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Research Article

ESTIMATION OF CLINICAL OUTCOME OF INTRAVENOUS CEFTAZIDIME AS AN INTENSIVE PHASE ANTIMICROBIAL IN MELIOIDOSIS

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ABSTRACT

Melioidosis caused by the bacterium *Burkholderia pseudomallei,* is an important cause of pyrexia of unknown origin, sepsis and multiple abscesses in several tropical areas including South-east Asia and Northern Australia. This disease entity can have acute and chronic presentation involving different organ systems. The purpose of this study is to see the clinical response of intravenous ceftazidime as an intensive phase antimicrobial in Melioidosis. We carried out a retrospective study of three culture proven cases of Melioidosis at Teaching Hospital Batticaloa, SriLanka. All patients had near total recovery after the intensive phase of chemotherapy for 28 days. The mean fever clearance time was 8.33 days. The mean time taken for highest CRP value to reduce by 50% was 6.66 days. Better outcome of these cases highlights the importance of early diagnosis with a high index of suspicion, correct use of antibiotic and improved microbiology services in our study. However, the adequate sample size is needed to determine the clinical significance of these findings. Delay in diagnosis may have been a factor contributing to the high mortality.

INTRODUCTION

Melioidosis, caused by the gram-negative Burkholderia pseudomallei bacillus, is an infectious disease associated with significant mortality due to an early onset of fulminant sepsis. It also known as "Whitmore's" disease and can grow on a variety of ordinary culture media producing wrinkled colonies with metabolic appearance. The clinical presentation is greatly variable and ranges from a mild localized infection to acute fulminant sepsis. It may present with recurrent abscess (Wijekoon *et al*. 2014). Predisposing factors include diabetes, chronic kidney disease, chronic lung disease and alcoholism (Cheng AC *et al* 2014). Diagnostic verification relies on culture of B. pseudomallei; lack of accurate microbiological services in many tropical countries may result in under-reporting of cases and an under-estimate of the global burden of this infection. Lack of understanding and the diversity of its presentation are probably responsible for under diagnosis and under reporting (Ray *et al*. 2016). A diagnosis of Melioidosis requires both clinical and laboratory evidence. A gold standard identification method has not yet been determined. However the definitive diagnosis depends on the isolation and identification of B.pseudomallei from clinical specimen (ministry of health, 2015). The molecular testing has shown excellent sensitivity and specificity. However, molecular methods are not always readily available, particularly in developing countries.

Case history

Case 1

A 67-year-old female presented with abdominal pain for 1 month and evening pyrexia with chills and rigors for 2 weeks duration. During the hospital stay she developed multiple skin abscesses over various parts of the body. She is a known diabetic with poor control, hypertension and ischemic heart disease. She had an exposure to muddy water during a period of flooding last year. Ultrasound abdomen revealed 4 splenic abscesses, largest of which was 8cm in diameter. Ultrasound guided aspiration was positive for *Burkholderia pseudomallei*. The Melioidosis antibody titer was more than 10240. She was managed with IV Ceftazidime and oral Co-trimoxazole for 28 days followed by oral antibiotics for further12 weeks. Her fever clearance time was 9 days and the time taken for CRP to reduce by 50% from its highest value was 7 days. She went on to make an uneventful recovery.

Case 2

A 56 year old female with poorly controlled diabetes, hypertension, ischemic heart disease and R/ parietal lobe CVA presented with fever and painful swelling of R/S knee joint for

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4 days duration. Severe septic arthritis of R/S knee joint was diagnosed and arthrotomy and washout was performed. The blood and pus cultures were positive for *Burkholderia pseudomallei*. She was started on IV Ceftazidime. Her fever clearance time was 6 days and the time taken for CRP to reduce by 50% from its highest value was 5 days. She made an uneventful recovery.

Case 3

A 62-year-old female with bronchial asthma and ischemic heart disease presented with fever for 5 days and productive cough. Chest X ray revealed right upper lobe consolidation, and her inflammatory markers were high. Tuberculosis was excluded and the sputum revealed *Burkholderia pseudomallei*. She was appropriately treated with IV Ceftazidime and oral Co-trimoxazole for 28 days. Her fever clearance time was 10 days and the time taken for CRP to reduce by 50% from its highest value was 8 days. She went on to make an uneventful recovery.

METHOD

This is retrospective study carried out over a period of 6 months from January 2017 at Teaching Hospital Batticalloa Sri Lanka. We harvested data from all culture proven cases with *Burkholderia pesudomallei* admitted to medical and surgical wards. We excluded culture negative cases from our study even though the patient with high clinical index. Intravenous Ceftazidime for 28 days with or without co-trimoxazole was given to all patients during the intensive phase. Patient's temperature pattern was studied from the medical records. The absence of fever and CRP reduction by 50% of its highest value were taken as the clinical remission.

RESULT

Three blood culture positive *Burkholderia pseudomallei* patients were recruited for our study.

Table 1

	Case 1	Case 2	Case 3
Age (Years)	67	56	62
Co – morbidities	Diabetes Hypertension Ischemic heart disease	Diabetes Hypertension Ischemic Heart disease CVA	Diabetes Bronchial asthma
Risk Factors	Exposure to flood water	nil	nil
Fever clearance time	9 days	6 days	10 days
Highest CRP (mg/dl)	234	249	487
Time taken to reduce CRP by 50%	7 days	5 days	8 days

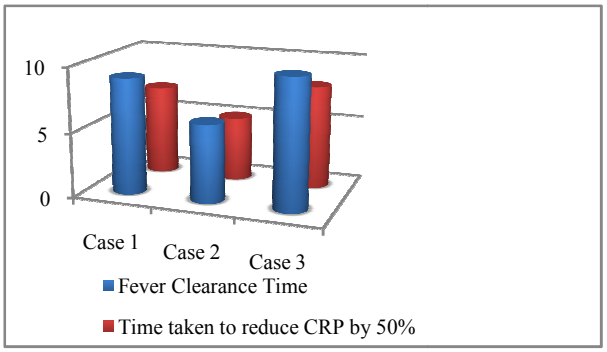

Figure 1

However, they showed broad clinical presentations ranges from skin abscesses, splenic abscesses, lung abscesses and septic arthritis. All patients had near total recovery after the intensive phase of chemotherapy for 28 days. Mean fever clearance time was 8.33 days (Table 1). The mean time taken for highest CRP value to reduce by 50% was 6.66 days. (Table 1 and Figure 1) Interestingly, all three patients had diabetes.

DISCUSSION

Since ten cases were reported in 1927 in Srilanka (Perera *et al*. 2012), several case reports were published sporadically in Srilanka. Clinical response with antibiotic among Melioidosis was not discussed in the available literature. In this study, we have noticed that fever responded within 8.33 days with ceftazidime. However, there are some Melioidosis cases were reported as pyrexia of unknown origin (Mulders *et al*. 2015). Combination of co-trimoxazole with ceftazidime is not recommended in the induction phase as there is no added benefit (JJT 2010). Oral co-trimoxazole and doxycycline were chosen for the eradication phase of antibiotics. They were overlapped with ceftazidime for one week as this is the vulnerable period where reactivation can occur. Our patient had intravenous ceftazidime for four weeks and oral co-trimoxazole in the acute phase.

The clinical management has two phase, intravenous intensive phase followed by the eradication phase (CR, 1927). At present, intravenous ceftazidime (2 g, 6 hourly) or meropenem (1 g, 8 hourly) plus high-dose cotrimoxazole are the drugs of choice in most of the center, and it is usually administered for at least 14 days. Meropenem and imipenem, have lower minimum inhibitory concentrations and superior results in vitro time-kill studies than ceftazidime, but a randomized comparative study in Thailand did not show a survival advantage of imipenem over ceftazidime. Furthermore, ceftazidime was associated an appreciably lower rate of mortality in cruel Melioidosis (White N *et al* 1989).

This study clearly showed that all three cases were associated with diabetes (Le Hello *et al*, 2005). Diabetes is the well-known risk factor for Melioidosis (Foong *et al*. 2014) (Kingsley *et al*. 2016) (Corea *et al*. 2012). In addition to that kidney disease; chronic lung disease and alcoholism were also considered as risk factors (Samy *et al*. 2017)(Currie *et al*. 2010). Diabetes mellitus results in impaired chemotaxis, phagocytosis, oxidative burst, and killing activity of granulocytes as a result of which, B. pseudomallei is able to survive and multiply within phagocytes. It is suggested that people with risk factors such as diabetes or immunosuppressive therapy stay in the house during periods of heavy wind and rain, when aerosolization of B. pseudomallei is possible. There is no proof to support direct human-to-human transmission through respiratory spread.

CONCLUSION

Better outcome of these cases highlights the importance of early diagnosis with high index of suspicion, correct use of antibiotic and improved microbiology services in our study. However, adequate sample size is needed to determine the clinical significance of these findings. A long course of intravenous antibiotics in the acute phase, overlapped and

followed by a prolonged course of a combination of oral antibiotics is needed to improve the prognosis of this potentially fatal, emerging infection. Laboratory capability in SriLanka should be enhanced. Further clinical and epidemiological studies are needed to identify the burden of Melioidosis in Sri Lanka.

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