ANTIMICROBIAL SENSITIVITY FOR *Burkholderia pseudomallei*: RETROSPECTIVE WITH LITERATURE REVIEW

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**ABSTRACT**

We have reviewed the antibiotic susceptibility profiles for 138 clinical isolates of *B. pseudomallei* obtained from the first positive clinical specimen from 138 melioidosis patients over 13 years. All isolates of *B. pseudomallei* (100%) tested against imipenem, amoxicillin/clavulanic acid, piperacillin/tazobactam and meropenem were sensitive. Whereas little resistance was reported against cefazidime (n=1, 0.7%), chloramphenicol (n=2, 2.1%), tigecycline (n=2, 0.4%) and cefpime (n=2, 2.3%). Up to half isolates tested for trimethoprim/sulphamethazole showed resistance (n=52, 38.3%). Results concurred with previous reports done in different geographical locations and showed the stability of the current treatment guidelines for melioidosis followed in our clinical settings.

**INTRODUCTION**

*Burkholderia pseudomallei* causes melioidosis that varies in clinical presentations (Currie, 2015). Therapeutic approaches of melioidosis comprise two phases: the acute phase for clinical relief of severe acute infectino to minimize fatal sepsis. The second phase, maintenance phase, in which eradication of residual intracellular infection is achieved by second-line oral drugs for several weeks to avoid relapse (Dance, 2014). This report has reviewed the antibiotic susceptibility profiles for 138 clinical isolates of *B. pseudomallei* obtained from the first positive clinical specimen from 138 melioidosis patients diagnosed in our hospital between January 2001 and December 2013. According to hospital laboratory standard operating protocols, *B. pseudomallei* is usually diagnosed by cultivation from different clinical specimens on routine culture media and their deferential identification is made using biochemical speciation (VITEK® 2; bioMérieux SA, Marcy-l’Étoile, France). In addition, results for minimum inhibitory concentrations (MIC) of antibiotics that were determined by Epsilometer test (E-test) were obtained. In this report, treatment was reported as given to patient only once included antibiotics administered in anti-melioidosis dose for acute and/or eradication phases or as empirical treatment in cases of admission with severe fever. Results of first-episode antibiotics sensitivity profiles were reviewed for all *B. pseudomallei* isolates from the year 2001 till 2013 and were analysed for descriptive statistical analysis. As additional step, about half of isolates were reactivated and typed by multi-locus sequence typing (MLST) described previously (Godoy et al., 2003) to investigate for genotype-resistance association. Ethical approval was obtained by the Universiti Sains Malaysia Research Ethics Committee (Human) (USM/PPP/JEPeM[235.4.(2.5)]) and data were analyzed anonymously.

Using CLSI criteria, all isolates (100%) of *B. pseudomallei* tested against imipenem, amoxicillin/clavulanic acid, piperacillin/tazobactam and meropenem were sensitive. Whereas little resistance was reported against cefazidime (n=1, 0.7%), chloramphenicol (n=2, 2.1%), tigecycline (n=2, 0.4%) and cefpime (n=2, 2.3%). Up to half isolates tested for trimethoprim/sulphamethazole showed resistance (n=52, 38.3%) (table 1). Results of MLST had confirmed the identity of all isolates and had revealed massive heterogeneity among them with no effect on susceptibility patterns (data not shown).
Meliodosis has emerged as an important cause of morbidity, mortality, and fatal community-acquired bacteraemic pneumonia in Northern Australia and Southeast Asia (Cheng et al., 2013). As many saprophytes, B. pseudomallei is intrinsically resistant to many antibiotics, such as penicillin, majority of first and second generation cephalosporins, colistin, macrolides, rifamycins and aminoglycosides. However, it is usually susceptible to other drug combinations such as amoxicillin/clavulanic acid (Augmentin), trimethoprim/sulfamethoxazole (co-trimoxazole) and piperacillin/tazobactam (Dance, 2014). However, resistance to ceftazidime and Augmentin was emerged, ultimately leading to treatment failure (Inglis et al., 2004). The carbapenems have been reported to have good bactericidal activities against B. pseudomallei and have been used effectively to treat patients with septicaemic melioidosis (Khosravi et al., 2014). Antibiotics resistance might be developed during both acute and eradication phases and could be associated with relapsed infection with the same strain (Wuthiekanun and Peacock, 2006). Resistance can be undetected and might be developed as a result of regular prescribing for melioidosis therapy and is more common in endemic areas (Sam et al., 2010).

Several mechanisms were studied and reported for resistance to antimicrobial agents including: exclusion of drug molecules by porins or lipopolysaccharide (resistance to aminoglycoside and polymyxin), efflux drug molecules out from cell cytosol via active transport channels (resistance to most of antibiotics), drug sequestration by specific binding proteins, enzymatic inactivation by substrate (drug) cleavage or chemical modification (M = phosphorylation, acetylation or adenyllyation) (resistance to β-lactams), target site mutation: alternation or deletion (β-lactams, clavulanate and fluoroquinolones), metabolic bypass by changing the enzyme or the pathway with others, and target overproduction by increased effective gene expression (Schweizer, 2012).

In this report results of routine medication antibiotic regime were consistent with previous reports and surveys preformed in Malaysia (Ahmad et al., 2013; Hassan et al., 2014). Moreover, resistance to carbapenems and amoxicillin/clavulanic acid was not reported, a single resistance for ceftazidime and 52/82 isolates were resistant to trimethoprim/sulphamethazol. Although carbapenem-resistance was reported for Pseudomonas aeruginosa, and other Gram negative bacteria, it was not yet reported for B. pseudomallei(Schweizer, 2012), except an intermediate resistance was reported in Malaysia by Ahmad et al., (2013). The efficiency of carbapenems were better in acute phase treatment than ceftazidime in terms of low relapse rate and complete organism eradication reported among patients (Cheng et al., 2004). A prospective study has reported similar outcomes of treatment with ceftazidime and imipenem/cilastatin on overall mortality of acute melioidosis. However, treatment failure resulted in relapse was significantly more common in patients...
treated with ceftazidime (Simpson et al., 1999). Another study showed overall mortality achieved by meropenem much lower in comparing with ceftazidime (Cheng et al., 2004). Resistance of *B. pseudomallei* to ceftazidime started to emerge in endemic countries. The first report of ceftazidime resistance *B. pseudomallei* in India was published by Behera et al., (2012). Resistance to amoxicillin/clavulanic acid is variable among reports ranging from full sensitive to very resistant. Surprisingly resistance was reported in non-endemic area, Brazil, in which the rates of resistance to ceftazidime was 10% and amoxicillin/clavulanic 30% (Bandeira Tde et al., 2013). The resistance to trimethoprim/sulphamethazol was frankly reported in our report. The rates of resistance to trimethoprim/sulphamethazol were 2.5% in Australia (Piliouras et al., 2002) and 13–16% in Thailand (Wuthiekanun et al., 2005). In this report, majority of aminoglycosides and early generations of cephalosporines were resistant due to intrinsic resistant of *B. pseudomallei* to many antibiotics including those empirically used to treat sepsis (Hassan et al., 2014) (Table 2). The current treatment guidelines for melioidosis seem to be satisfactory in the absence of unexpected patterns of primary resistance of *B. pseudomallei* to antibiotics, in particular ceftazidime, carbapenems and Augmentin. 

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