Clinical Characteristics and Outcome of Severe Melioidosis Requiring Intensive Care*

Kenneth P. W. Chan, MBBS, MMed, FCCP; Jenny G. H. Low, MBBS; Jagadeesan Raghuram, MBBS; Stephanie M. C. Fook-Chong, MSc; and Asok Kurup, MBBS

Study objective: To describe the clinical characteristics and outcome of patients with severe melioidosis requiring intensive care.

Design: Retrospective chart review.

Setting: Two ICUs from a tertiary-care teaching hospital.

Patients: Twenty-seven adult ICU patients with microbiologically documented melioidosis.

Interventions: None.

Measurements and results: The median age was 59 years with a male preponderance (26:1). Twenty patients (74%) had medical comorbidities, with diabetes mellitus being the most common (59.3%). Almost all patients (96.3%) were bacteremic. Twenty patients (74.1%) presented with pneumonia. Twenty patients (74.1%) were in septic shock, and 16 patients (59.3%) had ARDS. Twelve patients (44.4%) required hemodialysis. The patients had a median of three organ dysfunctions, and the median APACHE (acute physiology and chronic health evaluation II) score was 27. The overall mortality was 48.1%. Mortality among patients with septic shock was 60%. The median ICU length of stay for survivors and nonsurvivors was 11 days and 2 days, respectively. Multivariate analysis revealed that the number of organ dysfunctions is an independent predictor of mortality (odds ratio, 8.2; 95% confidence interval, 1.3 to 51.4).

Conclusions: The outcome of severe melioidosis requiring intensive care is poor, with death being predicted by the number of organ dysfunctions.

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Key words: acute physiology and chronic health evaluation II; intensive care; melioidosis; mortality; organ dysfunction; sepsis

Melioidosis is an infectious disease caused by Burkholderia pseudomallei, a soil organism that is endemic in many parts of South East Asia and northern Australia.1–5 It is a common cause of community-acquired sepsis in these parts of the world. Indeed, in northeastern Thailand, melioidosis accounts for 20% of all community-acquired septicemic episodes.4 Its manifestations range from a chronic debilitating illness to overwhelming sepsis with abscess formation and a high mortality rate of up to 86% in patients with septic shock.2,5

In Singapore, the incidence of melioidosis is increasing, with a mean annual incidence of 1.7 per 100,000 population.6,7 The overall mortality remains high, ranging from 19 to 60%, with many of these patients dying in the ICU.6,7 It is one of the most common causes of severe community-acquired pneumonia requiring intensive care in Singapore.8,9

While there have been many large case series reporting the epidemiology and outcomes of melioidosis in general, there have been no publications specifically studying the subgroup of patients who require intensive care. We report our experience with all critically ill patients with a diagnosis of melioidosis over a 7-year period (January 1996 until December 2002) who were admitted to the ICU at the Singapore General Hospital.

Materials and Methods

Selection of Patients

Patients were identified by review of a computerized database of microbiology records for positive culture findings of B pseudomallei isolated from any site during the period from January 1, 1996, to December 31, 2002. Patients were included if their medical record showed an admission to any ICU within our hospital related to the episode of melioidosis, eg, if the patients required mechanical ventilation for acute lung injury or inotropic support for septic shock. This study was approved by the hospital Ethics Committee, and the need for informed consent was waived.

Data Collection and Definitions

Specific information was recorded using a standardized data collection form. This included baseline demographic, laboratory, and microbiologic data. Possible risk factors for melioidosis, eg, diabetes mellitus, chronic renal failure, and occupational exposure to soil, were identified.10 APACHE (acute physiology and chronic health evaluation) II and organ dysfunction scores were collected prospectively as part of a separate ongoing project.11

Abbreviations: APACHE = acute physiology and chronic health evaluation; ARF = acute renal failure; CI = confidence interval; LOS = length of stay; OR = odds ratio
Outcomes collected included 28-day mortality, ICU and hospital length of stay (LOS), and relapse rates.

We defined preexisting renal failure as a previously recorded serum creatinine level of > 150 μmol/L (1.7 mg/dL). Soil exposure referred to any occupation or hobby that would involve prolonged or recurrent contact with soil. Examples include gardening, farming, camping, and construction work. Excessive alcohol intake was defined as more than six standard drinks (60 g of alcohol) for men and more than four standard drinks (40 g of alcohol) for women.² The wet season in Singapore is between November and March annually, corresponding to the Northeast monsoon.

We defined septic shock as sepsis with a systolic BP of < 90 mm Hg despite adequate fluid resuscitation or the use of inotropes. ARDS was defined according to the American-European Consensus Conference criteria.¹² Acute renal failure (ARF) was defined as a doubling of serum creatinine in patients with preexisting renal failure or a serum creatinine level > 300 μmol/L (3.4 mg/dL) in patients with normal baseline renal function.

Organ dysfunction was defined based on an adaptation of the definitions proposed by Fagon and coworkers (Appendix).¹³ Appropriate empiric antibiotic therapy referred to the ongoing use of antibiotics with known clinical activity against *B pseudomallei* at the time of microbiologic confirmation. Examples of these include imipenem, ceftazidime, chloramphenicol, trimethoprim-sulfamethoxazole, doxycycline, and amoxicillin-clavulanic acid.

**Statistical Analysis**

Statistical analysis was performed using statistical software (Statistical Package for Social Sciences, version 10.0.5; SPSS; Chicago, IL). Comparisons of continuous variables between survivors and nonsurvivors were performed using the Mann-Whitney U test. Categorical variables were compared using either the χ² test or Fisher Exact Test. Multivariate analysis was performed using a forward stepwise logistic regression analysis. Factors that were statistically significant by univariate analysis and believed to be biologically plausible were entered into the model.

**RESULTS**

During the 7-year period, there were 133 patients admitted to Singapore General Hospital with melioidosis. Of these, 27 patients (20.3%) required admission to ICU and formed the study population. Twenty-five patients were admitted to the medical ICU, and 2 patients were admitted to the cardiothoracic ICU. The baseline characteristics and demographics features are shown in Table 1. The median age was 59 years, and almost all (96.3%) were male. The proportion of patients classified by ethnic origin was similar to the ethnic composition of Singapore.¹⁴ Seventy-four percent of patients had medical comorbidities, and 85.2% had identifiable risk factors for melioidosis. Diabetes mellitus was the chief predisposing condition, present in 16 patients (59.3%). As a comparison, in a cross-sectional study performed at another hospital in 1990, diabetes mellitus was present in 13.1% of all hospitalized patients. Three patients (11.1%) had preexisting renal failure. Of the five patients with soil exposure, two were gardeners, two were construction workers, and one was a student who went hiking and camping approximately 1 week prior to the onset of symptoms. As this was a retrospective chart review, we could not further characterize the exact nature and extent of the soil exposure. We also could not exclude significant soil exposure in the other patients.

Seventeen patients (62.9%) were admitted to the ICU because of both septic shock and respiratory failure requiring mechanical ventilation. Five patients (18.5%) were admitted for respiratory failure only, and three patients (11.1%) were admitted for septic shock alone. Overall, 20 patients (74%) had septic shock and 22 patients (81.5%) required mechanical ventilation. Twelve patients (44.4%) required continuous venovenous hemofiltration. One patient was admitted after cardiopulmonary resuscitation and died soon after. One other patient was admitted to the cardiothoracic ICU for monitoring following an intraoperative myocardial infarction from excessive blood loss. This patient was undergoing a repair of a leaking mycotic aneurysm of the abdominal aorta due to melioidosis. Six patients (22.2%) were admitted directly to ICU from the emergency department. Of the remaining patients, the median duration in the general ward before admission to the ICU was 4 days (range, 1 to 10 days). There was a trend toward an increased mortality in patients who were admitted to the ICU directly (66.7% vs 40.0%, p = 0.365). The median number of organ dysfunctions at the time of ICU admission was 3, and the median APACHE II score was 27.

All but one of our patients (96.0%) had bacteremia. Of these, 20 patients (74.1%) presented with pneumonia, 2

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**Table 1—Demographic and Baseline Characteristics of 27 Patients With Melioidosis Requiring Intensive Care***

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>59 (20–77)</td>
</tr>
<tr>
<td>Male gender</td>
<td>26 (96.3)</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>18 (66.7)</td>
</tr>
<tr>
<td>Malay</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Indian</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Risk factors for melioidosis</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td>Occurrence during wet season</td>
<td>10 (37.0)</td>
</tr>
<tr>
<td>Soil exposure†</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Excessive alcohol intake</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Thalassaemia</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>None identified</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Presence of medical comorbidity</td>
<td>20 (74.1)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>20 (74.1)</td>
</tr>
<tr>
<td>ARDS</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>26 (96.3)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>27 (9–47)</td>
</tr>
<tr>
<td>No. of organ dysfunctions</td>
<td>3 (1–5)</td>
</tr>
<tr>
<td>Glycosylated hemoglobin among diabetics, %</td>
<td>8.5 (5.7–14)</td>
</tr>
</tbody>
</table>

*Data are presented as median (range) or No. (% of patients).

†Any occupation or hobby that would involve prolonged or recurrent contact with soil, such as gardening, farming, camping, and construction work.
patients had both splenic and liver abscesses (1 patient also had a prostatic abscess), 2 patients had mycotic aneurysms, and 3 patients had no obvious focus of infection despite a careful search utilizing clinical evaluation and CT of the abdomen and pelvis. Of the patients presenting with pneumonia, six patients (30.0%) had metastatic foci elsewhere (two patients had septic arthritis, four patients had splenic abscesses, and two patients had skin abscesses). This was the first episode of melioidosis for all but one of the patients. This patient is the one described above, whose relapse led to a mycotic aneurysm. The results of serologic testing, using an indirect hemagglutination method against melioidin-sensitized turkey RBCs, were positive in 19 of 22 patients (86.4%). The sera of our patients were sent to a centralized laboratory within the Department of Microbiology, National University of Singapore. We used a titer of 1:16 as our cutoff for a result to be positive.

Only nine patients (33.3%) received appropriate empiric antibiotic therapy. Twenty-five of our patients (92.6%) eventually received a ceftazidime-based regimen, usually in combination with doxycycline (40%), co-trimoxazole (12%), or both (24%). One other patient received imipenem and co-trimoxazole. This patient’s illness was complicated by a perforated duodenal ulcer with peritoneal soilage, and broader-spectrum coverage to include Gram-negative enteric organisms and anaerobes was indicated. One other patient never received appropriate antibiotic therapy for melioidosis, as the diagnosis was made postmortem. Five of our patients (18.5%) required surgery. Two patients had repairs of mycotic aneurysms, and one other patient underwent an arthroscopic washout of the left knee for septic arthritis. One patient underwent an exploratory laparotomy for presumed appendicitis, and the final patient is the one described above, with a perforated duodenal ulcer. All five patients survived.

Twenty-eight day mortality was 48.1%. Sixty percent of patients with septic shock died. Of the patients who presented with pneumonia, the mortality rate was 45.4%. For the patients who died, the median ICU LOS was 2 days (range, 0 to 13 days). The median ICU and hospital LOS among the survivors was 11 days (range, 1 to 26 days) and 35 days (range, 9 to 112 days), respectively. Among the survivors, five patients (35.7%) were unavailable for follow-up (two patients because they were foreigners who returned to their home countries). Of the remaining nine patients, two patients relapsed (22.2%) at 10 months and 12 months, respectively. One patient relapsed because of noncompliance to maintenance therapy with co-trimoxazole. He was treated successfully with ceftazidime and doxycycline. The reason for relapse was unknown in the other patient, who died after shock and multiorgan failure developed.

The results of the univariate analysis are shown in Table 2. Characteristics associated with risk of death were ARDS (odds ratio [OR], 6.67; 95% confidence interval [CI], 1.04 to 42.43), ARF (OR, 27.5; 95% CI, 2.62 to 289.13), number of organ dysfunctions, and APACHE II score. Patients with three or more organ dysfunctions had a much higher mortality rate compared to patients who had up to two organ dysfunctions (81.8% vs 30.0%; OR, 10.5; 95% CI, 1.4 to 81.1). These four variables were then entered into a multiple regression model and analyzed utilizing a forward stepwise method (Wald). Only the number of organ dysfunctions remained an independent predictor of mortality (OR of 8.2 for every increase in number of organ dysfunctions; 95% CI, 1.3 to 51.4; p = 0.02).

**DISCUSSION**

To our knowledge, this study is the first to specifically describe the clinical characteristics of patients with melioidosis requiring intensive care. Almost all of the patients

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**Table 2—Comparison Between Survivors and Nonsurvivors With Regard to Demographic, Laboratory, and Potentially Important Variables**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors (n = 14)</th>
<th>Nonsurvivors (n = 13)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>59 (30–72)</td>
<td>59 (20–77)</td>
<td>0.88</td>
</tr>
<tr>
<td>Male gender</td>
<td>13 (92.9)</td>
<td>13 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (71.4)</td>
<td>6 (46.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>Glycosylated hemoglobin among diabetics, %</td>
<td>8.4 (5.7–14)</td>
<td>10.4 (7.0–12)</td>
<td>0.02†</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>0</td>
<td>3 (23.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>0</td>
<td>2 (15.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Presence of medical comorbidity</td>
<td>11 (78.6)</td>
<td>9 (69.2)</td>
<td>0.68</td>
</tr>
<tr>
<td>Direct admission to the ICU</td>
<td>2 (33.3)</td>
<td>4 (66.7)</td>
<td>0.365</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>13 (92.9)</td>
<td>13 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Shock</td>
<td>8 (57.1)</td>
<td>12 (92.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>ARDS</td>
<td>6 (42.9)</td>
<td>10 (76.9)</td>
<td>0.03†</td>
</tr>
<tr>
<td>ARF</td>
<td>1 (7.7)</td>
<td>10 (76.9)</td>
<td>0.02†</td>
</tr>
<tr>
<td>No. of organ dysfunctions</td>
<td>2 (1–3)</td>
<td>3 (1–5)</td>
<td>0.01†</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>22 (9–30)</td>
<td>30 (24–47)</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>Appropriate empiric antibiotic therapy</td>
<td>3 (21.4)</td>
<td>4 (30.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Use of combination antibiotics for treatment</td>
<td>13 (92.9)</td>
<td>8 (61.5)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*Data are presented as median (range) or No. (% of patients).
†Statistically significant (p < 0.05).
(96.3%) were bacteremic, 74.1% had septic shock, 59.3% had ARDS, and 44.4% required continuous renal replacement therapy. The patients were severely ill, with a median APACHE II score of 27 and a median of three organ dysfunctions. Not surprisingly, almost half of the patients (48.1%) died. This is similar to the predicted mortality using the APACHE II model, which was 46.4%, as well as other published data17,18 on outcome of community-acquired bacteremia in critically ill patients. For example, in a large, prospective, multicenter study of community-acquired bacteremia in ICU patients by Valles and coworkers,18 the crude mortality rate was 41.5%. Factors in that study that were associated with mortality included the APACHE II score, septic shock, and inappropriate antibiotic treatment.

With regard to the clinical features and patient demographics, our study population representing a subset of critically ill patients with melioidosis was generally similar to previously published series4,7,19 of all patients with melioidosis. The patients were usually middle aged, had underlying medical comorbidities, and diabetes mellitus was the major predisposing factor. Nevertheless, there were two major differences that are worth highlighting.

Firstly, we were impressed by the overwhelming male preponderance in our series (male to female ratio of 26:1). This is much higher than the ratios published in other studies2,7,19 (range, 3.2:1 to 4.5:1). Also, when we examined our data for all patients who received a diagnosis of melioidosis during the study period, we found a male to female ratio of only 6:1. Why this discrepancy occurred is not apparent. It is interesting to note, however, that in a large epidemiologic study20 of sepsis in the United States, men were more likely to have sepsis than women (mean annual relative risk, 1.28; 95% CI, 1.24 to 1.32). The reason for this is unclear, although preliminary research by Hubacek and coworkers21 suggest that this gender-specific predisposition to sepsis may be genetic. They found that the presence of certain lipopolysaccharide binding protein genotypes with a less common Gly98 allele was associated with sepsis in males, a finding not repeated in females.

Secondly, we found that our ICU population had a higher incidence of bacteremia (96.3%) compared to the incidence of bacteremia in all patients with melioidosis. For example, in a prospective study over 10 years, Currie et al2 found that 46% of their cohort of all-comers with melioidosis was bacteremic. An epidemiologic study7 from Singapore of similar design found the rate of bacteremia to be 39.7%. In both these studies, bacteremia was associated with a higher mortality rate. As patients in the ICU would generally have a greater severity of illness and mortality rate, a higher incidence of bacteremia was not unexpected.

It was noteworthy that patients who presented with pneumonia had a mortality rate of 45.4%. This compared favorably with two previous studies8,9 of community-acquired pneumonia in the ICU from Singapore, both reporting a mortality of 100% among patients with melioidosis. We found it difficult to compare these previous studies (both performed in the early 1990s) with the present cohort, as the periods under study were different, and we have no comparable information with regard to severity of illness. We initially postulated that our better results could be due to better recognition of the prevalence of melioidosis in our region and, consequently, the use of ceftazidime empirically for severe community-acquired pneumonia. However, we found that only 20% of our patients who presented with pneumonia received appropriate antibiotics empirically. There was also no consistent trend in mortality rate from the beginning of the study period until the end, which could possibly have reflected better ICU care.

Our study was mainly limited by our small sample size. As such, our study was inadequately powered to examine the influence of certain characteristics. For example, septic shock was found to be associated with mortality in at least two other studies.5,7 Currie and coworkers2 found a mortality of 86% in patients with septic shock, as compared to an overall mortality of 19%. We found a trend toward an increased mortality rate in patients with septic shock, but this was not statistically significant (Table 2). Besides this, inappropriate empiric antibiotic therapy was not found to be associated with mortality in our study. This is in contradistinction with several other studies18,22–23 in which inappropriate empiric antibiotics have been clearly shown to be an independent risk factor for mortality in community-acquired as well as nosocomially-acquired bloodstream infections. Again, our results are possibly due to the limited sample size.

The rate of appropriate empiric antibiotic administration in our study cohort was disappointingly low. Overall, only one in three patients received appropriate empiric antibiotics. Among patients who presented with pneumonia, this rate dropped to 20%. This is likely due to the fact that the predominant clinical features of fever, tachycardia, cough, and dyspnea can be similar to other forms of sepsis and pneumonia. As such, underrecognition remains an issue that needs to be addressed, especially in endemic regions. More research is also needed to discriminate melioidosis from other causes of severe sepsis.

In conclusion, severe melioidosis requiring ICU care is a devastating illness with a high mortality rate. Patients are usually male, have bacteremia, and have multiorgan involvement. The prognosis is similar to other forms of severe sepsis, with death predicted by the number of organ dysfunctions.

APPENDIX

The following definitions of organ dysfunctions are adapted from Fagon et al.13

Respiratory dysfunction (presence of one or more of the following):

1. $\text{PaO}_2 < 60 \text{ mm Hg}$ on fraction of inspired oxygen of 0.21, or
2. need for ventilatory support.

Cardiovascular dysfunction (presence of one or more of the following, in the absence of hypovolemia):

1. systolic arterial pressure $< 90 \text{ mm Hg}$ with signs of peripheral hypoperfusion, or
2. continuous infusion of vasoressor or inotropic agents required to maintain the systolic pressure $> 90 \text{ mm Hg}$.
Renal dysfunction (presence of one or more of the following, excluding patients receiving long-term dialysis before hospital admission):
(1) serum creatinine level > 300 μmol/L (3.4 mg/dL),
(2) urine output < 500 mL/24 h or < 180 mL/8 h, or
(3) need for hemodialysis or peritoneal dialysis.

Neurologic dysfunction (presence of one or more of the following):
(1) Glasgow coma scale ≤ 6 (in the absence of sedation at any one point in day), or
(2) sudden onset of confusion or psychosis.

Hepatic dysfunction (presence of one or more of the following):
(1) serum bilirubin level > 100 μmol/L (5.8 mg/dL), or
(2) alkaline phosphatase level more than three times normal.

Hematologic failure (presence of one or more of the following):
(1) hematocrit ≥ 20%.
(2) WBC count < 2,000/μL, or
(3) platelet count < 40,000/μL.

ACKNOWLEDGMENT: We are indebted to Mrs. Tan Mee Lee and Associate Professor Yap En-Hian for assistance in review and collation of microbiologic records, and Dr. Tan Keng Leong for the development and maintenance of the ICU database of severity scores and outcomes.

REFERENCES

Alkaptonuria Diagnosed by Flexible Bronchoscopy*

Joseph G. Parambil, MD; Craig E. Daniels, MD; Kenton J. Zehr, MD, FCCP; and James P. Utz, MD, FCCP

A 68-year-old white man was evaluated for failure to wean from mechanical ventilation after cardiac surgery. Bronchoscopy performed prior to percutaneous dilatational tracheotomy revealed circumferential...