ORIGINAL ARTICLE

Melioidosis : The Johor Bahru Experience

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Summary

A 5 year retrospective review of cases of melioidosis was carried out in Sultanah Aminah Hospital, Johor Bahru. There were 44 new cases of melioidosis which was proven by either blood or pus culture growing *Burkholderia pseudomallei* from the period between January 1999 and December 2003. Of these, 38 (86.4%) were males compared to only 6 (13.6%) females. Thirty-one (70.5%) were Malays, 7 (15.9%) were Chinese, 5 (11.4%) were Indians and 1 (2.2%) was a Sarawakian. The peak age group was between 50 and 59 years (31.8%). Out of these 44 new cases, only 32 medical records could be retrieved and analysed.

Twenty-four out of 32 patients (75%) analysed had diabetes mellitus, 4 had chronic or end stage renal failure (CRF/ESRF) and only 1 had Human Immunodeficiency Virus (HIV). One case of "near drowning" was also recorded. Twenty-one out of 44 patients or 47.7% died, of which 8 (38.1%) died within 24 hours of admission. Pulmonary involvement was recorded in 62.6% of the patients but many had signs and symptoms of multiorgan involvement.

Key Words: Melioidosis, *Burkholderia pseudomallei*, Diabetes Mellitus

Introduction

Melioidosis is an unusual tropical bacterial infection. Melioidosis is caused by *Burkholderia pseudomallei*, a gram negative soil saprophyte that was first described by Whitmore and Krishnaswami in 1912 in 38 fatal cases of pneumonia amongst morphine addicts in Rangoon, Burma [1]. It is a normal inhabitant of soil and water and indigenous to the natural environment of Southeast Asia between 20º N and 20º S of the Equator [2].

While melioidosis can present as an acute rapidly fatal septicaemia, it can also cause localized soft tissue infection, acute necrotizing pneumonia or seroconversion without clinically evident infection (asymptomatic). There are reports of people developing the illness 24 to 26 years after leaving the endemic area.

In Australia and Thailand, the annual incidence ranges from 5.8 to 80 cases per 100 000 population in endemic and hyperendemic areas [3,4,5]. Twenty percent of community acquired pneumonia in Thailand and 7% in Singapore are due to *Burkholderia pseudomallei* [6,7].

In Malaysia, melioidosis is known to be endemic but the true incidence of infection is unknown. Detectable antibodies to *Burkholderia pseudomallei* was found in 17-22% of farmers and 26% of healthy blood donors in Malaysia [8,9]. Johor Bahru is the southern most city in the state of Johor in Peninsular Malaysia. Hospital Sultanah Aminah is the largest hospital in the state of Johor and the major referral centre for the state. A retrospective study was carried out to review the cases of melioidosis in Hospital Sultanah Aminah, Johor Bahru between January 1999 and December 2003.

Materials and Methods

This study was carried out to analyse all the cases of melioidosis between January 1999 and December 2003.

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We went through all the results of blood and pus culture from the microbiology department of Hospital Sultanah Aminah, Johor Bahru from 1999 to 2003. This was done manually by going through the record books of the laboratory and the names and the registration numbers of the culture proven cases were recorded.

A total of 44 new cases were detected from the laboratory records and this was traced retrospectively using the hospital computer to look for the age, ethnic group, identity card numbers, date of admission and discharge or the date and time of death of the patients. Subsequently, their medical records were traced from the medical record office of the hospital for further analysis.

Of these 44 cases, the records of only 32 patients were available for retrospective analysis. These 32 cases were analysed and the findings are presented here together with the epidemiological data obtained from the hospital's computer for all the 44 cases.

Results

The number of cases of melioidosis for each year from 1999 till 2003 is shown in Figure 1. There were a total of 38 (86.4 %) male patients compared to only 6 (13.6 %) female patients.

Figure 2 shows the age distributions of the 44 cases of melioidosis. 77.3% of the cases were between the ages of 30 and 59 years. The youngest patient was 13 years old which was a case of "near drowning".

Figure 3 shows the ethnic distribution.

Table I shows from where *Burkholderia pseudomallei* was isolated from, in the 32 cases analysed. There were 2 cases where only the pus grew the organism, 1 was from a right knee septic arthritis and the other from a left paracolic abscess aspiration.

Figure 4 shows the well known predisposing risk factors for developing melioidosis. 75% of the patients had diabetes mellitus. There was also a patient who was 16 weeks pregnant who presented with bronchopneumonia, subsequently aborted and died of septicaemic shock. She was not a diabetic. Pregnancy is not a known predisposing factor for melioidosis.

Table II shows the frequencies of various sites of involvement, but many presented with multiorgan involvement. There was one case where an end stage renal failure patient presented with embolism to the right brachial artery who was later found to have vegetation at the aortic valve. Her blood culture grew *Burkholderia pseudomallei* twice. There was also a patient who presented with severe periorbital cellulitis which later developed into an abscess. Even his corneal scrapping grew the organism.

Table III shows the mortality rate each year from 1999 till 2003. Twenty-one (47.7%) out of the 44 cases died. Eight out of the 21 patients (38.1%) died within 24 hours of admission and 9 (42.9%) died after 72 hours of admission.

Of the 32 cases analysed, only 5 patients were given appropriate empirical antibiotic of intravenous ceftazidime. Unfortunately, despite the appropriate antibiotic, 4 of the 5 patients died.

It was noted that 31.3% of the patients had normal white cell count and 15.6% had low white cell counts of below 4.6 x $10^3/\mu L$. 65.5% of the patients had low sodium levels of below 130 mmol/L.

All isolates in this series were sensitive to ceftazidime and imipenem. There were 4 isolates which were resistant and 9 isolates which were partially sensitive to ciprofloxacin. There were 21 isolates which were reported as resistant to co-trimoxazole.

Discussion

Burkholderia pseudomallei is a free living organism in the natural environment, especially in the surface water of rice paddies, fields newly planted with oil palm, drains, gardens and playgrounds in endemic areas. Melioidosis is mainly acquired by contact with infectious soil and water through penetrating wounds or existing skin abrasions, ulcers, burns or by inhalation of dust particles, by aspiration of contaminated water during near drowning episodes[10], iatrogenic inoculation and by laboratory accidents. It affects virtually every organ except the hair and nails.

Although the morbidity and mortality of melioidosis is very high, the true worldwide incidence is not known as it is not a notifiable disease except in Singapore. The peak age-specific incidence occurred from 50-59 years in women and 60-69 years in men in Thailand. In Malaysia, Puthucheary et al reported that the peak age incidence occurred from 41-59 years for both males and

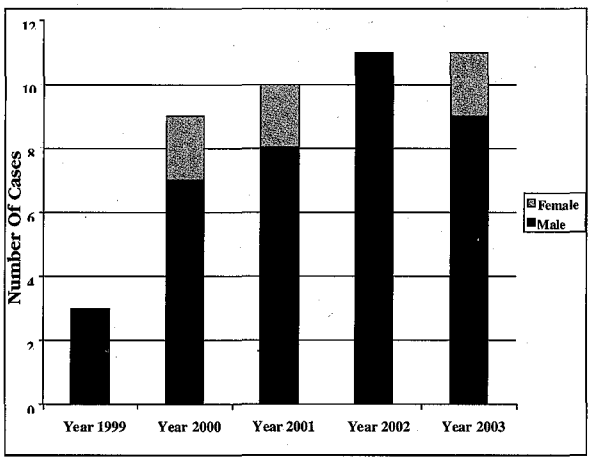

Fig. 1 : Number of Cases of Melioidosis (Male and Female) from 1999 till 2003

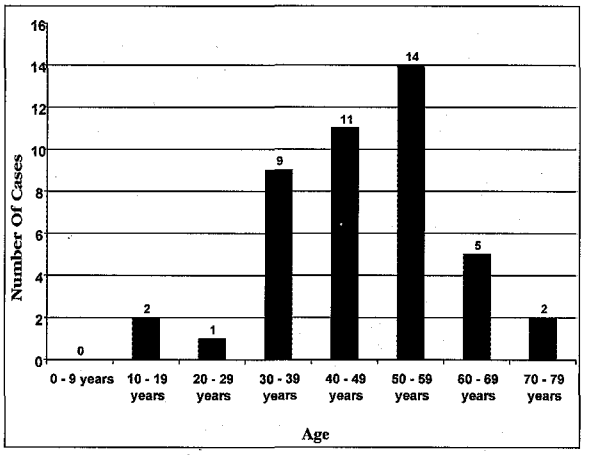

Fig. 2 : Age distribution for cases of Melioidosis

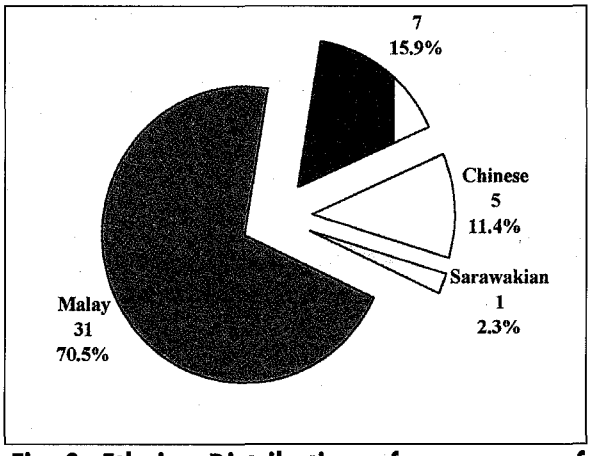

Fig. 3 : Ethnic Distribution for cases of Melioidosis

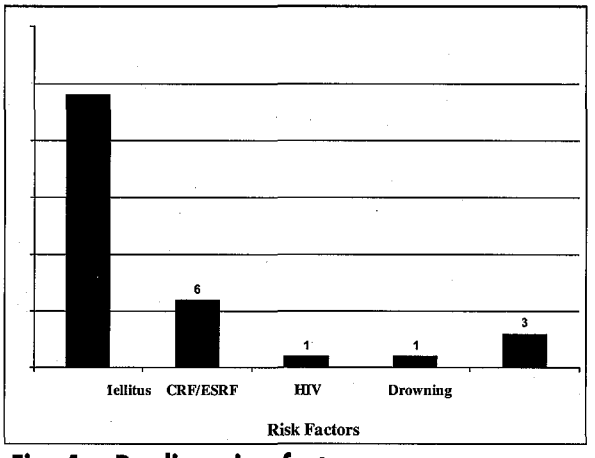

Fig. 4 : Predisposing factors

Table I : Source of *Burkholderia pseudomallei* isolate

Source of isolate	Number of cases
Blood only	26
Pus only	2
Blood and pus	2
Blood and bronchial washing	1
Blood and corneal scrapping	1
Total	32

Table II : Frequencies of site/organ involvement in 32 patients analysed

Lesion Site	Number of Cases
Pulmonary :	
Pneumonia	18 (56.3%)
Lung Abscess	2 (6.3%)
Intra-abdominal :	
Liver abscess	1
Spleen abscess	2
Spleen and Liver abscess	1
Spleen with paracolic abscess	1
Soft tissue/skin a	6 (18.8%)
Septic arthritis	2 (6.3%)
Heart vegetation	1
Septicaemia/no cause found	4 (12.5%)

[a] Sacral abscess 1; Right foot abscess 1; Left hand abscess 1;Right axilla abscess 1; Subcutaneous scalp abscess 1; Periorbital cellulitis and abscess 1.

Note: a. Some patients had multiple organs involved. Hence, the total cases in the table exceed 32 patents
b. Percentages are calculated out of the 32 patients

Table III : Case Mortality

Year	Total cases	Cases died	Percentage %
1999	3	0	0 %
2000	9	2	22.2 %
2001	10	5	50.0 %
2002	11	9	81.8 %
2003	11	5	45.5 %
Total	44	21	47.7 %

females while the male: female ratio was 3.2:1[11]. In Singapore the risk of melioidosis increased steadily with age, being maximal in those above 65 years old[12]. In every published case series, males have outnumbered females but the proportions varied considerably (ratio of male: female from 5:1 to 1.4:1). This is likely to reflect involvement in activities which lead to exposure to contaminated soil and water.

In this review of 44 cases, the peak incidence seems to be in the age group between 50 and 59 years (31.8%). However, the male to female ratio seem to be extremely high in this study at 6.3: 1. This is probably because there is a preponderance of males in the farm and oil palm plantations in our country.

In Singapore, where melioidosis is a notifiable disease, the overall case fatality rate is 51.2%. 74.3% of the patients suffered from diabetes mellitus. This is similar to 75% of patients having diabetes mellitus in this review and a mortality rate of 47.7%. Puthucheary et al reported a mortality rate of 65%[11] while reports from Thailand gave a mortality range of 17- 87%[13]. Overall mortality in Australia is considerably lower (19%) than that reported elsewhere[14].

The high mortality rate may have been due to delay in diagnosis and instituting appropriate antibiotic as well as the fulminant nature of the disease. The definitive diagnosis of melioidosis is only made by the isolation of *Burkholderia pseudomallei* from clinical specimens. Serology is of little use in these patients as it may be

negative in up to 1/3 of the fulminant cases and single titres may be difficult to interpret in endemic areas [15]. Raised antibody levels can be seen in healthy population in endemic areas.

In this review, the Malays seem to have the highest incidence followed by Indians and Chinese. This reflects the population of Johor which is a Malay majority state. The Malays in Johor are the main ethnic group involved in the agricultural sector such as oil palm plantations and farms followed by the Indians. Johor has many "FELDA" (Federal Land Development Authority) settlements with oil palm plantations and out of the 32 cases analysed, 10 cases were staying in "FELDA" settlements and 7 were from rural villages or "kampungs". The Malays also have the highest prevalence of diabetes mellitus which are most probably poorly controlled in rural areas.

Puthucheary et al reported that almost 50% of their patients were Chinese followed by Indians (25%) and Malays (18%) [11]. This was actually a close reflection of the racial composition of patients seen at their institution.

Of the 32 cases analysed, 62.6% of the patients had lung involvement of either pneumonia or lung abscess. Many had multiorgan involvement. In 4 (12.5%) of the patients, no primary source of infection was found. Puthucheary et al reported that 46% of their patients had Pneumonia [11]. In one of the largest series of 1000 culture proven cases seen at the Sappasithiprasong Hospital in Northeast Thailand, 15% of the patients did not have any obvious primary site of infection and 50% had lung as the commonest site of infection [16]. Unlike other pyogenic infections, hematological dissemination to the viscera involved the spleen more frequently then kidney or liver in the form of multiple abscesses [17]. Ultrasound of the abdomen should be mandatory in all culture proven case [18]. Parotid abscess and cervical lymph node are seen more common in children [19].

In this series of cases it was noted that 8 (38.1%) of the 21 patients who died, died within 24 hours of admission. This is comparatively lower than a figure recorded in Thailand where 74% of patients with a positive blood culture died within 24 hours [20]. This is probably due to the low number of culture proven cases analysed in this study and in many other fatal cases, culture may not have been taken. Another 9 (42.9%) of the patients died after 72 hours.

Relevant occupational history was identified only in 5 patients who include 1 rubber tapper, 1 estate supervisor, 1 construction worker, 1 farmer and 1 cook in an army camp. Eventhough occupation is said to be an important factor in suspecting a case of melioidosis, it correlates very poorly with the cases of melioidosis in this review. It seems to correlate more to the place of stay. In Northeast Thailand, the disease mainly affects rice farming families.

All the *Burkholderia pseudomallei* isolated in this study were sensitive to ceftazidime and imipenem. *Burkholderia pseudomallei* is intrinsically resistant to many antibiotics [21, 22]. Reports of susceptibility to trimethoprim and sulphonamides are confounded by unclear endpoints [21, 23](eg : gradual decrease in growth around a disc rather than a clear halo). This uncertainty has resulted in over-reporting of resistance to co-trimoxazole and contributed to a possibly false notion that the antibiotic is not very effective.

In this study 21 isolates were reported as resistant to co-trimoxazole. Only 5 of 32 patients (15.6%) analysed actually received appropriate empirical antibiotic of intravenous ceftazidime, out of which 4 died. Only 1 received imipenem as empirical therapy. Ceftazidime became the drug of choice for acute melioidosis following the publication "Halving of mortality of severe melioidosis by ceftazidime" [24] in the Lancet 1982. The carbapenems antibiotics also have an excellent all-round profile of activity against *Burkholderia pseudomallei* with the lowest MICs and the greatest bactericidal activity with a killing rate of 99.9% within 4 hours [25].

This review noted that only 53.1% had raised white cell count. Similar findings have been reported before 15. This is in contrast to septicaemia due to other Gram negative or Gram positive organism. Hyponatraemia has also been frequently reported in other studies as reported here.

This review demonstrates that there is a need to have an increase awareness among health care workers concerning melioidosis. Medical personal in every discipline should be aware of melioidosis as it can involve any organ in the body. With improved laboratory services and proper collection of culture specimens, we will be seeing increasing number of melioidosis cases in the future.

Conclusion

This review clearly illustrates that melioidosis is a major public health issue. With the number of patients with diabetes mellitus reaching epidemic proportion in our population as in the world, melioidosis should be borne in mind in treating any septic diabetic patients, patients with abscesses or pyrexia of unknown origin. It is suggested that melioidosis be made a notifiable disease to determine the exact incidence rate in this country.

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