Apichai Tuanyok

Abstract

Ceftazidime (CAZ) is the primary intravenous (IV) drug of choice recommended for treating melioidosis to prevent death from sepsis. Melioidosis is a zoonotic disease caused by one of the world's most dangerous pathogens – *Burkholderia pseudomallei*. *B. pseudomallei* is a Gram-negative bacterium that is found in soil and water in most tropical regions but predominantly in Southeast Asia and northern Australia. It has been estimated that global fatality for human melioidosis is comparable to deaths from measles and substantially greater than those from dengue or leptospirosis. The expanding range of melioidosis poses a significant risk to travelers and U.S. military personnel deployed to areas where endemicity is publicly unrecognized. Although the disease does not occur naturally in the United States, most human cases were found in immigrants and tourists who returned from countries where melioidosis is endemic. According to the CDC's most recent investigations, the importation of exotic ornamental freshwater fishes and household products from countries where melioidosis is endemic are associated with the multistate melioidosis outbreaks in the U.S. Treating melioidosis is complicated because the bacterial pathogen is resistant to most antibiotics used in empirical management of sepsis. CAZ is a third-generation cephalosporin antibiotic with bactericidal activity. CAZ resistance in melioidosis patients has emerged in several Southeast Asian countries recently. Our current study demonstrated that mutations of *penA*, a class A β-lactamase gene, can potentially cause CAZ resistance. Preliminary study on a large *B. pseudomallei* strain collection from human patients who had treatment failures in Northeast Thailand during 1987-2007 has suggested strong associations between the increased minimal inhibitory concentrations of CAZ and multiple amino acid substitution (AAS) mutations in PenA and/or a specific *penA* promoter-up mutation. However, there remains a group of CAZ resistant strains that do not contain these mutations. Therefore, the principal objectives of this proposal are to further identify the novel genetic and molecular basis of CAZ resistance mechanisms in this unique strain collection and develop a rapid test that can be used in detecting these specific mutations in *penA.* We hypothesize that the emergence of CAZ resistance is developed clinically due to insufficient dosing treatment of melioidosis, and the major mechanism is mediated by multiple site-specific mutations of *penA.* This project will not only empower clinicians with innovative tools to monitor drug susceptibility for *B. pseudomallei* in real- time, but also it will have a significant impact on alteration of treatment(s) for melioidosis in humans and animals. This project has two specific aims: 1) identify genetic markers of CAZ resistance in a collection of the clonal related *B. pseudomallei* strains, and 2) develop molecular surveillance for CAZ resistance in B. pseudomallei.

We are opening this research opportunity to CVM professional students to learn about drug resistance mechanisms and other One Health aspects of melioidosis and participate in our world-leading research on this important disease. Some information about this disease and our research program can be found from these links:

1. UF researchers develop first-ever protocol for treating rare infection in dogs | UF Health, University of Florida Health
2. A potential "biothreat agent" pathogen is being spread by a $4 aromatherapy spray sold at Walmart | Salon.com
3. Research News - EPI helps discover novel