Review article

Melioidosis: Bridging the gap from bedside to bench in Bangladesh

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Abstract

The potentially fatal infectious disease "Melioidosis", caused by the saprophyte *Burkholderia pseudomallei*, has remained in the shadows for far too long. Although, the bacterium has been described almost a century ago in Myanmar, and considerable progress in terms of diagnosis and treatment was achieved, *B.pseudomallei* is still "the unbeatable foe", for several reasons like under-recognition, high case-fatality rate, unacceptable relapse rate and a "time-bomb" effect for sero-positive individuals. Just like *Mycobacterium tuberculosis*, the organism can remain latent for decades before the onset of clinical signs and symptoms. The first case of melioidosis from Bangladesh was reported in 1964, in a 29 year old British sailor who was travelling through Bangladesh. Since then, around 68 culture proven melioidosis cases have been sporadically detected in Bangladesh over last several decades. However, the true melioidosis burden is unknown in this region due to lack of awareness and absence of systematic surveillance and research. The reasons for its under-recognition are unavailability of diagnostic microbiology laboratories serving the rural poor in the tropics, who are most likely to acquire melioidosis, and a lack of familiarity and awareness amongst medical and laboratory staff, where such laboratories are available. Clinical diagnosis is exceptionally challenging due to the varied clinical presentations, as the disease can mimic other infections. The most striking reason for this unawareness is that, melioidosis is still considered as one of the most neglected tropical diseases (NTDs), so much so that it is not even included in the WHO list of NTDs. The burden of melioidosis reveals the gaps in dealing with the disease, whereas the prevention mechanism clearly demands public health action in Bangladesh. Without early diagnosis and treatment and exploring better ways to prevent transmission, melioidosis will spread exponentially and claim more lives in the year to come. Therefore, clinicians and microbiologists should be made aware about this pathogen and its frequent misdiagnosis. Availability of validated diagnostic reagents for immunological and molecular tests and expansion of databases of commercial identification systems will likely remove the major hurdles in correct identification of *B. pseudomallei.* In conclusion, a high level of suspicion on the part of clinicians along with vigilant microbiologists and availability of discerning diagnostic assays may help in identification, reporting, and subsequent management of this "mimicker of maladies".

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Introduction

Melioidosis, caused by *Burkholderia pseudomallei* is one of the most neglected tropical disease worldwide, with a case fatality rate 50%.[1] The organism often resides in rice paddy fields, puddle soil and environmental niches affecting farmers and cultivators in contact with contaminated source.[2] The pathologist Alfred Whitmore and his colleague, C. S. Krishnaswami first discovered melioidosis in morphine addicted septicemia patients in Myanmar in 1911. Interestingly, it was not until a century later, in 2016, that the environmental prevalence of *B. pseudomallei* was confirmed in Myanmar.[3] The scenario is almost similar in most countries. In Bangladesh, the first case was a British sailor, whose ship was struck in Chattogram for three months owing to a cyclone, in 1960.[4] Today almost 60 years later, only 68 cases of melioidosis have been diagnosed, despite Bangladesh being a definite country for melioidosis.[5,6] In 2016, Limmathurotsakul et al predicted that 165,000 people are likely to get infected each year, of which 89,000 die. The study also concluded that South Asia contributed 44% of cases to this melioidosis burden, which raises the question of scarcity of case diagnoses as well as failure to detect the environmental source of the organism despite its endemicity in these regions.[7]

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The challenges faced in diagnosis and management of melioidosis

Melioidosis is a disease of the rural poor. As such, many cases remain unnoticed, undiagnosed and unreported. People are not aware of such a disease that exists, its complications and the precautions required for its prevention. Melioidosis may present with a myriad of clinical features that make the diagnosis confusing and delayed. When patients in rural areas present with symptoms of chronicity in Upazilla Health Complexes, often they are misdiagnosed and mistreated leading to fatality. Almost all the melioidosis cases that are detected in tertiary care hospitals in the capital provides a history of mismanagement at upazilla as well as district level hospitals and till today, to our best of knowledge, not one single case of melioidosis have been reported from outside Dhaka, with majority of cases being diagnosed in BIRDEM General Hospital, where doctors are familiar with the features and outcome of the disease. This clearly indicates a lack of awareness and lack of knowledge about this persisting tropical infectious disease among the clinicians and microbiologists along with insufficient diagnostic infrastructure countrywide.

Melioidosis- the great mimicker

Case-1: In 2009, a type-2 diabetic patient was admitted in BIRDEM hospital with high grade intermittent fever, dysuria and cough. On investigation, routine microscopic examination of urine revealed plenty of pus cells; radiological studies demonstrated, multiple opacities in the right lung; an enlarged prostate with multiple hypoechoic shadows suggestive of abscess. Previously, he was treated with injectable Ceftriaxone in a district level hospital out of Dhaka, for urinary tract infection.[8] The prostatic abscess fluid was aspirated endoscopically and culture revealed growth of *B. pseudomallei*.

This case is a classic example of how an immunocompromised patient infected with melioidosis can present with multiple clinical features. The patient presented with symptoms that reflected infection in the genitourinary tract as well as respiratory tract, making the diagnosis confusing. Melioidosis may present as a febrile illness with protean clinical manifestations, ranging from acute fulminant pneumonia and/or septicemia mimicking other community-acquired infections, to a chronic infection that may mimic tuberculosis or malignancy. The disease is characterized by abscess formation in multiple organs for which it is referred to as 'the great mimicker' because of its similarity to other infections that obscure its correct diagnosis.[9] Consequently, clinicians should have the awareness to suspect a patient with melioidosis if the patient residing in an endemic region, present with chronic fever, varied clinical manifestations, with a positive occupational history.

Misdiagnosis and mismanagement of melioidosis

Case 2- In 2019, a 55 year old non-diabetic man was admitted in Dhaka Medical College Hospital (DMCH) with the chief complaints of fever for almost a year, non-productive cough and weight loss. The patient was initially diagnosed as a case of tuberculosis at a regional hospital and was treated with anti-tubercular drugs for about three months. However, with deteriorating symptoms, the patient was admitted to DMCH and soon after, he developed pain and swelling in the left elbow followed by seizures and disorientation. Chest radiograph showed patchy and in-homogenous opacities in both lungs. Blood, sputum, urine and cerebrospinal fluid culture yielded no growth. Sputum for acid fast bacilli (AFB) and *M. tuberculosis* by Ziehl–Neelsen stain and MTB/RIF-GeneXpert test was negative respectively. Finally, pus aspirated from the left elbow yielded growth of *B. pseudomallei.*[10] The case reflects the difficulty that arises owing to inadequate knowledge about melioidosis. The patient was already misdiagnosed and mismanaged leading to worsening of symptoms. He had a Glasgow coma score of 3/15, but survived following treatment with standard antibiotic regimen for melioidosis. Likewise, several melioidosis patients remain on antitubercular drugs, while others are treated with high-end antibacterial agents like carbapenems with inadequate and shorter regimens leading to temporary suppression and recurrence of infection.[11] This case is a reflection of the worldwide scenario of melioidosis, where a lack of awareness and negligence about the infection results in undiagnosed, unreported, missed diagnosed and mismanaged cases, leading to the increasing mortality rate.

Clinical latency

B. pseudomallei infection may present as acute or chronic in most cases or remain latent in a dormant state. This disease may remain sub-clinical in immunocompetent individuals, as the bacteria remains in a quiescent state within the macrophage. In addition, wide use of broad-spectrum antibiotics at suboptimal doses suppresses the bacteria without eradicating the infection, leaving the chance of recurrence from its latency even after years.[1,12]

The diagnostic dilemma

In addition to melioidosis being a great mimicker of various diseases, obscuring the clinical diagnosis, the causative organism *B. pseudomallei* presents with atypical growth characteristics in culture, that may confuse the microbiologist as well. The colonies of Gram negative *B. pseudomallei* appear as mauve to pink colour in MacConkey agar media, just like the commonly isolated colonies of *Escherichia coli*. However, the colonies are wrinkled in appearance, oxidase positive and non-lactose fermenters, and a lack of prior knowledge about these features raises doubt in the minds of the microbiologists, who may discard the plates as environmental contaminants.[11,13] Molecular diagnosis or detection of the organism by Vitek, may yield better and confirmatory results, but are not done routinely in

developing countries due to expensive technologies and lack of expertise.

The multifactorial difficulties in diagnosing melioidosis that include its mimicry of other diseases, clinical latency, low culture sensitivity (60.2%), amount to case fatality of about 50% and relapse rate 20% in some settings.[1,14]

Measures to overcome the challenges

Raising awareness

Melioidosis is an extremely underrated and neglected disease in Bangladesh. Almost all cases have been diagnosed in tertiary care hospitals of Dhaka city till now. Melioidosis have a promising recovery rate, if the diagnosis can be made early and appropriate long term management with the correct antibiotic regimen is followed meticulously. For this, the clinicians and microbiologists all over the country should be trained on the clinical and laboratory diagnosis and management of the tropical disease. A dedicated team consisting of Clinical Microbiologists and Internal Medicine specialists from BIRDEM Hospital, Ibrahim Medical College as well as Bangabandhu Sheikh Mujib Medical University has been working diligently on raising awareness, by means of workshops through webinar, research and publications, maintaining collaboration with International Melioidosis Network. The topic of melioidosis may be extensively included in undergraduate and postgraduate medical courses to emphasize the importance of the disease. Most importantly, the disease must be included in the WHOs list of Neglected Tropical Diseases in order to promote large-scale substantial research on the worldwide prevalence, pathogenicity, adaptability and antimicrobial resistance mechanism.

Thailand, considered hyperendemic region for melioidosis, detected the first case of melioidosis in 1955. It may be noticed from 1955 to 1976, only 15 cases of melioidosis were reported. At present, due to utmost importance focused towards the diagnoses of the disease, implementation of laboratory training and improved communication between clinical and laboratory personnel, each year around 2000 cases are detected.[15] Over the years, scientists in Thailand have developed the "One Health" initiative for melioidosis investigation and promoted multidisciplinary melioidosis research in southern Thailand and as part of this initiative samples are collected from human, animals and soil.[16] In Bangladesh, similar strategy may be adopted to battle the public health threat imposed by melioidosis.

Development of a dedicated database for reporting melioidosis

International Melioidosis Network is a web-based open forum, maintained by the members of Mahidol University, Thailand, where melioidosis cases all over the world are reported. Similar network may be developed in Bangladesh which is essential to understand the prevalence, incidence, case fatality and mortality rate of the disease. The requirement for country-specific epidemiological melioidosis databases or registries as a neglected tropical disease is of utmost importance. Epidemiological studies should be conducted, that would provide information on a better understanding of disease transmission and preventable risk factors.

Prevention

Like any other infectious disease, prevention of infection remains the most important strategy. Melioidosis is transmitted by means of inoculation, inhalation, or ingestion from environmental sources. The disease is caused after exposure to *B. pseudomallei* in an immunocompromised person usually, through contact with cracked or damaged unprotected skin or less commonly by aerosol inhalation and contaminated water.[17] Therefore, basic public health measures include the primary provision of safe drinking water and sanitation, prevention of contact with contaminated soil or water, early case detection and appropriate management.[18] Other public health management approaches for increasing awareness and reducing exposure or con- tamination are information, education, communication activities for community education.

It is essential to increase the use of protective, water-resistant 'knee-high boots' in the paddy field and gloves when working outdoors to protect from rain, loose soil, and mud, where the bacteria reside. Precautions should be taken, especially during the rainy season and for farmers working in water-filled wet areas like rice fields.[15]

In Australia, groundwater (bore water) had shown contamination with *B. pseudomallei* in 33% of places. UV irradiation has been shown to decrease the burden of *Burkholderia* in the domestic water supply to an undetectable level.[19,20] Additionally, chlorination of potable water is also an effective disinfection method to control melioidosis.[21,22] In low-income and middle-income countries, where ultraviolet light treatment of water is not feasible, people must use traditionally boiled water before consumption.[19]

Conclusion

Although, 68 cases of melioidosis have been diagnosed in Bangladesh till now, the true extent of the disease still remains in the shadows. Due to the rising incidence of diabetes and population expansion in the country, the disease burden is anticipated to worsen. The greatest obstacle in reducing mortality in South Asian countries is the lack of adequate diagnostic laboratory facilities given the region's enormous population and growing melioidosis burden. In the regional context, establishing an efficient preventative program is a formidable undertaking. Improved surveillance, early diagnosis, case management, and preventative measures should be made possible by increased knowledge and understanding of the disease transmission dynamics.

Author contribution

SF wrote the manuscript and performed the literature search. FH contributed to literature search. SAS and AAS modified the literature search and revised the manuscript. MSAJ conceptualized the idea of the article, modified the search and revised the manuscript.

Declaration of interests

The authors declare no conflict of interest.

Reference

1. Birnie E, Virk HS, Savelkoel J, Spijker R, Bertherat E, Dance DA, Limmathurotsakul D, Devleesschauwer B, Haagsma JA, Wiersinga WJ. Global burden of melioidosis in 2015: a systematic review and data synthesis. The Lancet Infectious diseases. 2019 Aug 1;19(8):892-902.
2. Cheng AC, Currie BJ. Melioidosis: epidemiology, pathophysiology, and management. Clinical microbiology reviews. 2005 Apr;18(2):383-416.
3. Webb JR, Win MM, Zin KN, Win KK, Wah TT, Ashley EA, Smithuis F, Swe MM, Mayo M, Currie BJ, Dance DA. Myanmar Burkholderia pseudomallei strains are genetically diverse and originate from Asia with phylogenetic evidence of reintroductions from neighbouring countries. Scientific reports. 2020 Oct 1;10(1):1-0.
4. Maegraith BG, Leithead CS. Melioidosis: A Case-Report. Lancet. 1964:862-3.
5. Barai L, Saha MR, Rahman T, Sukanya M, Jafrin J, Ferdous J, Hasan MR, Jilani MS. Trends in laboratory detection of Burkholderia pseudomallei and their antibiotic susceptibility pattern from clinical samples over twenty one years from 2001 to 2021 in a tertiary care hospital of Bangladesh. Bangladesh Journal of Medical Microbiology. 2021 Jan 31;15(1):8-14.
6. Jilani MS, Robayet JA, Mohiuddin M, Hasan MR, Ahsan CR, Haq JA. Burkholderia pseudomallei: its detection in soil and seroprevalence in Bangladesh. PLoS neglected tropical diseases. 2016 Jan 15;10(1):e0004301.
7. Limmathurotsakul D, Golding N, Dance DA, Messina JP, Pigott DM, Moyes CL, Rolim DB, Bertherat E, Day NP, Peacock SJ, Hay SI. Predicted global distribution of Burkholderia pseudomallei and burden of melioidosis. Nature microbiology. 2016 Jan 11;1(1):1-5.
8. Barai L, Jilani MS, Haq JA. Melioidosis case reports and review of cases recorded among Bangladeshi population from 1988-2014. Ibrahim medical college journal. 2014;8(1):25-31.
9. Chandni R. Medicine Update. The Association of Physicians of India; Mumbai, India: 2013. Melioidosis: The great mimicker; pp. 14–18.
10. Farook S, Jilani MS, Akhter A, Haq JA. Melioidosis by aminoglycoside susceptible Burkholderia pseudomallei: First case in Bangladesh. IMC Journal of Medical Science. 2020;14(2):55-9.
11. Mohapatra PR, Mishra B. Burden of melioidosis in India and South Asia: Challenges and ways forward. The Lancet Regional Health-Southeast Asia. 2022 May 5.
12. Chaowagul W, Suputtamongkol Y, Dance DA, Rajchanuvong A, White NJ. Relapse in melioidosis: incidence and risk factors. Journal of Infectious Diseases. 1993 Nov 1;168(5):1181-5
13. Chen YS, Lin HH, Hung CC, Mu JJ, Hsiao YS, Chen YL. Phenotypic characteristics and pathogenic ability across distinct morphotypes of Burkholderia pseudomallei DT. Microbiology and immunology. 2009 Mar;53(3):184-9.
14. Wiersinga WJ, Virk HS, Torres AG, Currie BJ, Peacock SJ, Dance DA, Limmathurotsakul D. Melioidosis. Nature reviews Disease primers. 2018 Feb 1;4(1):1-22.
15. Hinjoy S, Hantrakun V, Kongyu S, Kaewrakmuk J, Wangrangsimakul T, Jitsuronk S, Saengchun W, Bhengsri S, Akarachotpong T, Thamthitiwat S, Sangwichian O. Melioidosis in Thailand: present and future. Tropical medicine and infectious disease. 2018 Apr 8;3(2):38.
16. Tuanyok A. One health initiative to uncover epidemiology of melioidosis in southern Thailand. Sri Lankan Journal of Infectious Diseases. 2017 Dec 20;7.
17. Chen PS, Chen YS, Lin HH, Liu PJ, Ni WF, Hsueh PT, Liang SH, Chen C, Chen YL. Airborne transmission of melioidosis to humans from environmental aerosols contaminated with B. pseudomallei. PLoS neglected tropical diseases. 2015 Jun 10;9(6):e0003834.
18. Savelkoel J, Dance DA, Currie BJ, Limmathurotsakul D, Wiersinga WJ. A call to action: time to recognise melioidosis as a neglected tropical disease. The Lancet Infectious Diseases. 2021 Dec 23.
19. McRobb E, Kaestli M, Mayo M, Price EP, Sarovich DS, Godoy D, Spratt BG, Currie BJ. Melioidosis from contaminated bore water and successful UV sterilization. The American Journal of Tropical Medicine and Hygiene. 2013 Aug 8;89(2):367.

20. Mayo M, Kaestli M, Harrington G, Cheng AC, Ward L, Karp D, Jolly P, Godoy D, Spratt BG, Currie BJ. Burkholderia pseudomallei in unchlorinated domestic bore water, Tropical Northern Australia. Emerging infectious diseases. 2011 Jul;17(7):1283.

21. Howard K, Inglis TJ. Disinfection of Burkholderia pseudomallei in potable water. Water Research. 2005 Mar 1;39(6):1085-92.

22. Inglis TJ, Garrow SC, Henderson M, Clair A, Sampson J, O'Reilly L, Cameron B. Burkholderia pseudomallei traced to water treatment plant in Australia. Emerging infectious diseases. 2000 Jan;6(1):56.