

Melioidosis in Australia

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Abstract. Melioidosis is a potentially fatal bacterial infection caused by the Gram-negative bacillus, *Burkholderia pseudomallei* following contact with a contaminated environmental source, normally soil or water in tropical and subtropical locations. The disease spectrum varies from rapidly progressive bacteraemic infection with or without pneumonia, to focal lesions in deep soft tissues and internal organs to superficial soft tissue infection and asymptomatic seroconversion with possible long-term dormancy. Most infections occur with a background of chronic illness such as diabetes, chronic kidney disease and alcoholic liver disease. Improvements in diagnosis, targeted antimicrobial treatment and long term follow up have improved clinical outcomes. Environmental controls following rare point source case clusters and heightened awareness of melioidosis appear to have reduced the disease burden in some parts of northern Australia. However, the impact of climate change on dispersal of environmental *B. pseudomallei*, and changing land use in tropical Australia is expected to change the epidemiology of melioidosis in future.

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Introduction

Melioidosis has fascinated Australian microbiologists since it was first encountered as a human infection in a 32-year-old Townsville man with diabetes in 1950¹. Human melioidosis has a remarkable ability to cause a broad spectrum of human disease from rapidly fatal bacteraemic infection and necrotising pneumonia, through persistent localised chronic lesions to asymptomatic dormant infections that convert to more serious infection after intervals of months to years². As a consequence, melioidosis challenges the logic of conventional clinico-pathological disease classifications and is best considered as a cluster of syndromes linked by a single bacterial aetiology, the Gram-negative, oxidase positive bacillus, *Burkholderia pseudomallei* and a history of environmental exposure.

Epidemiology

Melioidosis in Australia is endemic across the tropical north of Australia (Figure 1) where it occurs as a sporadic infection of people who have had exposure to contaminated soil or surface water through direct transdermal inoculation, inhalation and possibly ingestion³. Occasional point source case clusters have occurred related to contaminated water, medical solutions or hand wash products^{4–7}, and animal case clusters have been associated with flooding of pasture land⁸. The majority of acute febrile melioidosis occurs as a septicæmia with or without pneumonia, peaking during

the tropical wet season, and sometimes follows in the wake of tropical cyclones⁹, though not necessarily in all of northern Australia¹⁰. However, the potentially long symptom-free period leads to some subacute infections presenting during the dry season, or in residents of temperate Australia who previously travelled to the tropics¹¹, including endemic locations overseas. There is a higher risk of bacteraemic infections in people with one or more of a group of co-morbidities, most notably diabetes, chronic lung disease, chronic kidney disease and alcoholic liver disease¹².

Diagnosis

The lack of pathognomonic clinical features, wide range of clinical presentations and potentially dormant deep soft tissue infections create difficulties for the diagnosing physician. In patients from tuberculosis-endemic settings, there is a risk of misdiagnosis of melioidosis as tuberculosis and subsequent inappropriate treatment¹³. Attempts have been made to standardise clinical definitions of melioidosis¹⁴. Other than in the few centres in tropical Australia that encounter enough cases to gain experience applying such classification, maintaining awareness of melioidosis is more easily said than done. The most reliable laboratory confirmation comes from isolating *B. pseudomallei* in blood, sputum, abscess fluid or other culture¹⁵ (Figure 2). However, confirmation of the identity of *B. pseudomallei* can be challenging in clinical laboratories that have not previously handled the species. Referral of a suspect isolate

(Gram-negative bacillus, oxidase positive, Gentamicin and Colistin resistant) to a reference laboratory may be needed, although this will add further delays to reporting results. Laboratories in the melioidosis endemic zone will often use advanced bacterial identification methods such as specific PCR assays, MALDI-TOF mass spectrophotometry or gene sequencing to produce a definitive identification^{17,18}. Serological assays are used as a complementary diagnostic method, particularly in the absence of a positive culture, but background antibody levels in endemic regions may confound result

interpretation¹⁹. Moreover, high risk exposure activities that result in confirmed infection do not necessarily cause seroconversion²⁰.

Treatment

Detailed treatment regimens can be found in the Therapeutic Guidelines and are updated periodically by specialists with current clinical experience²¹. In summary, acute bacteraemic and other severe infections are treated with an intravenous beta-lactam agent such as Ceftazidime or Meropenem in an intensive phase for between 2 and 8 weeks, then followed by an extended period of eradication with one or more oral antimicrobial agents to counter the risk of relapse in an eradication phase lasting 3–6 months. The revised guidelines vary with presence and location of focal disease. Control of co-morbid conditions such as diabetes and chronic kidney disease during this eradication phase is likely to be an important contributor to eventual success of eradication therapy, but can be confounded by poor compliance with oral treatment regimens²². The restricted range of antimicrobial agents effective against *B. pseudomallei* reflects its natural habitat as a soil-dwelling bacterium, where it has evolved a range of mechanisms for antibiotic inactivation, notable among these being a collection of efficient efflux pumps²³. Though the success of the Darwin treatment protocol is clear from improved treatment outcomes, high levels of intrinsic antimicrobial resistance and concerns about emerging acquired resistant have prompted the application of genomics to predict antimicrobial resistance in *B. pseudomallei*²⁴. Moreover, the ability of *B. pseudomallei* to sequester in cells and tissues where

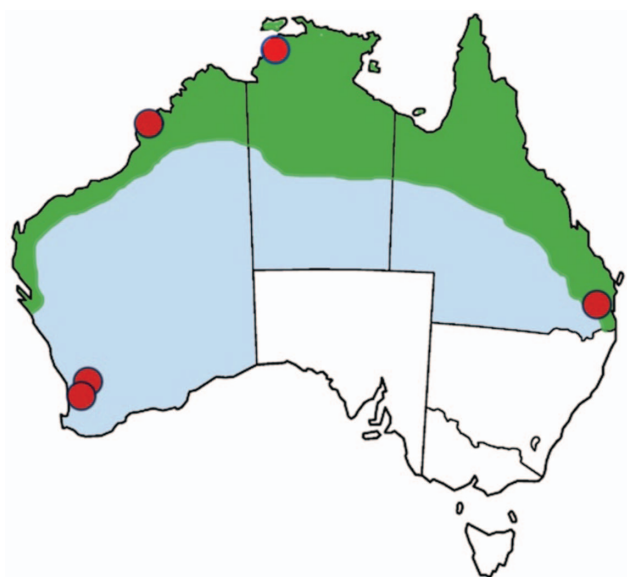


Figure 1. Melioidosis distribution in Australia (blue), and the main endemic area (green), showing the location of case clusters (red spots).

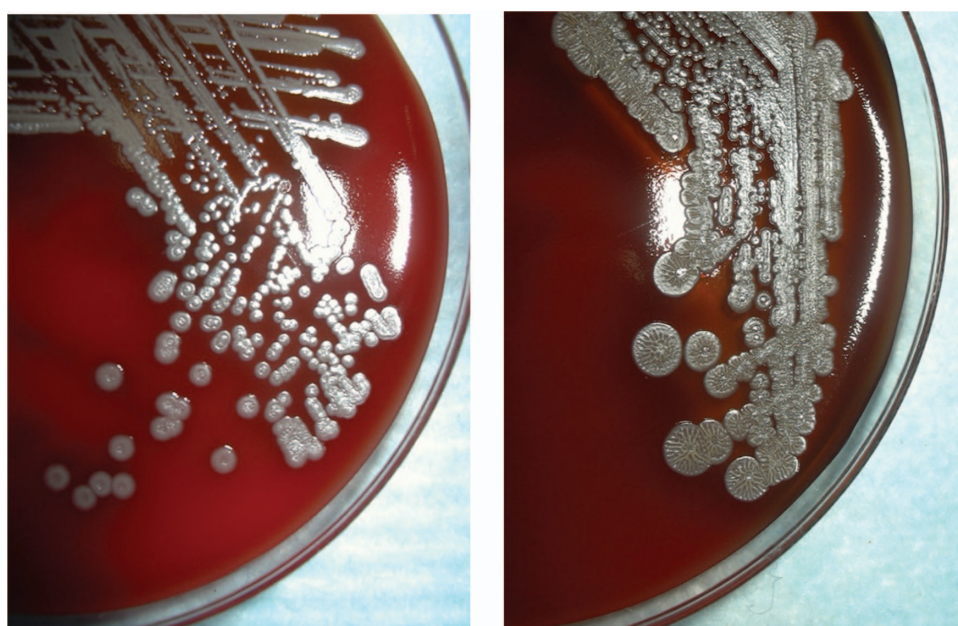


Figure 2. *B. pseudomallei* growth on horse blood agar after 24 (left) and 48 h (right), demonstrating the development of wrinkled colony appearance. Some strains do not wrinkle at all. An earthy odour is often noticed when agar plates are opened, due to the production of volatile organic compounds¹⁶.

antimicrobial bioavailability is poor presents a challenge to guaranteeing effective intracellular antimicrobial activity.

Pathogenesis

The unusually broad range of clinical presentations of melioidosis have yet to be fully explained at a mechanistic level, but it is becoming clear that virulence of infection is predominantly a function of host risk factors²⁵. *B. pseudomallei* is a facultative intracellular bacterial pathogen capable of entry into and prolonged survival within professional phagocytic cells²⁶. Like other facultative intracellular bacteria associated with infections of public health interest, *B. pseudomallei* deploys a range of molecular mechanisms that likely reflect its evolutionary history as a soil-dwelling species. Indeed, its ability to invade and persist in naturally occurring soil microbiota such as free-living amoebae suggest a possible environmental origin for its cellular virulence²⁷. However, a subset of *B. pseudomallei* possess a *Burkholderia mallei*-like sequence variation in the actin-based motility gene whose presence correlates with rapid dissemination and replication at a range of locations including the nervous system and thus have a molecular basis for neurotropism²⁸.

Genomics

The explosion of microbial genomics has led to important insights into the molecular biology and immunology of melioidosis. Whole genome sequencing indicates that *B. pseudomallei* has one of the largest known bacterial genomes at around 6.5 Mb, arranged in two chromosomes of unequal size²⁹. The operons associated with virulence are mainly located on the smaller of the two. Recent phylogeographic analysis indicates that the Southeast Asian clade arose from an ancient Australian clade, which may have early remnants in Papua New Guinea and the Torres Strait islands³⁰. Non-pathogenic near neighbour species such as *Burkholderia ubonensis* and *Burkholderia thailandensis* have also been found in pristine wilderness locations during *B. pseudomallei* environmental survey work, raising questions about the phylogeographic origins of the wider *B. pseudomallei* group³¹. At a more pragmatic level, genotyping studies have been instrumental in confirming single points of origin for melioidosis case clusters^{4–7} and have shown the plausibility of occasional long-distance translocation of *B. pseudomallei* strains associated with human infection⁹.

A changing public health threat

All Australian jurisdictions in the tropics have made melioidosis a notifiable infection. Following controls applied in the aftermath of

the Western Australian case cluster in 1997³², bacteraemic melioidosis is now rare in WA and almost eliminated in our indigenous population. The majority of cases are in long distance travellers¹¹ and even these have fallen recently due to pandemic travel restrictions. However, the recent Southwestern WA case cluster was a stark reminder of the greater difficulty detecting *B. pseudomallei* soft tissue infections⁶, particularly when geographic location, clinical presentation and exposure history are unexpected. We have to ask how many subacute and initially asymptomatic infections are missed. Noting the association with cyclone tracks, and the changing patterns of cyclone behaviour as a consequence of climate change⁹, we should be alert to the possibility of an extension of the Australian melioidosis endemic zone. The increased political instability of our region due to the effects of the COVID pandemic should also alert us to the deliberate dissemination of *B. pseudomallei*. This may seem far-fetched, but was under active consideration in the wake of anthrax spore/white powder events in 2001.

Conclusion

Melioidosis is a disease complex attributed to a multi-competent Gram-negative bacillus, *B. pseudomallei*. High rates of mortality in acute melioidosis survivors remain an unresolved problem³³. The clinical and scientific experience built up in Australian centres of excellence, particularly in our tropics, has advanced diagnosis, treatment and prevention of severe and subacute disease variants. However, the natural environmental habitat of *B. pseudomallei* ensures that the principal reservoir of human infection cannot be eliminated. Changing patterns of land use, human encounter with environmental *B. pseudomallei*, and environmental influences like climate change guarantee further challenges for Australian microbiologists in years to come.

Conflicts of interest

The author declares no conflicts of interest.

Declaration of funding

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Biography



Dr Inglis is Head of Pathology and Laboratory Medicine at the University of Western Australia, and appointed as a Medical Microbiologist at PathWest Laboratory Medicine WA. He qualified in Medicine at the University of Southampton, and followed this with a Doctor of Medicine thesis on ventilator associated pneumonia. After three years in Singapore where he first encountered melioidosis, he moved to Western Australia to take up his position with the state pathology service. Shortly afterwards he investigated the Kimberley melioidosis outbreak and its aftermath, completing a PhD on the environmental biology of *Burkholderia pseudomallei*. Since then he has expanded on laboratory biopreparedness, regional pathology capability building and the laboratory response to emerging infectious diseases, including the current pandemic.

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