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Short Report

ANTIMICROBIAL SENSITIVITY FOR *BURKHOLDERIA PSEUDOMALLEI*: RETROSPECTIVE WITH LITERATURE REVIEW

***AbdelRahman Zueter, Chan Yean Yean, Zakuan Z. Deris and Azian Harun**

Department of Medical Microbiology and Parasitology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

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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 ceftazidime (n=1, 0.7%), chloramphenicol (n=2, 2.1%), tigecycline (n=2, 0.4%) and cefipime (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 sittings.

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 infectionto 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).

MATERIALS AND METHODS

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. 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.

****Corresponding author: AbdelRahman Zueter,***
Department of Medical Microbiology and Parasitology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.

RESULTS

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 ceftazidime (n=1, 0.7%), chloramphenicol (n=2, 2.1%), tigecycline (n=2, 0.4%) and cefipime (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).

DISCUSSION

Melioidosis 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-trimethoxazole) and piperacillin/tazobactam (Dance, 2014). However, resistance to ceftazidime and Augmentinwas 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 septicaemicmelioidosis (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 (resistance to β-lactams), target site mutation: alternation or deletion (β-lactams, clavulanate and fluoroquinolones, metabolic bypass, 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, in contrast to resistance for ceftazidime and trimethoprim/sulphamethazole. 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 case 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

Table 1. First-episode antibiotic sensitivity results

Antibiotic	Number tested isolates	Sensitive N(%)	Resistant N(%)
Ceftazidime	138	137(99.3%)	1(0.7%)
Imipenem	104	104(100%)	0(0.00%)
Meropenem	93	93(100%)	0(0.00%)
Amoxicillin/clavulanic acid	130	130 (100%)	0 (0.00%)
Trimethoprim/sulphamethazole	134	82(61.7%)	52(38.3%)
Chloramphenicol	94	92(97.9%)	2(2.1%)
Ciprofloxacin	92	75(81.6%)	17(18.4%)
Piperacillin	42	42(100%)	0(0.00%)
Piperacillin/tazobactam	88	88(100%)	0(0.00%)
Tigecycline	44	42(99.6%)	2(0.4%)
Ceftriaxone	93	78(83.9%)	15(16.1%)
Cefipime	84	82(97.7%)	2(2.3%)
Cefuroxime	94	29(30.9%)	65(69.1%)
Coilstin	47	0(0.00%)	47(100%)
Netilmicin	90	3(3.1%)	87(96.9%)
Amikacin	96	2 (2%)	94 (98%)
Gentamycin	94	1(1.1%)	93(98.9%)
Ampicillin	94	0 (0.00%)	94 (100%)

Table 2. Reported antimicrobial susceptibilities for *Burkholderia pseudomallei* clinical isolates

Author/year/location	No. of isolates tested	Method	Antimicrobial susceptibility [n (%)]			
			Carbapenem	Ceftazidime	TMP/SMX	Amox/Clav
(Hassan *et al.*, 2014). Malaysia	228	DD[1]	41(90.2%) Imipenem	41(97.6%)	41(63.0%)	41(78.0%)
(Crowe *et al.*, 2014). Australia	234	E test	234(100%) Meropenem	234 (100%)	232(99.1%)	
(Khosravi *et al.*, 2014). Malaysia[3]	81	DD, BMD[2], E test	81(92.5%) Imipenem 81(93.8%) Meropenem	81(91.3%)	81(55.5%)	81(28.3%)
(Ahmad *et al.*, 2013). Malaysia	170	E test	170(100%) Meropenem 169(99.4%) Imipenem	169(99.4%)	153(90.0%)	
(Paveenkittiporn *et al.*, 2009). Thailand	Variable[4]	DD	> 98.5% Meropenem > 98.5% Imipenem	> 98.5%		> 95.0%
(Thibault *et al.*, 2004). Pooled[5]	50	DD	50(100%) Imipenem	49(98.0%)	16(32.0%)	49(98.0%)
This study, Malaysia. 2015	138	E test	104(100%) Imipenem 93(100%) Meropenem	137(99.3%)	82(61.7%)	130 (100%)

[1]Disk diffusion method.[2]Broth microdilution test.[3]In this study, intermediate results were not included. [4]Variable number of isolates tested for each antimicrobial.[5]ATCC strains isolated from different countries worldwide.

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 few 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/sulphamethazole was frankly reported in our report. The rates of resistance to trimethoprim/sulphamethazole 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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