Study of incidence of Melioidosis for a period of one year and eight months in a Tertiary care Hospital, Kerala, South India

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ABSTRACT

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Melioidosis is caused by a gram-negative bacterium Burkholderia pseudomallei is geographically restricted to South East Asia & Northern Australia. In India many cases have been reported in recent years. This study was undertaken to analyze the varied clinical presentation and increased incidence of melioidosis. We carried out a retrospective study of eight cultures proven cases of melioidosis at a tertiary care hospital in Kerala, South India between July 2014 and Feb 2016.

Melioidosis infection in human beings may present as two forms, acute or chronic. The clinical presentation of melioidosis is highly variable and may mimic those of tuberculosis. Microbiological culture remains the standard method for the diagnosis of melioidosis. Treatment is usually divided into two phases, intensive phase for 10-14 days and eradication phase for a minimum of 12- 24 weeks. Currently there is no licensed vaccine available for melioidosis.

The commonest risk factor in our study was diabetes and alcoholism was the second commonest risk factor for melioidosis. But host immunity compromise may not a prerequisite for Melioidosis, as it can occur in any healthy children or adults. The disease has been shown to mimic tuberculosis. Abscess was the most common clinical presentation (87.5%) in contrast to earlier studies which showed fever as most common presentation.

The incidence of melioidosis cases are increasing in India, as in rest of the world. Increase in diabetic patients in Indian population is one of the important risk factor for increased incidence and also increased awareness among clinicians and microbiologists resulting in better recognition and reporting.

Keywords: Burkholderia pseudomallei, Melioidosis, Incidence of melioidosis in Kerala

*See End Note for complete author details

INTRODUCTION

Melioidosis (synonym 'Whitemore disease') caused by Burkholderia pseudomallei, a highly pathogenic bacterium, which was previously classed as part of the Pseudomonas genus and until 1992 it was known as Pseudomonas pseudomallei. The name melioidosis is derived from the Greek 'melis' meaning a disease of asses (glanders) and 'eidos' meaning resemblance. It is phylogenetically related closely to Burkholderia mallei which causes glanders (a disease primarily of equine animals- horses, donkeys, mules, asses but capable of being transmitted to other animals and human beings). The disease was first described in human beings by Whitmore and Krishnaswami (1912) in Rangoon (now known as Yangon), Burma. Whitmore isolated the bacillus in the year 1913.[1, 2,3,4,5]

Burkholderia pseudomallei is a mobile, obligatory aerobic, non-spore forming gram-negative baillus found in soil, water, paddy fields.[4, 6] The bacillus on microscopy shows typical bipolar "safety pin appearance". Infection usually acquired by inoculation, inhalation or ingestion. Percutaneous inoculation (contamination of abrasion wounds with soil and water containing the organism) is the most frequent route for natural infection, e.g., agricultural workers, having close and regular contact with soil[7]. The higher incidence melioidosis may occur during heavy monsoon rains because of the occupational and recreational exposure to surface water and mud, particularly with flooding of paddy fields and planting at the commencement of the monsoon season. Transmission can also occur through inhalation of aerosolized bacteria from surface water and soil during winds and heavy rainfall.[7, 8]

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The peak in incidence of natural infection occurs among adults 40–60 years of age.[7] Diabetes mellitus is the major risk factor for disease. Excessive alcohol consumption, chronic renal failure, and chronic lung disease, renal stones, thalassaemia, severe burns are also independent risk factors. Malignancies and cystic fibrosis are other risk factors but in these, disease associations are not as well established. HIV infection does not appear to be a risk factor.[7, 2, 3,4] The incubation period for melioidosis can be quite variable because it can be unclear or not known when the exposure occurred. In a study of 52 cases in Australia and Papua New Guinea, the average incubation period was 9 days (range 1–21 days).[9] The longest known period between exposure and clinical infection is 62 years in a World War II veteran.[10]

Melioidosis infection leads to bacteremia, followed by formation of abscesses in the lungs, liver, and spleen. Melioidosis infection in human beings may present as two forms. Acute melioidosis is a generalized infection presenting as acute septicemia or subacute typhoid-like disease or pneumonia and hemoptysis. Chronic melioidosis presents as multiple caseous or suppurative foci, with abscess formation in the skin and subcutaneous tissues, bones and internal organs. The symptoms of melioidosis may mimic those of tuberculosis. Acute meliodosis has high case fatality rate.[1,2,3] The death rate for sepsis-associated melioidosis is 50%–90%.[7]

Microbiological culture remains the standard method for the diagnosis of melioidosis. Culture specimens should be obtained from blood, throat, urine, respiratory secretions, pus, and surface lesions as appropriate, for all patients with suspected cases.[7] Isolation of even a single colony of B. Pseudomallei from any part of the body site is indicative of disease.[7, 11] It is relatively slow/late lactose fermenter and produces grey lytic colonies in McConkeys agar or blood agar. Timely communication between the clinical and microbiology team could potentially improve the diagnostic yield, especially when reported as gram-negative organisms that are oxidase positive, gentamicin and colistin resistant and susceptible to amoxicillin/clavulanic acid should be strongly suspected to be B. pseudomallei. PCR to detect B. pseudomallei and B. mallei in clinical samples has been described, but is less sensitive than culture.[7] Indirect hemagglutination test can be helpful in travelers.[3]

Treatment is usually divided into two phases. Intensive phase for 10-14 days with the aim of preventing death from overwhelming sepsis; Ceftazidime, 100 mg/kg (2g 8-hourly) is drug of choice. For treatment failures or severe infections, carbapenems like meropenem(0.5 – 1 g, 8-hourly) or imipenem (1 g, 6-hourly) is reserved.[2] Amoxicillin/clavulanic acid (co-amoxiclav) used as second-line therapy. Eradication phase with the aim of preventing relapse includes extended period of oral antimicrobial therapy for a minimum of 12- 24 weeks.[2, 3, 8, 11, 12,13] Cotrimoxazole (Trimethoprim 320 mg plus sulfamethoxazole 1600 mg, 12-hourly) is preferred for the eradication phase. Doxycycline (200 mg daily) or co-amoxiclav can be used in cotrimoxazole resistant cases or for those who cannot tolerate.[3,7]

Cotrimoxazole has been given with doxycycline in Thailand, but comparative trial showed that the addition of doxycycline to cotrimoxazole did not provide statistically relevant improved efficacy over cotrimoxazole alone.[7,2,3] Abscesses should be drained surgically.

The duration of the intensive phase treatment should be 4 or more weeks and addition of cotrimoxazole to be done, especially in septicemic cases of neurological, prostrate, bone or joint melioidosis.[12,14] Patients with blood cultures positive for B. pseudomallei should repeat blood cultures every week after the start of antimicrobial therapy until negative. A repeat positive blood culture after ≥1 week of antimicrobial therapy is indicative of treatment failure and these patients should be investigated for the presence of undrained abscesses and a change from ceftazidime to meropenem might be considered. If the patient has persistent bacteremia and is already being treated with a carbapenem drug, consideration should be given to the addition of cotrimoxazole.[7]

Symptoms of B. pseudomallei infections resolve in a much slower. The average time for fever resolution is 9 days, however fever fluctuation may continue for as long as 1 month in patients with internal abscesses.[8] Clinicians should be aware that a lack of marked improvement within 24 h of initiating antimicrobial therapy is not uncommon. The relapse rate after the full eradication regimen is ≈10% but rises to 30% if the oral therapy is taken for ≤8 weeks.

MATERIAL AND METHODS

In a retrospective clinical study of patients admitted to Jubilee Mission Medical College & Research Institute, Thrissur, Kerala, South India, for one year and eight months (between July 2014 and February 2016), 8 cases of culture proven melioidosis were included in the study. These patients were studied with respect to age gender, area of residence, suspected risk factors and

Table 1. Demographic data of 8 patients with Melioidosis

Characteristics	No (%) of patients with Characteristics
Age in years: median (range)	36.5 (2-82)
Sex: male	5 (62.5%)
Sex: female	3 (37.5%)
Age group <10 yrs	2 (25.0%)
18-65 yrs	5 (62.5%)
> 65 yrs	1 (12.5%)
District of Origin	
Thrissur	4
Palakad	3
Malappuram	1
Residence in rural area	8 (100%)
Underlying risk factor	
Diabetes mellitus(DM)	5 (62.5%)
Alcohol consumption	3 (37.5%)
Renal failure	2 (25.0%)

Table 2. Clinical presentation of 8 patients with Melioidosis

Symptoms	No (%)
Abscess	7(87.5%)
Neck swelling	3 (37.5%)
Splenic abscess	2 (25%)
Abscess in foot	1 (12.5%)
Abscess in wrist & arm	1 (12.5%)
Parotid/ prostatic/ scrotal abscess	0
Abscess along with fever	5 (62.5%)
Abscess without fever	2 (25.0%)
Fever	6 (75%)
Breathlessness	2 (25%)
Lung lesions (pnemonia)	2 (25%)
Erythema nodosum	1 (12.5%)
Joint pain	0
Lymphadenopathy	4 (50%)
Hepatospleenomegaly	3 (37.5%)

Table 3. Laboratory values of 8 patients with Melioidosis

Lab test	No (%)
Total count (Range:2020- 32160 cells/cmm)	
Elevated total count	7 (87.5%)
Low total count	1 (12.5%)
Thrombocytopenia	3 (37.5%)
Serum creatinine increased	2 (25%)
Serum bilirubin increased	2 (25%)
Elevated liver enzymes	3 (37.5%)
Albumin/ Globulin reversal	3 (37.5%)
Isolation of B. pseudomallei from	
Blood culture	3 (37.5%)
Pus culture	4 (50%)
Culture of lymphnode biopsy material	1 (12.5%)
Isolation of B. pseudomallei both from blood & pus culture	1 (12.5%)
Outcome:	
Cured on follow up	7(87.5%)
Septic shock and death	1 (12.5%)

analyzed for its various clinical presentations, severity, culture sensitivity of the organism and outcome. **(Table 1, 2 and 3)**

ANALYSIS OF THE STUDY

1. The patient's age varied from 2 to 82 years with a median age of 36.5 years. Out of 8 patients, majority were below the age of 60 yrs (7 out of 8)
2. Males constituted 62.5% (5 out of 8) of cases.
3. All cases were from rural areas.
4. The average duration of illness was 25.5 days; shortest duration was 10 days and longest being 60 days.
5. Diabetes mellitus was present in 5 patients (62.5%). Along with DM two patients had renal failure and two patients were chronic alcoholics. One patient had multiple risk factors like excessive alcohol intake, renal failure along with DM. There were no other risk factors like- renal stones, cirrhosis liver, thalassemia or severe burns. Co-morbidities like HIV, internal malignancy, connective tissue disorder were not present in any patient.
6. Although 37.5% (3 out of 8 patients) were immunocompetent without any risk factors, still had melioidosis.
7. The most common symptom was abscess found in 7 patients (87.5%). Three patients had abscess in the neck, two patients had splenic abscess, one patient had abscess in foot & one patient had abscess in wrist & arm. No patient had parotid, prostatic or scrotal abscess.
8. The second common symptom was fever, presented by 6 patients (75%)
9. Abscess along with fever was present in 5 patients (62.5%) and 2 patients (25.0%) presented with only abscess without fever, in these one patient had abscess in neck and the other had abscess in the left foot.
10. Lymph node enlargement was present in 50% (4 out of 8) of patients.

Table 4. Antibiotic sensitivity pattern of 8 patients with Melioidosis

	1	2	3	4	5	6	7	8
Name	Athira	Babu	Gopi	Radha	Aliza	Jacob	Thanseen	Ubaid
Age/Sex	7yrs/F	39yrs/M	52yrs/M	50yrs/F	2yrs/F	82yrs/M	22 yrs/M	38yrs/M
Date of admission	27/7/2014	15/12/2014	21/7/2015	4/10/2015	13/11/2015	16/12/2015	28/12/2015	20/2/2016
Antibiotic sensitivity. S-Sensitive, R-Resistant								
Ceftazidime	S	S	S	S	S	S	S	S
Meropenam	S	S	S	S	S	S	S	S
Imipenam	S	S	S	S	S	S	S	S
Ceftriaxone	-	S	-	-	S	-	-	-
Cotrimoxazole	S	S	S	**R**	**R**	S	S	**R**
Amoxicillin + clavulanic acid	S	S	-	S	S	S	-	S
Cefoperazone + Sulbactum	-	S	-	S	S	S	-	S
Pipericillin + Tazobactum	-	S	-	S	S	S	S	S
Ciprofloxacin	S	S	-	S	-	S	-	S
Levofloxacin	-	-	-	-	-	-	S	-
Tetracycline	-	S	-	-	S	-	-	-
Cholramphenicol	S	S	S	-	-	-	S	S
Tigecycline	-	-	-	-	-	-	-	S
Amikacin	R	R	R	R	R	R	R	R

11. Only 2 patients had respiratory symptoms like history of breathlessness (25%), in this one patient was in Adult respiratory distress syndrome. Two patients had pneumonia, in these one patient had synpneumonic effusion.
12. Joint involvement, septic arthritis was not present in any patient.
13. One of our patients had erythema nodosum, one of the rare presentations in a melioidosis.[22]
14. Infection was localized in 5 patients (62.5%) and disseminated in 3 patients (37.5%).
15. In disseminated melioidosis, all the 3 patients had hepato-spleenomegaly, thrombocytopenia, elevated liver enzymes and reversal of albumin- globulin ratio. Two patients had elevated serum bilirubin, serum creatinine and elevated total count. One patient with disseminated melioidosis had low total count (2020 cells/cmm).
16. In the localized melioidiosis group one patient had presented with very rare skin manifestation - erythema nodosum, along with fever for 2 months and lymphnodenopathy. Lymphnode biopsy report showed chronic suppurative granulomatous lesions suggestive of tuberculosis, the culture of biopsy material was necessary to isolate the organism.
17. Burkholderia pseudomallei was isolated from blood culture in 3 patients. In the remaining patients the organism was isolated either from pus culture (4 patients) or from culture of the lymph node biopsy material (1 patient).
18. All our patients' culture reports showed sensitivity to Ceftazidime, meropenam, imipenam and resistant to aminoglycosides. Sensitvity was also observed for other antibiotics like ciprofloxacin, levofloxacin, cefoperazone + sulbactum, amoxicillin + clavulanic acid, pipericillin + tazobactum, ceftriaxone, amoxicillin + clavulanic acid **(Table 4)**
19. Three patients showed resistance to Cotrimoxazole
20. Only one patient developed septic shock & expired. All other patients had good outcome and cured on further follow up.
21. The patient who expired was 82 yrs male, had risk factors like diabetes mellitus, renal failure. The patients had shorter duration of illness (1 week) with symptoms of fever and breathlessness, pneumonia, no abscess. He had very high blood total count (32610 cells/cmm) with low platelets. The patient had developed septicemia, acute on chronic kidney disease, adult respiratory distress syndrome and was put on ventillatory support also.

DISCUSSION

Melioidosis is public health importance in endemic areas. It is geographically restricted to South East Asia & Northern Australia. Also occurs in south pacific islands, Africa, Middle East, Central & South America with occasional cases in countries such as India and china.[1,2,3,4] Melioidosis is a potential emerging infec-

tious disease in many tropical countries like Northeast Thailand, Singapore and India.

With increasing awareness of melioidosis more cases have now been reported from various regions of India including Kerala, Maharashtra, Karnataka, Tamil Nadu, and Pondicherry in recent years.[11,15-17] Many case reports have been published from different parts of Kerala.[18-21] Our study is the first of its kind in Kerala to identify the increased incidence of melioidosis.

As comparable to other studies men were predominantly affected, perhaps due to greater incidence of alcoholism.[11] There was no specific age group at risk, with the youngest case being a 2 year old girl and the oldest one being 82 years old. There were two children below the age of 10 yrs. Most of the patients affected were between age group of 18-65 yrs (5 out of 8) and only one patient was elderly, above 65 yrs. Five patients had diabetes mellitus, showing the importance of increasing incidence of melioidosis due to increase in diabetic patients in India. In contrast to children, most of the adults (5 out of 6) tend to have at least one risk factor that affects host immunity and predispose to melioidosis. But host immunity compromise may not a prerequisite for melioidosis as it can occur in any healthy children or adults. The disease has been shown to mimic tuberculosis.[11]

The commonest risk factor in our study was diabetes (62.5%) and alcoholism (37.5%) was the second commonest risk factor for melioidosis. The importance of excessive alcohol intake as a risk factor for melioidosis was recognized in an earlier study from the Northern Territory of Australia and also in a study from north Queensland.[11] The predisposition to melioidosis in individuals with diabetes and those with excessive alcohol intake appears to be related primarily to impaired neutrophil function such as mobilisation, delivery, adherence and ingestion.[11]

Abscess was the most common clinical presentation (87.5%) in contrast to earlier studies which showed fever as most common presentation.[11] Fever was the second common clinical presentation (75%). Five patients (62.5%) presented with abscess along with fever. The wide diversity of local syndromes in our series such as pneumonia and focal abscess is well known in melioidosis. But none of the patient had parotid, prostatic, scrotal abscess and joint involvement like septic arthritis was not seen in any patient. One of rare presentation, erythema nodosum was present in one patient.[22]

Despite disseminated disease of our patients were treated successfully except only one patient died, in contrast to other studies which reported high mortality.[15,16] High index of suspicion, starting ceftazidime early in illness with good supportive care and prolonging the consolidation phase with oral co-trimoxazole may have contributed to the good outcome.

All our patients were treated with ceftazidime 100 mg/kg (2g 8-hourly) for 14 days in the intensive phase followed by eradication phase treatment with either doxycycline (100 mg, twice daily) or cotrimoxazole (Trimethoprim 320 mg plus sulfamethoxazole 1600 mg, twice daily) for 12-24 weeks. Pediatric patients were treated according to the body weight.

CONCLUSION

The incidence of melioidosis is increasing worldwide. Approximately there are 1,65,000 (95% credible interval 68,000–4,12,000) human melioidosis cases per year worldwide from which 89,000 (36,000–2,27,000) people die. Melioidosis is severely underreported in the 45 countries in which it is known to be endemic and that melioidosis is probably endemic in a further 34 countries that have never reported the disease.[5] The bacterium is intrinsically resistant to a wide range of antimicrobials and treatment with ineffective antimicrobials may result in case fatality rates exceeding 70%.[5] No licensed vaccine for melioidosis is currently available.

The clinical presentation is highly variable and ranges from pneumonia[13, 23] to multiple abscesses in internal organs like liver, spleen, prostate etc., osteomyelitis, septic arthritis,[8,13,23] pyomyositis, cellulitis, fasciitis, abscess in skeletal muscle, skin abscess or ulcers and septicemia with or without focus.[8,13] Some of the rare presentations in melioidosis are brain abscess, abscess at root of mesentery,[24] thoracic meliodosis,[25] mediastinal lymphadenitis,[26] acute cholangitis,[27] erythema nodosum,[22] cutaneous polyarteritis nodosa.[28]

Melioidosis was under-diagnosed in India, due to a low index of suspicion and the fact that it mimics commoner diseases like tuberculosis.[8] Melioidosis should be considered in the differential diagnosis of a febrile illness in any person, especially diabetics having multiple abscesses in liver and spleen or multiple pustular skin or subcutaneous tissue lesions. Also in patients presenting with pneumonia and radiologic pattern of tuberculosis from which tubercle bacilli cannot be demonstrated or developing fulminant res-

piratory failure. In such cases, a high index of clinical suspicion is required and timely consultation with microbiology staff could facilitate prompt diagnosis.[8]

Melioidosis should be treated as intensive phase, consisting of in-patient treatment for at least 10-14 days with ceftazidime or carbapenems (imipenem or meropenem) and eradication phase consisting of treatment with oral cotrimoxazole for 3-6 months. Doxycycline or amoxicillin-clavulanic acid can be used in cotrimoxazole resistant cases or not tolerable cases.[13]

Melioidosis is a treatable emerging infection in India especially in males from rural areas with diabetes and alcoholism being the commonest risk factors.[11] Skin inoculation is considered the main route of infection in agricultural workers in developing countries like India.[5] The increase in diabetes may be one of the possible reasons for the increased incidence of melioidosis in India and also increased awareness among clinicians and microbiologists resulting in better recognition and reporting, rather than a truly increasing incidence of the disease.

END NOTE

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