Melioidosis – an uncommon but also under-recognized cause of pneumonia in Papua New Guinea

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SUMMARY

Melioidosis is being increasingly recognized as an important cause of severe, acute community-acquired pneumonia in various tropical regions. The chronic form of melioidosis can also mimic tuberculosis. Studies have established that, while uncommon in the Port Moresby region, melioidosis is an important cause of pneumonia and sepsis in the Balimo region of Western Province. Phylogenetic analyses of strains of Burkholderia pseudomallei from Papua New Guinea have shown them to be more closely related to strains of B. pseudomallei from Australia than to strains from Southeast Asia. This is consistent with the proposed origins of B. pseudomallei in Australia, with subsequent spread out of Australia to Southeast Asia during the last ice age. Further surveillance across Papua New Guinea is likely to unmask other locations where B. pseudomallei occurs in the environment and where melioidosis is currently not being diagnosed.

Background

It is 100 years since Whitmore and Krishnaswami first described the clinical disease melioidosis in Burmese patients dying from sepsis with pneumonia and multi-organ abscesses (1). Melioidosis is caused by the environmental bacterium Burkholderia pseudomallei, which is present in soil and surface water in endemic locations (2). It is most commonly found in northeast Thailand, Singapore, Malaysia and northern Australia but is being increasingly recognized elsewhere in the tropical and subtropical regions of Asia and Southeast Asia (3). Recent cases have also been documented from Africa, countries in the Indian Ocean, Central and South America and the Caribbean (4). Around half of patients with melioidosis present as a community-acquired pneumonia and case fatality ranges from under 15% in locations with state-of-the-art intensive care facilities to over 50% in some rural locations with limited health resources. Up to 80% of patients with melioidosis have an identified predisposing risk factor, with diabetes being the most common, present in 40-60% of cases (5). The majority of cases of melioidosis pneumonia present as an acute community-acquired pneumonia. Around half are bacteraemic and those at the most severe end of the spectrum die rapidly from fulminant septicaemic pneumonia. Around 20% of patients with melioidosis pneumonia have a more chronic illness, with cough, fever and weight loss that may be present for 2 months or longer and with chest X-ray changes that mimic tuberculosis. Indeed it is not unusual in endemic locations for cases of melioidosis to be incorrectly diagnosed and treated as ‘smear-negative’ tuberculosis.

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The history of melioidosis in Papua New Guinea

In 1963 *B. pseudomallei* was reported to have been isolated from a tree-climbing kangaroo in Port Moresby (6). The first suggestion that human melioidosis may occur in Papua New Guinea was when two fatal cases of chronic/reactivated melioidosis reported from Australia were attributed to World War 2 service in Papua New Guinea more than 20 years earlier (7,8). Between 1965 and 1980 at least 5 other human cases of melioidosis were documented from Port Moresby, with 3 being fatal (9-11). A further fatal case of melioidosis from Port Moresby occurred in 1987 (12).

Laboratory diagnosis of melioidosis requires facilities which are not present in much of Papua New Guinea and even in the laboratory recognition and identification of *B. pseudomallei* can be problematic (13). The difficulties diagnosing melioidosis were illustrated by the 1987 case reported from Port Moresby General Hospital (12). In that case a 28-year-old male died the day after being admitted with severe community-acquired pneumonia (Figure 1). A Gram-negative bacillus was recovered from blood cultures but was unable to be identified. The organism was sent to the Papua New Guinea Institute of Medical Research in Goroka, where it was recognized to be an unusual pathogen and referred to the New Zealand Communicable Disease Centre. Eventually it was identified in New Zealand as *B. pseudomallei*, by which time it was several months after the patient had died.

Nevertheless, despite the sporadic confirmation of melioidosis from Port Moresby, past serological studies indicated that melioidosis is indeed rare in that location within Papua New Guinea; two limited studies failed to detect antibodies to *B. pseudomallei* (9,14), in contrast to a seroprevalence of 5.7% seen in north Queensland (15).

Figure 1. Chest X-ray from a rapidly fatal case of melioidosis in a 28-year-old male at Port Moresby General Hospital.
A focus of melioidosis in the Balimo region of Western Province

In contrast to the rarity of melioidosis in Port Moresby, an endemic focus of melioidosis has been found and evaluated in the Balimo region of Western Province. Investigations followed an unpublished 1983 case report of fatal melioidosis from the Balimo Health Centre. 8 cases of culture-confirmed melioidosis from the Balimo region were diagnosed during 16 months of study which spanned two periods in the 1990s (16). Notable was that 6 of the 8 cases were children under the age of 15 years. Unmasking this focus of melioidosis in a remote rural location in Papua New Guinea was only possible through the establishment of laboratory procedures specific for the culture and identification of \textit{B. pseudomallei}. Serological surveys also undertaken as part of that project showed a seroprevalence for \textit{B. pseudomallei} of 8.2\% in local children, which is at the higher end of the seroprevalence rates seen in endemic northern Australia (3,15). Subsequent environmental studies confirmed the presence of \textit{B. pseudomallei} in soil from the region, especially in wet locations near the lagoon where children frequently had close contact with the environment during robust play (17). Overall 2.6\% of 274 soil samples were culture-positive for \textit{B. pseudomallei}.

The Balimo studies highlighted not just the difficulties in diagnosing melioidosis in locations with limited or no laboratory facilities, but also the potentially severe nature of the disease and the especially high mortality when antibiotics for effectively treating melioidosis are not affordable or available. While chloramphenicol, cotrimoxazole and doxycycline have activity against \textit{B. pseudomallei}, the importance of using ceftazidime or a carbapenem such as meropenem for initial therapy of melioidosis was shown in a major study from Thailand, where the use of ceftazidime halved the mortality from melioidosis (18). In the Balimo Health Centre, as elsewhere in Papua New Guinea, ceftazidime and meropenem are not available and in the Balimo study all four patients with bacteraemic melioidosis died (16). Nevertheless, where gold standard therapy for melioidosis is not available, high-dose cotrimoxazole should be considered for presumptive therapy if melioidosis is confirmed or suspected, such as in patients with tuberculosis-like pulmonary infection but not responding to standard tuberculosis therapy (3).

Results from further Port Moresby studies

Between 2000 and 2002 we undertook enhanced laboratory surveillance for \textit{B. pseudomallei} at the Port Moresby General Hospital Pathology Department and at the Central Public Health Laboratory, Port Moresby. From 2285 blood cultures tested from patients at Port Moresby General Hospital, 2 (0.09\%; 95\% CI 0.01\% - 0.32\%) were positive for \textit{B. pseudomallei}. At the Central Public Health Laboratory, 1309 sputum samples from 529 patients were selectively cultured for \textit{B. pseudomallei}. These patients were being assessed for possible tuberculosis and 112/529 (21\%) were confirmed as smear positive for tuberculosis on microscopy, indicative of the extremely high rates of tuberculosis seen in Papua New Guinea. When the same sputum samples were cultured for \textit{B. pseudomallei} by placement in Ashdown's selective broth, only 1/1309 was positive for \textit{B. pseudomallei}. Therefore in this extensive surveillance for cases of melioidosis in Port Moresby, 3 cases were identified over a 2-year period, confirming that melioidosis does occur in Port Moresby but is a very uncommon cause of community-acquired pneumonia in that region and is rarely being mistaken for tuberculosis.

The origins of \textit{Burkholderia pseudomallei} in Papua New Guinea

Recent phylogenetic analysis of a large set of \textit{B. pseudomallei} from many locations globally has provided strong evidence that \textit{B. pseudomallei} most likely originated in Australia, having evolved in the local environment from an ancestral \textit{Burkholderia} species (19). Subsequent spread is thought to have occurred across Wallace’s Line to Southeast Asia, most likely during the last ice age (20,000 years ago or earlier) when sea levels were much lower. During that period a land bridge connected Papua New Guinea to Australia. Preliminary analysis of \textit{B. pseudomallei} strains from Papua New Guinea using multilocus sequence typing (MLST) (20) has confirmed that they are more closely related to Australian \textit{B. pseudomallei} strains than to \textit{B. pseudomallei} from Southeast Asia.

\textit{B. pseudomallei} from the Balimo endemic
region show limited genetic diversity, with multilocus sequence type (ST) ST 267 predominant. Strains from cases from Port Moresby show different STs. One strain from Papua New Guinea (ST 246) shares 5/7 MLST alleles with two different STs from the Darwin region of the Northern Territory of Australia (BJC and M. Mayo, unpublished data), where incidence rates of melioidosis are amongst the highest in the world (5).

In conclusion, melioidosis is uncommon in the Port Moresby region but is an important cause of pneumonia and sepsis in the Balimo region of Western Province. Further surveillance across the country is likely to unmask other locations where B. pseudomallei occurs in the environment and where melioidosis is currently not being diagnosed. Nevertheless, given the difficulties with laboratory diagnosis of melioidosis in rural settings with limited facilities and given that the best antibiotics for decreasing the mortality from melioidosis are expensive and generally not available in Papua New Guinea, mortality from this enigmatic infection will continue to occur and will mostly remain unrecognized.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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