Ten-year experience of *Burkholderia pseudomallei* infections in a Singapore Tertiary Hospital

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ABSTRACT

Background: *Burkholderia pseudomallei* is endemic in the tropics and associated with high mortality. We performed a retrospective study analyzing the clinical and microbiologic features of melioidosis, and predictors of mortality. Patients with culture-positive melioidosis from 2006-2016 were identified from microbiologic records.

Methods: Clinical data including demographics, treatment and outcomes were extracted from medical records. Categorical variables were compared using $\chi 2$ test or Fisher exact test while continuous variables were compared using Student's t-test or Mann-Whitney U test.

Results: Forty-three cases of melioidosis were identified. Presentations included fever (41.9%), respiratory symptoms (20.9%) and joint swelling (9.3%). 76.7% were bacteremic and 69.7% were culture-positive from a non-blood source. Mean time from presentation to positive microbiological data was 5.1 ± 6.4 days. Infection sites included pulmonary (62.8%), spleen (27.9%), skin/soft tissue (25.6%) and bone/joint (25.3%). Antibiotic susceptibility were as follows: ceftazidime (97.5%), imipenem (100.0%), trimethoprim-sulfamethoxazole (92.1%), amoxicillin-clavulanate (94.7%), doxycycline (94.7%). Mean time from presentation to melioid-active coverage was 6.8 ± 9.1 days. Thirty-day all-cause mortality occurred in 9 patients (from first positive culture); 1 patient died within 5 months. Univariable analysis associations with 30-day all-cause mortality were: intensive care unit (ICU) admission (OR 26.3, 95% CI 4.0-173.1, *P* <0.01), mechanical ventilation *(*OR 15.0, 95% CI 2.6-85.0, *P*<0.01), higher median Pitt Bacteremia Score (PBS) (4.0 vs 2.0; *P* <0.01), receipt of ceftazidime (vs a carbapenem) as primary induction antibiotic therapy (OR 0.2, 95% CI 0.03-0.91, *P*=0.047) and not receiving melioidosis-active induction intravenous antibiotics (*P*=0.04). Multivariable analysis found ICU stay to be an independent predictor for 30-day mortality (*P* = 0.018, OR 12.1 95% CI 1.5-96.0).

Conclusions: ICU admission, a high PBS, and in particular, receipt of mechanical ventilation may help identify patients with high mortality risk. Delays in melioid-active therapy were not uncommon. Prompt recognition of melioidosis and early institution of active therapy, especially in the critically ill, may reduce mortality.

BACKGROUND

- *Burkholderia pseudomallei* is a gram-negative saprophytic soil endemic in Singapore and the tropics
- *Burkholderia pseudomallei* infections are associated with high mortality
- We performed a retrospective study analyzing
  - Clinical and microbiologic features of melioidosis
  - Predictors of mortality

METHODS

- Culture-positive melioidosis (from blood and non-blood sources) patients between 2006-2016 were identified from microbiologic records
- Clinical data including demographics, treatment and outcomes were extracted from medical records
- Categorical variables were compared using $\chi 2$ test or Fisher exact test
- Continuous variables were compared using Student's t-test or Mann-Whitney U test
- *P* values <0.05 were regarded as statistically significant
- Multivariable backward logistic regression was performed for variables with *P* < 0.2
- All data was analyzed using SPSS

RESULTS

See Table 1 for summarised key points

(A) Demographic Data

- Forty-three cases of melioidosis were identified
- Median age of presentation was 60.0 years old. (IQR 51.0 – 68.5)
- Patient ethnicity were as follows: Chinese (65.1%), Indians (20.9%), Malays (14.0%)
- Majority of patients were male (83.7%)
- Presentations included fever (41.9%), respiratory symptoms (20.9%) and joint swelling (9.3%)
- Thirty four patients (79.1%) were diabetic, with mean glycated haemoglobin (HbA1C) level at presentation of 10.1%
- Diabetes mellitus was not significantly associated with 30-day mortality (OR 0.4, 95% CI 0.3 – 2.2, *P* = 0.37)

(B) Microbiological data

- 76.7% were bacteremic
- 69.7% were culture-positive from a non-blood source
- Culture-positive infection sites included pulmonary (62.8%), spleen (27.9%), skin/soft tissue (25.6%) and bone/joint (25.3%)
- Mean time from presentation to positive microbiological data was 5.1 ± 6.4 days
- Mean time from presentation to melioidosis-active coverage was 6.8 ± 9.1 days
- Antibiotic susceptibility were as follows: Ceftazidime (97.5%), Imipenem (100.0%), Trimethoprim-sulfamethoxazole (92.1%), Amoxicillin-clavulanate (94.7%), Doxycycline (94.7%)

Table 1: Important clinical features of Melioidosis patients[1]

	All Patients (n=43)	Patients who lived (n=34)	Patients who died (n=9)	Alive vs Dead	
				P value	OR (95% CI)
Past Medical Conditions					
Diabetes mellitus, no. (%)	34 (79.1)	28 (82.4)	6 (66.7)	0.37	0.4 (0.3 – 2.2)
Mean HbA1C at presentation, no. (SD)	10.1 (3.0)	10.0 (2.8)	10.4 (3.9)	0.77[2]	-
Disease Characteristics					
Any positive blood cultures, no. (%)	33 (76.7)	25 (73.5)	8 (88.9)	0.66	2.9 (0.3–26.4)
Mean time from presentation to any positive culture, days (S.D)	5.1 ± 6.2	5.2 ± 6.5 (n=30)	4.6 ± 6.4 (n=8)	0.81	-
Mean time from presentation to Melioid-active coverage, days, (S.D)	6.8 ± 9.1	6.5 ± 6.7 (n=31)	9.7 ± 17.9 (n=6)	0.44	-
Median Pitt Bacteraemia score (IQR)	2.0 (0.0 – 4.0)	2.0 (2.0 – 4.0)	4.0 (2.5 – 10.0)	0.002[3]	-
Need for ICU stay, no. (%)	11 (25.6)	4 (11.8)	7 (77.8)	< 0.001	26.3 (4.0 – 173.1)
Requiring mechanical ventilation, no. (%)	10 (23.3)	4 (11.8)	6 (66.7)	0.002	15.0 (2.6 – 85.0)
Septic shock, no. (%)	20 (46.5)	13 (38.2)	7 (77.8)	0.06	5.7 (1.0 – 31.5)
Treatment					
Use of Ceftazidime (referent group) vs Carbapenem as initial induction antibiotic therapy, no. (%)	31/41[3] (75.6)	28/34 (82.4)	3/7 (42.9)	0.047	0.2 (0.0 – 0.9)
Non-recipient of melioidosis-active therapy	2 (4.7)	0 (0.0)	2 (22.2)	0.04	-

1: P values by Fisher exact test except as indicated. Values given as no./no. indicate number of patients for whom results were available (if less than total no. patients in category). ICU, intensive care unit; OR, odds ratio; CI, confidence interval
2: Student T test
3: Mann-Whitney U test
4: Excluded patients not on melioidosis-active therapy (n=2)

RESULTS

(C) Predictors of mortality

- Thirty-day all-cause mortality occurred in 9 patients (from first positive culture); 1 patient died within 5 months
- Univariable analysis showed that the following features were associated with 30-day all-cause mortality
  - Intensive care unit (ICU) admission (OR 26.3, 95% CI 4.0-173.1, *P* <0.01)
  - Mechanical ventilation *(*OR 15.0, 95% CI 2.6-85.0, *P*<0.01)
  - Higher median Pitt Bacteraemia Score (PBS) (4.0 vs 2.0; *P* <0.01)
  - Receipt of ceftazidime (vs a carbapenem) as primary induction antibiotic therapy (OR 0.2, 95% CI 0.03-0.91, *P*=0.047)
  - Not receiving melioidosis-active induction intravenous antibiotics (*P*=0.04)
- Septic shock was present in 20 patients (46.5%), although it was not significantly associated with 30-day mortality (OR 5.7, 95% CI 1.0-31.5, *P*=0.06)
- Multivariable analysis was performed using two different models
  - Model 1: Backwards (Wald) (for risk factors with *P* <0.2 on univariate analysis) found mechanical ventilation to be an independent predictor for 30-day mortality (*P* = 0.03, OR 18.8, 95% 2.7-131.0)
  - Model 2: Backwards (LR) (for the 3 most significant variables) found ICU stay) to be an independent predictor for 30-day mortality (*P* = 0.18, OR 12.1, 95% CI 1.5-96.0)

CONCLUSIONS

- ICU admission, a high PBS, and in particular, receipt of mechanical ventilation may help identify patients with high mortality risk
- Delays in melioidosis-active therapy were not uncommon
- Prompt recognition of melioidosis and early institution of active therapy, especially in the critically ill, may reduce mortality