Endemic Melioidosis in Tropical Northern Australia: A 10-Year Prospective Study and Review of the Literature


In a prospective study of melioidosis in northern Australia, 252 cases were found over 10 years. Of these, 46% were bacteremic, and 49 (19%) patients died. Despite administration of ceftazidime or carbapenems, mortality was 86% (43 of 50 patients) among those with septic shock. Pneumonia accounted for 127 presentations (50%) and genitourinary infections for 37 (15%), with 35 men (18%) having prostatic abscesses. Other presentations included skin abscesses (32 patients; 13%), osteomyelitis and/or septic arthritis (9; 4%), soft tissue abscesses (10; 4%), and encephalomyelitis (10; 4%). Risk factors included diabetes (37%), excessive alcohol intake (39%), chronic lung disease (27%), chronic renal disease (10%), and consumption of kava (8%). Only 1 death occurred among the 51 patients (20%) with no risk factors (relative risk, 0.08; 95% confidence interval, 0.01–0.58). Intensive therapy with ceftazidime or carbapenems, followed by at least 3 months of eradication therapy with trimethoprim-sulfamethoxazole, was associated with decreased mortality. Strategies are needed to decrease the high mortality with melioidosis septic shock. Preliminary data on granulocyte colony-stimulating factor therapy are very encouraging.

Melioidosis, or infection with *Burkholderia pseudomallei*, is endemic in southeast Asia and northern Australia [1–3]. In parts of northeastern Thailand, it is the most common cause of severe community-acquired sepsis [4]. The tropical “Top End” of the Northern Territory of Australia has a population of ~150,000 individuals in an area of 516,945 km² with 6200 km of coastline. Darwin (latitude, 12°S), which has a population of ~90,000 inhabitants, is the only city and is much closer to Jakarta, Indonesia, than to Sydney. One quarter of the Top End population is comprised of Aboriginals, many of whom live in small, remote communities. The summer monsoonal wet season (November through April) is followed by virtually no rain for 6 months.

The first reported case of melioidosis in a human patient in the Northern Territory occurred in 1960 [5], and melioidosis is now recognized as the most common cause of fatal community-acquired bacteremic pneumonia at Royal Darwin Hospital [6]. We have been prospectively studying all cases of melioidosis that have occurred in the Top End since October 1989 [7], and we present here the clinical data on 252 patients over a 10-year period.

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Table 1. Primary diagnoses and outcomes of 252 cases of melioidosis.

<table>
<thead>
<tr>
<th>Type of melioidosis diagnosed.</th>
<th>No. of patients</th>
<th>No. who died</th>
<th>Mortality rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With septic shock</td>
<td>37</td>
<td>31</td>
<td>84</td>
</tr>
<tr>
<td>Without septic shock</td>
<td>29</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Genitourinary infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With septic shock</td>
<td>5</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>Without septic shock</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Osteomyelitis and/or septic arthritis</td>
<td>5</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>With septic shock</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Without septic shock</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With septic shock</td>
<td>7</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>Without septic shock</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonbacteremic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>61</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Genitourinary infection</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin abscess</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Soft tissue abscess</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neurological</td>
<td>10</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Osteomyelitis and/or septic arthritis</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>252</td>
<td>49</td>
<td>19</td>
</tr>
</tbody>
</table>

NOTE. All data are no. of patients, unless otherwise indicated.

Results

During the 10 years of the study, we diagnosed 252 cases of confirmed melioidosis. The age of affected patients ranged from 16 months to 91 year (mean, 47 years; median, 49 years). Nine patients (4%) were children aged 16 months to 91 year (mean, 47 years; median, 49 years). Nine confirmed melioidosis. The age of affected patients ranged from...
Melioidosis, with only 1 fatality occurring in this group (2%), compared with 48 fatalities (31%) occurring in the group of 153 patients with 1 or more risk factors (RR for death, 0.08; 95% CI, 0.01–0.58; P = .0009).

Many patients had internal organ abscesses or other collections evident, as shown in table 3. Sometimes these were seen on CT as incidental findings separate from the primary diagnosis. Most striking was the presence of prostatic abscesses in 18% of men, usually as the primary diagnosis. The 6 patients with mediastinal masses had a widened mediastinum on chest radiographs and had collections involving mediastinal lymph nodes on CT scans. In contrast to prostatic abscesses, other internal collections usually resolved with medical therapy without drainage. In addition, 10 patients had osteomyelitis or septic arthritis develop after presentation with another primary diagnosis.

Discussion

As in parts of northeastern Thailand [4, 13], melioidosis is the most common cause of severe community-acquired pneumonia in the tropical north of the Northern Territory of Australia. Because of northeastern Thailand’s far greater population, more cases of melioidosis are seen each wet season in northeastern Thailand than in northern Australia. From 1987 through 1998, 1440 adults with melioidosis were admitted to Sappasitprasong Hospital in Ubon Ratchatani Province, Thailand [14]. Melioidosis is also relatively common in Malaysia [15] and Singapore [16]. Although melioidosis was originally described in patients from Burma (Myanmar) and was recognized in patients in Vietnam and Indonesia decades before cases were described in patients from Thailand and Australia [1], recent data on the importance of melioidosis in these countries are sparse.

To our knowledge, this is the largest prospective study of melioidosis outside Thailand, and it enables important comparisons regarding clinical presentations, risk factors, and treatment. In this study, 46% of cases were bacteremic, and the frequency of genitourinary presentation, the distinct but uncommon encephalomyelitis syndrome seen in tropical Australia. In this study, there have been no cases of parotitis, whereas in Thailand, it accounts for up to 40% of cases of melioidosis in children [20, 21]. This finding may simply be a reflection of the low number of children in our study, or it may relate to epidemiological or behavioral factors yet to be elucidated in Thailand.

Prostatic melioidosis has been well described [22], but the presence of prostatic abscesses in 18% of men is far higher than that reported elsewhere. This in part reflects increased ascertainment; early in the study, concerns about delayed clinical improvement caused by undiagnosed internal abscesses resulted in a policy of routinely performing abdominal and pelvic CT scans on all patients with melioidosis. An earlier study from the Northern Territory of Australia showed that genitourinary melioidosis was common in the region and attributed this to sexual transmission [23]. However, further comparative clinical and epidemiological studies are required to confirm any regional differences and to define the nature of transmission of B. pseudomallei in these circumstances.

The neurological presentations of melioidosis in northern Australia have been summarized and discussed recently [12]. The clinical presentations of brain stem encephalitis with peripheral motor weakness, including acute flaccid paraparesis, are likely to be due at least in part to direct bacterial invasion of the brain and spinal cord, although involvement of a bacterial neurotoxin has also been suggested [9]. It is likely that these syndromes occur elsewhere, but further studies are needed to exclude regional organism differences in tissue tropism.

This prospective study has enabled characterization of the frequency of unusual foci of infection previously described as case reports, such as adrenal abscesses [24–26] and mycotic aneurysms [27–29]. The importance of diabetes as the most commonly associated risk factor for melioidosis has been clearly documented in previous studies [4, 13, 15, 16, 30, 31]. Chronic renal disease is also a recognized risk factor [4, 13, 15, 16, 31]. The importance of excessive alcohol intake as a risk factor for melioidosis was recognized in an earlier study from the Northern Territory of Australia [32] and also in a study from north Queensland [30], but this finding is not apparent in studies from Thailand [4, 13, 31], and it appears to be only

<table>
<thead>
<tr>
<th>Table 3. Prevalences of internal organ abscesses and other collections in 252 patients with melioidosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal organ abscess or other collection</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Prostate</td>
</tr>
<tr>
<td>Spleen</td>
</tr>
<tr>
<td>Kidney</td>
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<tr>
<td>Mediastinal mass</td>
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<tr>
<td>Liver</td>
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<tr>
<td>Adrenal</td>
</tr>
<tr>
<td>Psoas</td>
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<tr>
<td>Cervical lymph node</td>
</tr>
<tr>
<td>Mycotic aneurysm</td>
</tr>
<tr>
<td>Pericardial collection</td>
</tr>
</tbody>
</table>

* Male patients only.
a minor factor in Malaysia [15] and Singapore [16]. Although this may reflect the differences in alcohol consumption by the various populations, further comparative studies are required to explain the differences.

The association of melioidosis with the consumption of kava has recently been recognized in Australia [7]. Kava, an extract of the root of the plant *Piper methysticum*, was introduced as an alternative to alcohol by missionaries to remote Aboriginal communities. Whether consumption of kava is an independent risk factor for melioidosis and other infectious diseases is currently being studied.

Elucidation of the nature of the predisposition to melioidosis in those with recognized risk factors has important implications for therapy. Serologic studies suggest that the majority of individuals exposed to *B. pseudomallei* have asymptomatic infection [3, 33]. *B. pseudomallei* is a facultative intracellular pathogen and can be resistant both to lysis by human serum and, once phagocytosed, to killing by polymorphonuclear leukocytes (PMNL) and macrophages [34, 35]. Recent work indicates that bactericidal activity is correlated with the production of nitric oxide by interferon γ-activated macrophages, with reactive nitrogen intermediates’ killing being more important than reactive oxygen intermediates–dependent mechanisms [36]. Despite these findings, there is a lack of published data indicating that clinical disease with *B. pseudomallei* infection is more severe when there is coinfection with HIV, suggesting that CD4 cell–mediated defense mechanisms may not be of critical importance in the immune response to *B. pseudomallei*.

It is possible that the predisposition to melioidosis in individuals with diabetes, those with excessive alcohol intake, and those with chronic renal disease relates primarily to impaired PMNL functions, such as mobilization, delivery, adherence, and ingestion. Clinical and laboratory observations have demonstrated that PMNL function is impaired in patients with diabetes, [37, 38], alcoholics [39–41], and individuals with chronic renal disease [42–44]. The majority of diabetic patients in our study had hyperinsulinemia (type 2), making the laboratory observation that insulin suppresses growth of *B. pseudomallei* [45] an unlikely explanation for the predisposition of patients with diabetes to melioidosis.

On the basis of the possible primary role of PMNL function in containing *B. pseudomallei*, we have recently begun treating patients with melioidosis and strictly defined septic shock [8] with granulocyte colony-stimulating factor (G-CSF). All 6 such patients treated with G-CSF to date (3 in this study and 3 treated subsequently) have survived, in comparison with only 1 survivor among the previous 21 patients with melioidosis septic shock who were ventilated in intensive care (Fisher exact test, *P* < .0001; B. Currie, D. Stephens, and D. Fisher, unpublished data). Although these data are only preliminary and comprise an uncontrolled retrospective comparison, they are very encouraging. Further data are needed to confirm that patients with melioidosis are one defined subgroup of patients with severe sepsis who may benefit from G-CSF therapy [46].

In some patients, the persistence of positive *B. pseudomallei* cultures for prolonged periods, despite therapy with the most-bactericidal agents (carbapenems or ceftazidime), is not fully explained; however, it probably reflects the survival of organisms in abscesses and inside cells. It may also reflect defective PMNL function. This is one reason, in addition to the theoretical benefits of decreasing the emergence of antimicrobial resistance, why some centers initially added a second antibiotic with better intracellular penetration, such as trimethoprim/sulfamethoxazole (TMP-SMZ) [47]. Another possible factor in organism persistence is the potential for *B. pseudomallei* to exist in a biofilm, which may confer in vivo resistance to many antibiotics [48].

Despite the persistence of *B. pseudomallei* in some patients, the use of ceftazidime as initial therapy has halved the mortality of severe melioidosis in those surviving beyond 48 h [49]. A recent large study from Thailand has shown imipenem to be at least as effective as ceftazidime for initial therapy [19]. However, current therapy with these antibiotics is still inadequate for melioidosis septic shock, as shown by the mortality rate of 86% in our series, despite the availability of sophisticated intensive care facilities. This remains similar to the findings of an earlier Australian study [30] and to those from studies from Thailand [4, 19, 49], Malaysia [15], and Singapore [16]. Studies of G-CSF and other adjuvant therapies are needed to determine whether the terrible outcomes in those who are critically ill with melioidosis can be significantly improved. Thailand is probably the only country with enough cases of severe melioidosis to undertake a prospective randomized, controlled study of G-CSF. However, resource limitations, as noted in the imipenem study from Thailand [19], make it unlikely that such expensive therapies will be obtainable for many patients in countries in which melioidosis is endemic.

Other than the 3 patients who were successfully treated with G-CSF, the decreased mortality in the second half of our study and the overall mortality of only 19% of patients reflect the minimization of mortality in those patients without septic shock. Treatment usually consisted of an intensive phase (at least 14 days) of iv antibiotics—primarily ceftazidime but, more recently, meropenem or imipenem for critically ill patients. This was followed by an eradication phase of oral antibiotics, which usually consisted of monotherapy with doxycycline (adult dosage, 200 mg/day) or TMP-SMZ (adult dosage, 320 mg of TMP b.i.d. and 1600 mg of SMZ b.i.d.) for at least 3 months. We also added TMP-SMZ to the intensive phase, as is done in some centers in Thailand [47].

Minimization of treatment failure and relapse in patients with melioidosis is dependent on an adequate duration of initial intensive therapy and adherence to an adequate eradication phase [50]. In those patients well enough for early discharge from the hospital, we give outpatient infusions (adult dose, 6
g of ceftazidime over 24 h) through a peripherally inserted central catheter with an elastomeric infusion device (Baxter, Sydney, Australia). This is occasionally continued for 8 weeks or longer for patients such as those with deep tissue or organ collections, osteomyelitis, septic arthritis, or extensive pulmonary involvement. Regular follow-up to ensure compliance with eradication therapy is critical and is a major component of our program.

After noting some failures of doxycycline eradication therapy, we now use TMP-SMZ as first-line therapy for eradication of *B. pseudomallei* after the initial intensive phase. A recent study from Thailand confirmed that eradication therapy with doxycycline was inferior to combination therapy with chloramphenicol, TMP-SMZ, and doxycycline [51]. However, use of the traditional combination antibiotics may be problematic because of side effects and problems with compliance. Further studies done in Thailand should ascertain whether eradication with combination antibiotics is preferable to monotherapy with TMP-SMZ. To date, we have had only 1 failure of eradication in >60 patients treated with TMP-SMZ monotherapy.

In summary, we now focus on early treatment with meropenem for those patients who are critically unwell; G-CSF is added if criteria for septic shock are present. We emphasize the importance of at least 14 days of initial intensive therapy with ceftazidime or meropenem or imipenem, and we arrange close supervision and follow-up, wherever possible, for at least 3 months of eradication therapy with TMP-SMZ, including plans for default action. Internal abscesses and other collections are sought with CT imaging, with prostatic abscesses usually needing drainage.

Acknowledgments

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