioidosis. Poor neutrophil function has been implicated in the pathogenesis of melioidosis [5, 14, 22, 23], and it may be that the intact neutrophil and other phagocyte function of those with no risk factors protected against both dissemination of disease and death.

Leukocytosis, lymphopenia, and hypoalbuminemia, all of which can be markers of severity of infection, were less common at the time of hospital admission among patients with primary skin melioidosis. Patients with primary skin melioidosis were more likely, as determined by univariate analysis, to have chronic melioidosis (duration of symptoms, ≥2 months) and positive serological test results for melioidosis at presentation. These findings reflect the localized, nonsevere nature of most cases of primary skin melioidosis.

The current recommended management for all forms of melioidosis in Australia, including skin melioidosis, is generally a minimum of 10–14 days of intravenously administered antibiotics (ceftazidime or a carbapenem) and a prolonged eradication course of oral antibiotics (e.g., 3 months of high-dose trimethoprim/sulfamethoxazole) [6, 11]. In our study, 9 (16%) of those with primary skin melioidosis received only oral antibiotics, and all patients had good outcomes. There have been no clinical trials of oral antibiotics alone for the treatment of localized melioidosis; however, patients with localized melioidosis (including skin and soft-tissue lesions and parotid abscesses) have had successful treatment with oral antibiotics alone (with or without incision and drainage of collections) [19–21, 24–26]. However, in 1 case report, this approach failed and intravenous antibiotics were required [27]. In addition, 1 child in our study recovered without antibiotic treatment or surgery. In a case series from Malaysia [20], cure without antibiotic treatment was documented in 4 children with localized melioidosis after incision and drainage of abscesses, but there are no other earlier reports of resolution of a diagnosed case of melioidosis without any treatment.

On a more cautionary note, complicated or disseminated melioidosis was detected in 4 patients in our study who presented with primary skin melioidosis. This highlights the importance of thorough investigation for disseminated melioidosis in all patients who present with primary skin melioidosis. We recommend that culture of blood samples, chest radiography, and abdominal CT be performed for all patients with melioidosis, even if the patient presents with a single skin lesion.
Those with disseminated melioidosis require treatment with intravenously administered as well as oral antibiotics.

In summary, our patients with primary skin melioidosis were younger, had fewer risk factors for melioidosis, were more likely to present with chronic and less severe disease, and had better outcomes, compared with those with other forms of melioidosis. Although there have been no clinical trials addressing the safety of omitting parenteral therapy for patients with localized skin melioidosis, several patients in our study received successful treatment with oral antibiotics alone, and this approach warrants further investigation.

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