EDITORIAL

Melioidosis - Should it Be a Notifiable Disease in Malaysia?

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In 1911 Alfred Whitmore and C.S. Krishnaswami noticed that morphine addicts in Rangoon were afflicted by a lethal illness bearing a striking similarity to glanders[1,2]. Autopsy findings were characterized by widespread caseous consolidation of the lungs with abscesses in the liver, spleen, kidney and subcutaneous tissues. Glanders, an infection caused by *Burkholderia mallei*, is predominantly a disease of horses characterized by abscess formation. Whitmore proposed the name *Bacillus pseudomallei* for the newly discovered bacterium.

In 1913 a severe distemper-like illness affected the animal facility at the Institute of Medical Research in Kuala Lumpur. This was identified to be Melioidosis several years later. In 1932 Stanton and Fletcher, from the same institute, published their definitive monograph on the disease which they named Melioidosis (Greek; *melis*, a distemper of asses; *eidos*, resemblance)[3].

After various earlier names, the causative bacterium was called *Pseudomonas pseudomallei*[4]. Due to 16s ribosomal RNA sequences, DNA homology values, the cellular lipid and fatty acid composition, and phenotypic characteristics within the *Pseudomonas* genus, seven species were moved to a new genus *Burkholderia* in 1992[5]. The new genus was named after the US microbiologist Walter Burkholder. *Burkholderia pseudomallei* is a soil saprophyte readily recovered from wet soils in rice fields in endemic areas. It is a motile, aerobic, oxidase-positive, gram-negative bacillus whose genome has recently been sequenced. Gram stain shows the characteristic bipolar staining gram-negative rods ('safety-pin' appearance). It is gentamicin and colistin resistant.

Transmission of this disease appears to be due to percutaneous inoculation or inhalation of the organism present in soil and surface water in endemic regions[6]. In both North-East Thailand[7] and Northern Australia[8], 75% and 85% of cases respectively occur in the wet season. Rice farmers, by virtue of their occupation, are particularly prone[9]. Uncommon routes of transmission include near drowning, nosocomial or laboratory transmission, vertical transmission at childbirth and sexual transmission[10-12]. Underlying predisposing factors include diabetes mellitus, renal failure, cirrhosis, thalassemia, alcoholism, chronic lung disease, cystic fibrosis and immunosuppression. Diabetes mellitus is by far the most common risk factor occurring in up to 50% of patients. The association with HIV infection is infrequent. Of note is that there may be no evident risk factors in 20-36% of patients[13].

For many years Melioidosis was regarded as a rare disease. Apart from case reports from the Vietnam war little was known about its epidemiology. It became recognized as a disease of veterinary importance in Northern Australia. Very few cases were reported from south and east Asia probably because of poor laboratory facilities[9]. Today the vast majority of cases are reported from Thailand and Northern Australia. It is also a significant cause of morbidity and mortality in Malaysia[14-16] and Singapore[17,18]. The average annual incidence may vary from 1.7 per 100,000 in Singapore[19] to 16.5 per 100,000 in the Northern Territory in Australia[8]. In Northeast Thailand the average annual incidence is estimated to be 4.4 per 100,000[7]. An increasing number of cases are also being reported among travelers returning from tropical countries[13]. The current data on the prevalence of Melioidois are probably a gross underestimate.

Most infection with *B. pseudomallei* is asymptomatic[20]. In north-east Thailand, a majority of the rural population

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is seropositive by indirect haemagglutination (IHA)[7], with most seroconversion occurring between 6 months and 4 years[21]. These antibodies have not been shown to be protective. The incubation period is from 1 – 21 days[22]. Analagous to tuberculosis, *B. pseudomallei* has the potential for reactivation and hence the term 'Vietnamese time-bomb' which was applied to soldiers returning from the Vietnam war. Latent periods prior to reactivation have been documented to be as long as 29 years[23]. The rate of relapse after appropriate treatment is 10%, which rises to nearly 30% if antibiotic treatment lasts for 8 weeks or less[24].

The clinical diversity of Melioidosis, 'the great mimicker', is truly astounding and therein lies the challenge of the diagnosis. A clinical classification has been proposed[4]. The spectrum includes asymptomatic, localized, bacteraemic, septicaemic, disseminated septicaemic Melioidosis and finally Melioidosis with septic shock. This is a disease with a significant mortality. Mortality figures range from 19% in Northern Australia[8] to 44% in Thailand[7] and 46% in Singapore[25]. The mortality rate with septic shock is 80-95%. The lung is involved in half the cases and manifestations include pneumonia, lung abscess, lung masses and empyema. As the disease is characterized by multiple abscesses, it is particularly important to exclude abscesses in the liver, spleen and kidneys. Other sites for abscesses include the prostate, muscle, skin, brain and parotids (in children)[13]. Osteomyelitis and septic arthritis can prove a therapeutic challenge. More exotic presentations include mycotic aneurysms, brain-stem encephalitis and flaccid paraparesis[8]. Chest radiography and abdominal ultrasonography are mandatory investigations. Radiolabelled white-cell scanning can reveal occult abscesses[26]. The definitive isolation of *B. pseudomallei* from any site confirms the diagnosis. Gram staining is useful for a presumptive diagnosis with direct immunofluorescence microscopy, where available, for rapid identification. Culture on blood agar or Ashdown's medium is recommended. Definitive diagnosis requires positive bacterial culture and confirmation of the organism, which usually takes at least 48 hours. Various antigen and nucleic acid detection tests and serologic assays have been developed to expedite diagnosis[27]. These need validation, however.

Melioidosis is difficult to treat and clinicians should be aware of the often slow response to antibiotics. The organism is resistant to many antibiotics used for sepsis. Ceftazidime is the beta-lactam of choice[28]. Co-trimoxazole may be added to ceftazidime[29]. The carbapenems, imipenem and meropenem, have the lowest minimal inhibitory concentrations[30]. Cefoperazone-sulbactam has also proved effective[31]. Amoxicillin-clavulanate has been associated with a higher rate of treatment failure compared to ceftazidime[32]. Initial intensive antibiotic therapy should be for a minimum of 10 days and longer (2 to 4 weeks) in the critically ill, those with organ abscesses, bone and joint disease or neurological melioidosis[13]. Addition of G-CSF to current state-of-the-art intensive care management may improve mortality[8]. Large abscesses, if accessible, should be drained urgently.

For maintenance therapy, doxycycline and cotrimoxazole in combination are the recommended therapy[33,34] given to complete 20 weeks of treatment. If chloramphenicol is added, it is given for the initial 4 weeks only.

In this issue of the Journal, How and colleagues from Pahang[35] and Pagavalan[36] from Johor have made a valuable contribution to the epidemiology of Melioidosis in Malaysia. The overwhelming predominance of males in both studies (78.5%:21.5%)[35] is probably reflective of the male preponderance in the Malaysian agricultural sector. The median age of approximately 50 is in concordance with previous data from Puthucheary et al[15]. In accordance with the racial composition of the population, there was a preponderance of Malays. The average annual incidence of 6 per 100 000 in Pahang is similar to that reported in Thailand[7]. Diabetes appears to be the main risk factor with 75% of the patients (cf. 50% in Thailand) being diabetic. Renal failure and chronic lung disease were also significant predisposing factors. What was especially interesting was the presence of HIV infection as a probable risk factor among 2 -3% of patients. This is an uncommon association[33]. As expected the lung was most commonly involved (40.7%[35] vs 62.6%[36]) and multi-organ involvement was noted in 15.6% of patients. No primary site could be ascertained in 12.5% of cases. Clinicians should be alert to the frequency of hyponatraemia (65.5%) in Melioidosis. Approximately half the patients (53.5%[35] vs 47.7%[36]) succumbed to the illness. Pneumonia and multi-organ involvement were risk factors for mortality. The majority of deaths occurred in the initial 72 hours. There was a clear difference in the proportion of patients prescribed appropriate antibiotics in the two studies (51.1%[35] vs 15.6%[36]). How and colleagues noted no significant difference in mortality between those with and without appropriate antibiotics. However, no comment was made about the presence or absence of septic shock

which is an adverse prognostic factor. The risk of relapse was 11.1% for those on appropriate antibiotics and 40% for those who were not. The organism was uniformly sensitive to the first-choice antibiotics i.e. Ceftazidime and Imipenem. Cotrimoxazole resistance was significant (34.4%[35] vs 50%[36]). This may have been an overestimate as disc diffusion, rather than the E-test or MIC determination, was the test used[37].

Melioidosis should be suspected in any severely ill febrile patient with an underlying predisposing condition who lives in, or has travelled from an endemic area[9]. Reliable confirmation of a presumptive identification of *B. pseudomallei* requires a combination of the initial recognition that the species might be present, a well-appointed clinical microbiology testing facility, and a high level of scientific skill. Appropriate antibiotic therapy should be commenced immediately upon suspicion (and not confirmation) of this disease. There is a need for more data on the epidemiology of this disease in Malaysia. There is also a need for research on the appropriate antibiotic regmens both for the intensive phase as well as for maintenance therapy, perhaps as a multi-centre trial in the Malaysian setting. The role of co-trimoxazole in intensive therapy as well as the role of dual versus triple therapy for maintenance merits study. Is there an argument for it to be made a notifiable disease in Malaysia? We cannot ignore the available Malaysian data and that published in this issue of the Journal. Twenty percent of community-acquired septicaemia and 36% of fatal community-acquired pneumonia in north-east Thailand[7] and 7% of community-acquired pneumonia in Singapore[38] is due to Melioidosis. A recent Malaysian study on community-acquired pneumonia noted that 1.6% of cases were due to melioidois[39]. This is a disease with a mortality not dissimilar to avian flu! *Burkholderia pseudomallei* has also been touted as a potential bioterrorism weapon[40]. These are issues that merit concern. We should take the cue from our Singaporean neighbours and make it a notifiable disease. This will ensure proper epidemiological surveillance of this very important disease. The time to act is now.

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