

Nasal-Associated Lymphoid Tissue and Olfactory Epithelium as Portals of Entry for *Burkholderia pseudomallei* in Murine Melioidosis

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Background. *Burkholderia pseudomallei*, the causative agent of melioidosis, is generally considered to be acquired via inhalation of dust or water droplets from the environment. In this study, we show that infection of the nasal mucosa is potentially an important portal of entry in melioidosis.

Methods. After intranasal inoculation of mice, infection was monitored by bioluminescence imaging and by immunohistological analysis of coronal sections. The bacterial loads in organ and tissue specimens were also monitored.

Results. Bioluminescence imaging showed colonization and replication in the nasal cavity, including the nasal-associated lymphoid tissue (NALT). Analysis of coronal sections and immunofluorescence microscopy further demonstrated the presence of infection in the respiratory epithelium and the olfactory epithelium (including associated nerve bundles), as well as in the NALT. Of significance, the olfactory epithelium and the brain were rapidly infected before bacteria were detected in blood, and a capsule-deficient mutant infected the brain without significantly infecting blood.

Conclusions. Neurologic abnormalities and invasion of the brainstem and spinal cord occur in 4% of melioidosis. *B. pseudomallei* travel along nerves to invade the CNS directly whereas brain abscesses may occur via the blood stream. These data suggest that the olfactory nerve is the route of entry into the brain and that this route of entry may be paralleled in cases of human neurologic melioidosis. NALT is part of an integrated system of mucosa-associated lymphoid tissue which includes gut-associated lymphoid tissue, which is known to provide a portal of entry for enteric pathogens. The upper respiratory tract as a portal of entry, specifically focusing on NALT may be the route for the development of systemic infection via the bloodstream and on the olfactory epithelium as a direct route to the brain.

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