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Science of the Skin and Respiratory Tract, and Related Countermeasures Pertinent to Chemical/Biological Defense

Aerosolized Ceftazidime for Propyhlaxis and Treatment of Melioidosis

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Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*, a Category B bioterrorism agent with no available vaccine. The disease is responsible for a high proportion of human pneumonia and fatal bacteremia in the endemic areas of the world, and is highly resistant to most commonly available antibiotics. The current treatment method for melioidosis is sub-optimal for military applications because some of the most efficacious antibiotics against *B. pseudomallei* have no oral bioavailability, thus the antibiotics are administered intravenously at least every 8 hours. In addition, the current antibiotic regimen regularly fails, leading to chronic infection in 5-25% of the infected population. A critical need exists to develop non-intravenous prophylactic and therapeutic antibiotic regimens that may be stockpiled and rapidly deployed in the event of a suspected biological attack.

Delivering intravenous antibiotics via the respiratory route mirrors the bacteria exposure route, deposits a high concentration of drug at the initial site of replication, and drug can persist in the lung tissue for extended periods. The intravenous antibiotics tobramycin and vancomycin have been converted to highly effective aerosols (TOBI Podhaler and AeroVanc). Our team recently reported the pharmacokinetics in mice administered aerosolized ceftazidime, a potent antibiotic against *B. pseudomallei*. Intraveneous administration of ceftazidime resulted in rapid elimination, while inhaled ceftazidime persisted in lung tissue, followed by slow absorption into blood. Next, team members at USAMRIID exposed mice to aerosolized *B. pseudomallei*, then treated these mice with aerosolized ceftazidime. Mice treated with aerosolized ceftazidime were protected from the infection to the same level as mice receiving intraveneous ceftazidime. Finally, we developed a stable, easily deployed dry powder aerosol of ceftazidime. Future studies aim to identify prophylactic and therapeutic antibiotic regimens to rescue mice challenged with *B. pseudomallei* and to expand this approach to other pathogens and active pharmaceutical ingredients.

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