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Melioidosis: Current perspectives

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Melioidosis is considered as an emerging infectious disease of public health importance caused by *Burkholderia pseudomallei*. In 1912, Sir Alfred Whitmore first identified this bacterium to be different from bacilli causing glander's disease [1]. In 1932, Stanton and Fletcher further characterized and categorized it under the family *Pseudomonadaceae*. Based on rRNA homology family Pseudomonadaceae was further subdivided into 5 groups and genus *Burkholderia* was grouped under group II. Group II is also known as **"**group of opportunistic pathogens**"** as the bacteria in this group have the potential to cause biological warfare and biologic terrorism. As per CDC, *Burkholderia pseudomallei* has been categorized under group B biological hazardous agent [1].

Melioidosis is described as a "Great imitator". It is presented with a wide range of clinical features, which can vary from mild subclinical infection to fatal septicaemia [2]. The disease can be transmitted by inoculation/inhalation/ingestion, inoculation being the most common route [3]. The causative agent is found in the soil and stagnant water in endemic areas [1]. Animals such as cat, dog, pig, cattle, sheep, deer etc. are susceptible to this infection. Reports from the nonendemic areas are mainly observed among the travelers or person having a history of exposure to soil/animals of endemic area [4]. The agent has a special ecological niche, hence found in latitude 20°N to 20°S of equator. Currently, the disease is endemic in 48 countries with probably endemic in another 34 countries which yet to be confirmed [5]. Maximum incidence was reported from Thailand, Malaysia, Northern Australia, and Singapore [1]. It is representing just the tip of the iceberg as the disease is severely under reported due to lack of infrastructure, lack of laboratory facility and awareness. The crude fatality rate in the endemic areas varies from 14% in Australia to 49% in Thailand [6]. Mortality rate may increase upto 80% due to delay in the start of the treatment. Although it can affect any age group but the highest predilection is observed among the adult of 40-60 years. Diabetes remains most important risk factor in all the regions [1]. The incubation period is highly variable varies from 1-21 days with average 9 days [7].

B. pseudomallei is a motile gram-negative bacillus shows bipolar staining. It is oxidase positive and contains two megagenome of size 4.04 and 3.17 megabase pair [8]. The genetic elements of the larger genome are involved in physiological functions and virulence whereas smaller genome is associated with accessory functions. The major virulence factors are capsular polysaccharide, lipopolysaccharides, type three secretory system (TTSS), and enzymes like proteases, elastase, lipases, superoxides, catalases and peroxidases etc. Capsular polysaccharide and type IV pilli help in the initial attachment of the bacterium to aGM1-aGM2 ganglioside receptors of the epithelial cells [9]. The products of TTSS cause actin polymerization and cytoskeletal rearrangement of the epithelial cell. This helps in penetration, and replication inside the epithelial cells. *B. pseudomallei* forms actin comet tails at one end of the cell which help in cell to cell transfer. Its secretory system products fuse the cell membrane of adjacent cell thereby forming multinuclear giant cell. Intracellular survival within macrophage and other inflammatory cells are possibly due to suppression of synthetic nitric oxide expression. Once the replication is sufficient, the bacterium stimulates autophagy mechanism to lyse the cell [8]. Bacteraemia remains the most common clinical presentation followed by pulmonary infection and other localized infection.

Timely and accurate diagnosis is highly important for the management of Melioidosis. As per the diagnostic workshop by US CDC, any suspected case from the endemic area with community acquired sepsis or pneumonia with an underlying risk factor of diabetes should be immediately investigated for Melioidosis [10]. Blood, throat swab and urine sample should be collected from all the patients irrespective of symptoms. Culture is taken as the gold standard for the diagnosis. Since *B. pseudomallei* is not a part of normal flora any growth from any site is considered as diagnostic. It can able to grow in ordinary medias like blood agar, MacConkey agar. But samples from the nonsterile site should be processed in selective media (e.g. Ashdown media) to avoid contamination. Typical antibiogram showing sensitive to Co-trimoxazole, Amoxycillin-clavulanic acid and resistant to Aminoglycoside, Colistin is another clue for the detection of *B. pseudomallei*. For Co-trimoxazole, MIC based method is observed to be better than disc diffusion testing method. Serological tests like Immuno Fluorescent Assay, Indirect haemagglutination test, Lateral Flow Immunoassay, ELISA etc. cannot be recommended alone for routine diagnosis in endemic areas because of low sensitivity and specificity. These can be used in adjunct to culture. PCR and real time PCR targeting 16SrRNA, 23SrRNA, TTSS can be used for diagnosis of *B. pseudomallei*. The 16srRNA difference between *B. pseudomallei* and *B. thailandensis* is observed to be 1% only. Hence, other conserved genes like groEL gene can be considered to increase sensitivity and specificity [11]. Treatment is given in two phases such as intensive phase and eradication phase. The intensive phase should be atleast for 14 days with first line antibiotics like ceftazidime, imipenem/meropenem/trimethoprim-sulphamethoxazole followed by eradication phase. The eradication phase may continue for 3-6 months after completion of intensive phase with trimethoprim-sulphamethoxazole alone or with doxycycline. Adherence to treatment is highly important as recurrence of the disease is one of the most common complications of Melioidosis.

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