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"Diabetes-Driven Dilemma: Tackling The Rise of Melioidosis in India"

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Abstract

Melioidosis is a potentially fatal infectious disease that requires an extended period of treatment for complete resolution of the infection. It can lead to chronic and severe infections, and it is more common in diabetic patients. Melioidosis is also a significant concern in India primarily because its chronic nature, potential for dissemination, extended treatment requirements, and the risk of relapse lead to its resemblance to tuberculosis. This case series included osteomyelitis patient presented in emergency with sepsis MODS, disseminated melioidosis patient with systemic involvement including spleen, kidney and lungs, skin abscess at more than one site, urosepsis, splenic abscess, Melioidotic arthritis. Many of these patients had altered blood sugar levels, and in 3 cases, individuals were even diagnosed with diabetes during their episode of melioidosis the treatment duration generally involved an 8-week course of intravenous antibiotics. However, oral medications may need to be continued for several months if necessary for complete recovery.

Keyword: *Diabetes, Health, Recovery*

Introduction:

Melioidosis is an infectious and potentially fatal disease caused by a gram-negative soil saprophyte and a potential biothreat agent *Burkholderia Pseudomallei*. It has the ability to invade macrophages and persist within them. Recognition of the bacteria by toll-like receptors (TLRs) on host cells activates the immune response, leading to the release of proinflammatory cytokines and the initiation of the nuclear factor-κB (NF-κB) pathway. The bacterium possesses various mechanisms to evade immune defences, including resistance to complement, lysosomal defensins, and cationic peptides. B. pseudo mallei produces enzymes, toxins, and a glycocalyx polysaccharide capsule that aid in its survival, replication, and biofilm formation. Lipopolysaccharide (LPS), an immunodominant antigen in the bacterial cell wall, elicits an antibody response that is associated with improved survival (1,2).

Melioidosis today has been reported from various regions in the world yet remains highly endemic to the northern regions of Australia, Northeast of Thailand, Malaysia, Singapore, Vietnam, Cambodia, Laos, areas of the Indian subcontinent, southern China, Hong Kong, Taiwan, various Pacific and Indian Ocean islands, and parts of the Americas, with melioidosis now reported in over 50 countries (3). India being the largest South-Asian country, with the world's largest population, the diabetes capital and a primarily tropical agrarian country, stands as a fertile soil of the growth of melioidosis, yet the actual extent of melioidosis in India remains elusive due to insufficient awareness and limited laboratory resources across the country, hence termed 'tip of the iceberg' (4).

Accurately diagnosing the disease poses significant difficulties in clinical settings, given its diverse range of clinical manifestations and thus the name, 'the great mimicker'(5,6). This complexity is further compounded

by the fact that melioidosis can resemble other infections like tuberculosis, which is highly prevalent in economically disadvantaged nations like India.

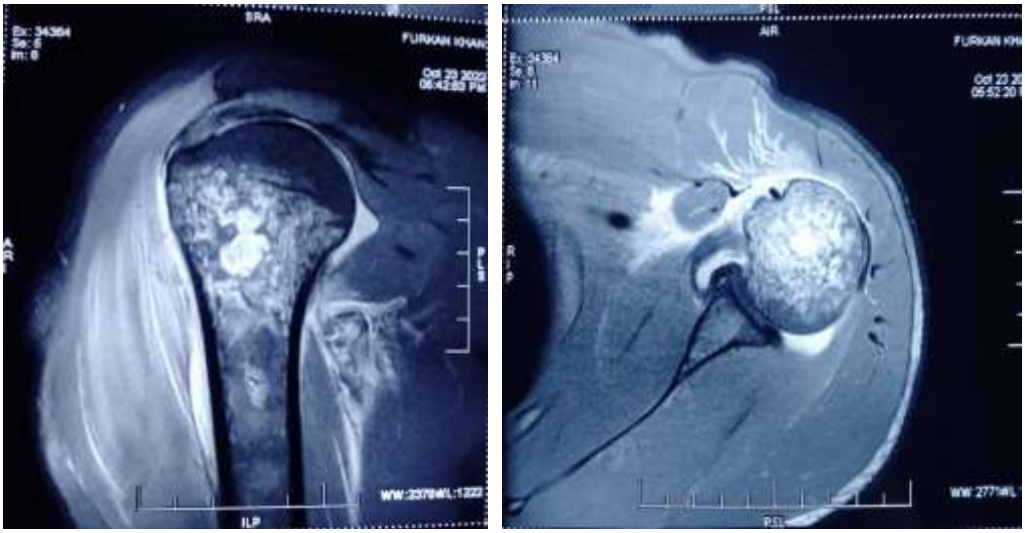
Melioidosis primarily affects individuals who come into regular contact with soil and water. Infection can occur through percutaneous inoculation, inhalation, or ingestion (3). The disease is predominantly seasonal, with 75 to 81% of cases occurring during the rainy season (7). While the incidence peaks between 40 and 60 years of age, melioidosis can also affect children and can be transmitted through breast milk (8). Up to 80% of melioidosis patients have one or more risk factors, suggesting it as an opportunistic infection (9). The incubation period can vary depending on factors such as the infecting dose, strain virulence, mode of infection, and host's risk factors. Clinical manifestations range from acute septic illness to chronic infections resembling cancer or tuberculosis. Common presentations include pneumonia, genitourinary infections, skin infections, bacteraemia, septic arthritis or osteomyelitis, and neurologic involvement (1,3,10,11) Herein we present various cases where causative agent is B. pseudo mallei in a tertiary care teaching hospital in central India.

Case Presentations

left humerus osteomyelitis with ARDS and septic shock

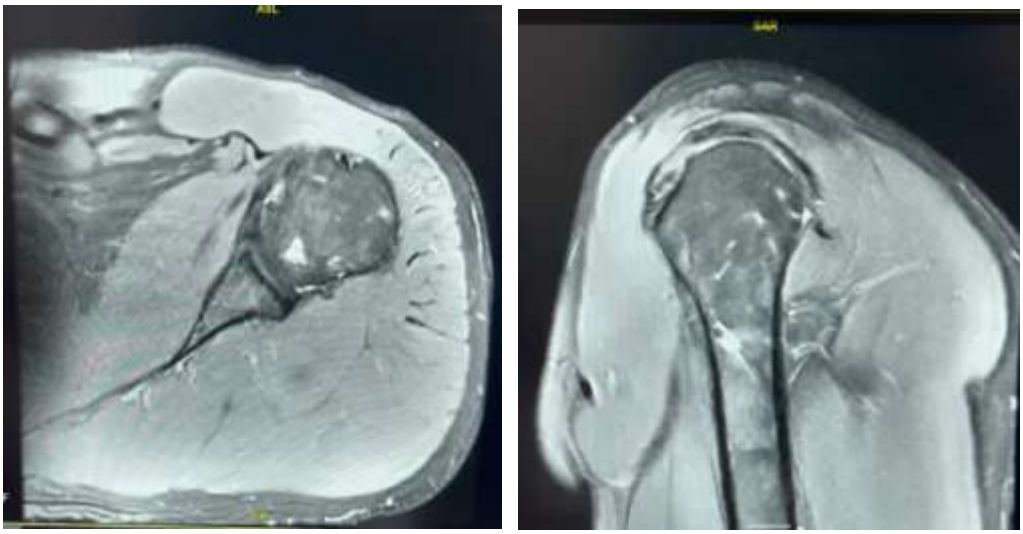
A middle-aged male, chronic alcoholic, farmer by profession with no previous comorbidities came with complaints of high-grade fever with chills and rigors, pain in left upper limb (MRI done outside suggestive of osteomyelitis of left humerus). He was brought to AIIMS with complaints of altered sensorium, fever and yellowish discoloration of eyes and skin. Patient developed hypoxia was shifted to ICU for the same. Initial treatment was targeted for sepsis and MODS. Blood cultures were suggestive of *Burkholderia*. He was intubated in view of poor GCS and respiratory distress. Diagnosis once stabilised and condition improved, was then shifted to ward and managed with IV antibiotics as per the culture reports and supportive treatment. Patients HBA1C was 14.1. Blood sugar was controlled. Patient gradually became afebrile, hemodynamically stable and was discharged with oral medication. Patient was followed monthly for 6 months and a review MRI was done showing radiological improvement.

Before treatment



MRI revealed hypointense lesions on T1 hyperintense on T2 weighted images on the left humerus, indicative of a chronic draining osteomyelitis of the humerus.

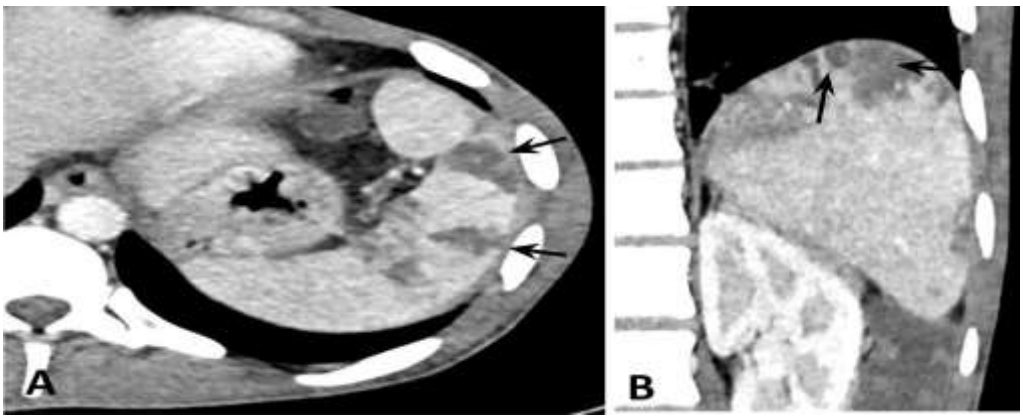
After treatment



MRI of left shoulder reveals: resolved/healed intraosseous abscesses.

Liver and Splenic abscess

A middle-aged Indian male, watchman by profession, chronic alcoholic with no previous comorbidities presented with chief complaints of high-grade fever with chills and rigor, right shoulder pain, episodes of vomiting. Patient was admitted in the ward and evaluated for the same. On investigation USG- W/A was s/o mild hepatomegaly, ill-defined hypoechoic segment VI lesion and splenomegaly, indicating liver and splenic abscess. Initially he was started on broad spectrum iv antibiotics and supportive treatment. On 2nd day liver abscess was drained using Pigtail catheter and was found to be positive for *Burkholderia Pseudomallei* susceptible to imipenem, meropenem, cotrimoxazole, so, the patient was shifted to iv antibiotics as per culture reports, Patient's fever gradually improved and his blood sugar levels were controlled with antidiabetic medications.



(A-B): Axial (A) and coronal (B) contrast-enhanced CT images of the abdomen reveal multiple discrete and confluent hypodense areas predominantly involving the periphery of the splenic parenchyma.

Left ureteric calculi with mild HUN and urosepsis

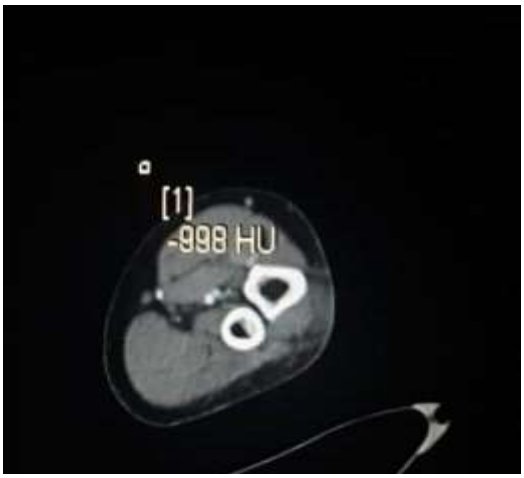
A 67year old male known patient of diabetes mellitus, CAD came with complaints of pain in Right flank region, associated with episodes of vomiting, high grade fever assisted with chills and rigors. Patient was admitted and evaluated for the same. USG-W/A+KUB- suggestive of mild HUN.NCCT-KUB was planned and patient was admitted under urology, NCCT-KUB suggestive of left obstructive proximal ureter calculus causing left mild HUN. Post procedure (left DJ stenting) patient had continuous fever spikes, urine and blood cultures sent. Urine culture was positive of *Burkholderia* susceptible to ceftazidime, meropenem and intermediate susceptibility to minocycline so he was started on culture suggested antibiotics lead to drastic improvement of patient and discharged on oral medications.

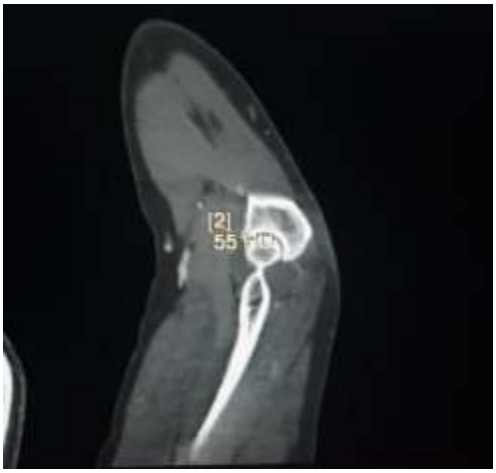
Melioidotic arthritis of left elbow

43 years aged male patient, forest officer by occupation with no known comorbidities presented to the emergency with chief complaints of swelling and pain in the left elbow, fever with chills and rigor. Patient was admitted and evaluated for the same. CECT left elbow joint reported that there is moderate to gross joint effusion with peripheral enhancing mild thickened synovium representing synovitis. HRCT elbow was suggestive of hypodense collection around the left elbow joint representing joint effusion, no e/o of fracture

and erosive changes seen. Orthopaedic opinion was sought and planned for Arthrotomy. On examination, Synovial fluid collected from the procedure was found to have pus cells 8-10/ hpf and also positive to *Burkholderia Pseudomallei* susceptible to ceftazidime, imipenem, meropenem.so patient was started on culture suggested iv antibiotics. Patient improved symptomatically and his blood sugar levels were controlled and was discharged with antibiotic medications as per need.

CECT of elbow





Left elbow joint reported that there is moderate to gross joint effusion with peripheral enhancing mild thickened synovium representing synovitis

Elbow lesion

follow up after 2 months

Skin abscesses with disseminated infection (spleen, lung, skin)

21 years aged male patient, chronic alcoholic with no known comorbidities presented with c/o fever associated with chills and rigor and cough, nausea and vomiting, significant weight loss, and skin ulcers on thigh and right arm, he also had episodes of dyspnoea and chest pain, palpitations. Patient was admitted and evaluated for the same. On investigations CT revealed septic emboli, central cavitation in lung, abscesses and blood culture were positive to *Burkholderia Pseudomallei* so was initiated so he was started on culture suggested iv antibiotics. Patient gradually improved and discharged with oral medication and further followed up in medicine OPD.

Skin ulcer on thigh and right arm

Figure 1

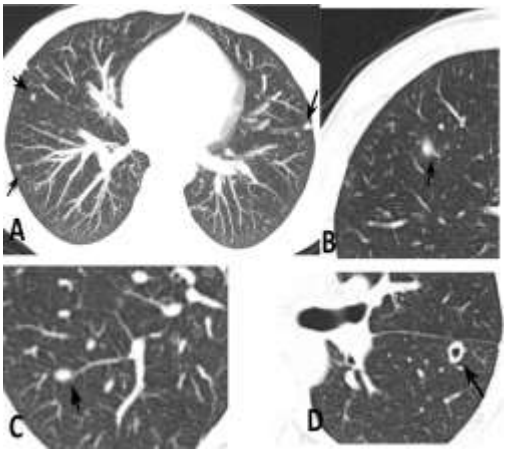


Figure 2

FIGURE 1 Axial contrast-enhanced CT of the abdomen shows few well-defined peripherally enhancing abscesses anterior to left kidney giving honeycomb-like appearance.

FIGURE 2 (A-D): Axial CT sections of the lungs demonstrate multiple subcentimetric nodules scattered in bilateral lung parenchyma with few of the nodules showing feeding vessel sign (B, C) and central cavitation (D), suggestive of septic emboli.

Healed skin lesions at the end of 2 months
Culture plates as demonstrated in one of our patients



Haematological parameters of the patients on their admission

Investigations	Case 1	Case 2	Case 3	Case 4	Case 5
Haemoglobin (g/dl)	14.5	9.9	10.9	13.1	7.6
TLC(/dl)	9.45	14.96	10.8	9.23A	22.1
Platelets (lakhs/dl)	0.31	232	336	266	174
Urea (Mg/dl)	105.81	19.67	72	7.16	-
Creatinine (Mg/dl)	1.85	0.65	2.4	1.26	-
Total.Bil(Mg/dl)	14.29	0.42	1.96	0.9	0.93
Direct.Bil(Mg/dl)	8.64	0.10	0.72	0.3	0.27
AST(U/L)	89.4	91.1	196	61.9	46
ALT(U/L)	89.9	11.7	182	99	26.5
ALP(U/L)	335.4	372	560	104.6	408.8
HbA1c (%)	14.1%	13.3%	6.9%	6.6%	5.9%
Sodium (Mmol/L)	124	125	130	129.1	137
Potassium (Mmol/L)	5.05	4.03	3.2	4.3	3.46

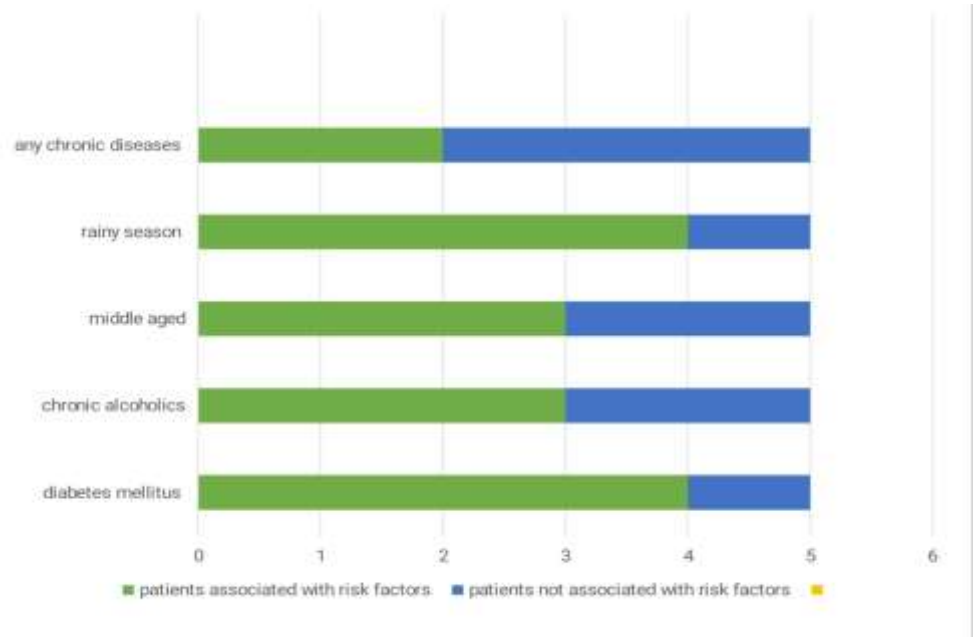
In the post-pandemic era, tropical infectious diseases have been of rising concern due to increasing antimicrobial resistance among pathogens.

Case	Age	Sex	Occupation	Clinical presentations	Cultures where Burkholderia is positive	HbA1c
1	38	Male	Farmer	left humerus osteomyelitis	Blood	14.1
2	32	Male	Watchman	Liver and splenic abscess	Drained Abscess	13.3
3	67	Male	Retired	Mild HUN and urosepsis	Urine	6.9
4	43	Male	Forest officer	Melioidotic arthritis	Synovial fluid	6.6
5	21	Male	Student	Skin abscesses with dissemination	Blood	Non diabetic

The complexity of diagnosing melioidosis becomes evident when considering its presence in various body fluids. Herein infectious disease's influence extends to multiple body organs, encompassing the lungs, liver, spleen, urinary system, and bones and joints, underscoring its broad spectrum of infectivity.

Risk factors	Case 1	Case 2	Case 3	Case 4	Case 5
Diabetes mellitus	Yes	Yes	Yes	Yes	No
Chronic alcoholic	Yes	Yes	No	No	Yes
Middle Aged	Yes	Yes	No	Yes	No
Rainy season	Yes	Yes	No	Yes	Yes
Any chronic diseases	Yes	No	Yes	No	No

Rainy season in India is considered between June to September, October Associated risk factors observed in case series



In the existing literature, there is a growing concern regarding the increased incidence of melioidosis, particularly in diabetic populations as there is altered release of cytokines (16,17). Our case series have reported a strong correlation between diabetes and melioidosis, with a substantial portion i.e. 4 out 5 of affected individuals with diabetes, of which 3 were newly diagnosed as diabetics.

Additionally, this case series also has highlighted the potential association between melioidosis and alcohol use as 3 out 5 were chronic alcoholics, as well as the role of soil contact and rainy seasons in the transmission of the disease where 4 out of 5 cases were reported in the rainy season. These environmental factors seem to contribute to the higher incidence of melioidosis in certain regions, especially in middle aged male individuals where all cases were males here

Over the past two decades, there has been a notable increase in research publications related to melioidosis in India, highlighting a growing awareness and improved diagnostic capabilities within the country.

While melioidosis may have been considered rare in the past in central India, this burgeoning literature suggests a need to re-evaluate that perception. It serves as a call to action for healthcare providers to be vigilant and consider melioidosis as a potential diagnosis, especially in high-risk groups such as diabetics, individuals with soil contact, and during rainy seasons.

Furthermore, the similarities between melioidosis and tuberculosis in terms of chronicity, dissemination, antibiotic resistance, and the risk of relapse have led experts to express worries about melioidosis potentially evolving into a major health concern, especially for diabetic individuals where we can relate the melioidosis being the next Tuberculosis in diabetics

Melioidosis is a challenging as cure without a prolonged course of appropriate antibiotics. *B. pseudomallei* is inherently resistant to several antibiotics including penicillin, ampicillin, cephalosporins, aminoglycosides, and polymyxin (14). Among newer antibiotics, ertapenem, tigecycline, and moxifloxacin have limited activity against B. pseudo mallei, while doripenem has similar efficacy to meropenem. Acquired antibiotic resistance mechanisms include efflux pumps, enzymatic inactivation, impermeability of bacterial cell membranes, alterations in antibiotic target sites, and amino acid changes in pen A gene encoding β-lactamase (15,18).

The rising concern is not limited to the obstacles of management and threat as a bioterror agent but also as a diagnostic challenge due to the extremely varied presentations of the disease and limited resources. (14).

The case series included osteomyelitis patient presented in emergency with sepsis MODS, disseminated melioidosis patient with systemic involvement including spleen, kidney and lungs, skin abscess at more than one site, urosepsis, splenic abscess with frequent relapse. All cases were admitted, culture proven to have *Burkholderia*. The targeted treatment and controlled blood glucose levels caused drastic clinical improvement in all our patients. The treatment mainly includes antibiotics for the intensive and eradication phase which may last for 6 to 8 months.

It's important to closely monitor patients with melioidosis, as relapse can be a serious complication. The studies you mentioned from Australia, Thailand, Southern India, and China have reported cases of recurrence (13)
A complex epidemiological triad favours the increasing incidence of melioidosis today, wherein incidence rates exceed dengue and stands second only to Tuberculosis and HIV in many endemic countries such as Thailand.

The growing rates of other non-communicable diseases and behavioural factors such as diabetes mellitus and alcoholism also serve as strong ground. Diabetes serves as one of the strongest risk factors of disease acquisition as reported by multiple case studies. (3,6,9,10,11). The mainstay of management in our patients was antibiotic based medical management, in contrast to surgical interventions having limited scope. (19,1)

Conclusion:

This case series was documented to raise clinical suspicion in tropical regions like central India and the rest of the world to newer infectious diseases, with more atypical presentations. In developing nations with limited resource settings, increased clinical suspicion should be developed for organisms similar to 'pseudomonas like organisms', in diabetic patients or other significant risk factors of the disease. As melioidosis requires long term therapy including intensive and eradication antibiotic therapy and can be potentially fatal in cases of delay, early detection warrants much stronger clinical suspicion. The mainstay of treatment remains carbapenems and cotrimoxazole until proved otherwise in such situations.

References

1. Wiersinga WJ, Virk HS, Torres AG, Currie BJ, Peacock SJ, Dance DAB, Limmathurotsakul D. Melioidosis. Nat Rev Dis Primers. 2018 Feb 1;4: 17107. doi: 10.1038/nrdp.2017.107. PMID: 29388572; PMCID: PMC6456913.
2. Bzdyl NM, Moran CL, Bendo J, Sarkar-Tyson M. Pathogenicity and virulence of Burkholderia pseudomallei. Virulence. 2022 Dec;13(1):1945-1965. doi: 10.1080/21505594.2022.2139063. PMID: 36271712; PMCID: PMC9635556.1230
3. Cheng AC, Currie BJ. Melioidosis: epidemiology, pathophysiology, and management. Clin Microbiol Rev. 2005 Apr;18(2):383-416. doi:10.1128/CMR. 18.2.383-416.2005. Erratum in: Dance DA. Melioidosis: the tip of the iceberg? Clin Microbiol Rev. 1991 Jan;4(1):52-60. doi: 10.1128/CMR.4.1.52. PMID: 2004347; PMCID: PMC358178.
4. Singh M, Mahmood M. Melioidosis: the great mimicker. J Community Hosp Intern Med Perspect. 2017 Sep 19;7(4):245-247. doi: 10.1080/20009666.2017.1348875. PMID: 29046753; PMCID: PMC5637701.
5. Yee KC, Lee MK, Chua CT, Puthucheary SD. Melioidosis, the great mimicker: a report of 10 cases from Malaysia. J Trop Med Hyg. 1988 Oct;91(5):249-54. PMID: 3184245.
6. Currie BJ, Jacups SP. Intensity of rainfall and severity of melioidosis, Australia. Emerg Infect Dis. 2003 Dec;9(12):1538-42. doi: 10.3201/eid0912.020750. PMID: 14720392; PMCID: PMC3034332.
7. Rodríguez JY, Huertas MG, Rodríguez GJ, Vargas-Otalora S, Benıtez-Peñuela MA, Esquea K, Rios R, Mendoza LR, Diaz L, Reyes J, Álvarez-Moreno CA. Case Report: Gestational Melioidosis through Perinatal Transmission. Am J Trop Med Hyg. 2020 Nov;103(5):1838-1840. doi: 10.4269/ajtmh.20-0223. PMID: 32748772; PMCID: PMC7646751.
8. Zueter A, Yean CY, Abumarzouq M, Rahman ZA, Deris ZZ, Harun A. The epidemiology and clinical spectrum of melioidosis in a teaching hospital in a North-Eastern state of Malaysia: a fifteen-year review. BMC Infect Dis. 2016 Jul 16; 16:333. doi: 10.1186/s12879-016-1583-2. PMID: 27423906; PMCID: PMC4947242.
9. Birnie E, Virk HS, Savelkoel J, Spijker R, Bertherat E, Dance DAB, Limmathurotsakul D, Devleesschauwer B, Haagsma JA, Wiersinga WJ. Global burden of melioidosis in 2015: a systematic review and data synthesis. Lancet Infect Dis. 2019 Aug;19(8):892-902. doi: 10. 1016/S1473-3099(19)30157-4. Epub 2019 Jul 5. PMID: 31285144; PMCID: PMC6867904.
10. Risk Factors for Mortality in Melioidosis: A Single-Centre, 10-Year Retrospective Cohort Study. Scientific World Journal. 2021 Jul 5;2021: 8154810. doi: 10. 1155/2021/ 8 154810. PMID:M34285680; PMCID: PMC8275413.
11. Cheng AC, Fisher DA, Anstey NM, Stephens DP, Jacups SP, Currie BJ. Outcomes of patients with melioidosis treated with meropenem. Antimicrob Agents Chemother. 2004 May;48(5):1763-5. doi: 10.1128/AAC.48.5.1763-1765.2004. PMID: 15105132; PMCID: PMC400582.
12. Currie BJ, Fisher DA, Anstey NM, Jacups SP. Melioidosis: acute and chronic disease, relapse and re-activation. Trans R Soc Trop Med Hyg. 2000 May-Jun;94(3):301-4. doi: 10.1016/s0035-9203(00)90333-x. PMID: 10975006.
13. Yamamoto T, Naigowit P, Dejsirilert S, Chiewsilp D, Kondo E, Yokota T, Kanai K. In vitro susceptibilities of Pseudomonas pseudomallei to 27 antimicrobial agents. Antimicrob Agents Chemother. 1990 Oct;34(10):2027-9. doi: 10.1128/AAC.34.10.2027. PMID: 2291671; PMCID: PMC171985.
14. Hoffmaster AR, AuCoin D, Baccam P, Baggett HC, Baird R, Bhengsri S, Blaney DD, Brett PJ, Brooks TJ, Brown KA, Chantratita N, Cheng AC, Dance DA, Decuypere S, Defenbaugh D, Gee JE, Houghton R, Jorakate P, Lertmemongkolchai G, Limmathurotsakul D, Merlin TL, Mukhopadhyay C, Norton R, Peacock SJ, Rolim DB, Simpson AJ, Steinmetz I, Stoddard RA, Stokes MM, Sue D, Tuanyok A, Whistler T, Wuthiekanun V, Walke HT. Melioidosis diagnostic workshop, 2013. Emerg Infect Dis. 2015 Feb;21(2):e141045. doi: 10.3201/eid2102.141045. PMID: 25626057; PMCID: PMC4313648.
15. Moore RA, DeShazer D, Reckseidler S, Weissman A, Woods DE. Efflux-mediated aminoglycoside and macrolide resistance in Burkholderia pseudomallei. Antimicrob Agents Chemother. 1999 Mar;43(3):465-70. doi: 10.1128/AAC.43.3.465. PMID: 10049252; PMCID: PMC89145.
16. Morris J, Williams N, Rush C, Govan B, Sangla K, Norton R, Ketheesan N.Burkholderia pseudomallei triggers altered inflammatory profiles in a whole-blood model of type 2 diabetes-melioidosis comorbidity. Infect Immun.

2012Jun;80(6):2089-99. doi:10.1128/IAI.00212-12. Epub 2012 Apr 2. PMID: 22473609; PMCID: PMC3370601.

17. Hodgson KA, Govan BL, Walduck AK, Ketheesan N, Morris JL. Impaired early cytokine responses at the site of infection in a murine model of type 2 diabetes and melioidosis comorbidity. Infect Immun. 2013 Feb;81(2):470-7. doi: 10.1128/IAI.00930-12. Epub 2012 Dec 3. PMID: 23208607; PMCID: PMC3553796.
18. Somprasong N, Hall CM, Webb JR, Sahl JW, Wagner DM, Keim P, Currie BJ, Schweizer HP. Burkholderia ubonensis Meropenem Resistance: Insights into Distinct Properties of Class A β-Lactamases in Burkholderia cepacia Complex and Burkholderia pseudomallei Complex Bacteria. mBio. 2020 Apr 14;11(2):e00592-20. doi: 10.1128/mBio.00592-20. PMID: 32291300; PMCID: PMC7157819.
19. Liu Y, Zong Z. Prolonged intermittent fever and massive splenomegaly in a miner working in the tropical jungle, China. PLoS Negl Trop Dis. 2020 Jul 9;14(7):e0008278. doi: 10.1371/journal.pntd.0008278. PMID: 32644997; PMCID: PMC7347091.