International Journal of Infectious Diseases (2009) 13, e331–e332

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LETTER TO THE EDITOR

A role for carbapenem in the treatment of melioidosis in developing countries?

Melioidosis, a disease caused by *Burkholderia pseudomallei*, is endemic to Southeast Asia and northern Australia. Patients with diabetes and chronic renal failure have a higher risk of contracting melioidosis. Therapeutic approaches are targeted at either the clinical resolution of acute infection (acute phase) or the eradication of residual intracellular infection to prevent relapse (maintenance phase). In Thailand, the first-line regimen in the acute phase is intravenous ceftazidime with or without trimethoprim-sulfamethoxazole (TMP-SMX). For maintenance therapy, a four-drug regimen of chloramphenicol, doxycycline and TMP-SMX is recommended. We report a case of persistent septicemic melioidosis that failed to respond to ceftazidime plus TMP-SMX, but subsequently gave a clinical response to meropenem and surgical debridement.

A 56-year-old male Thai farmer with poorly controlled diabetes mellitus was admitted to the hospital with a week-long history of fever, chills and frontal headache. One month earlier, he fell and hit his head on the floor near a chicken coop. His headache was accompanied by painful swelling of his forehead. On admission, physical examination revealed a temperature of 39 °C, a blood pressure of 100/60 mmHg, respiratory rate of 20/min, and a 3×4 cm fluctuated forehead mass with erythema, warmth and tenderness to palpation. His white blood cell count was 16.3×10^9/L (neutrophils 85%, lymphocytes 15%), whereas hemoglobin, blood chemistry, transaminases and chest roentgenogram were normal. Gram stain of exudate from the forehead lesion showed Gram-negative bacilli. Blood cultures and drainage cultures grew *B. pseudomallei*. The patient was treated with ceftazidime (2 g every 8 hr) and TMP-SMX (160/800 mg every 8 hr). Based on the Clinical and Laboratory Standards Institute (CLSI) disk diffusion interpretative guidelines for Acinetobacter spp.,[1] this isolate was susceptible to ceftazidime, TMP-SMX, imipenem, meropenem and doxycycline. On hospital day six, he developed a right lower lung infiltrate and rapidly progressive swelling, erythema and fluid-filled bleb of the right leg. Ultrasound of the abdomen showed no evidence of liver and splenic abscesses. Transthoracic echocardiogram demonstrated no vegetation. The patient underwent surgical debridement of the right leg for presumptive necrotizing fasciitis; tissue cultures were obtained. Bacteremia persisted despite the seven-day treatment course of ceftazidime and TMP-SMX. Tissue cultures subsequently grew *B. pseudomallei* with a similar susceptibility pattern to the previous isolate. Using the E-test method (AB Biodisk, Sweden), minimal inhibitory concentrations (MICs) of ceftazidime, imipenem and meropenem were 4, 1 and 0.5 μg/ml, respectively. Based on the MIC results, meropenem was initiated; ceftazidime and TMP-SMX were discontinued. Over the next week, the patient steadily improved clinically and was discharged on doxycycline and TMP-SMX to complete the 24-week course. The patient had full resolution of his illness at a three-month follow-up after completion of therapy.

Several reasons favor the use of ceftazidime with or without TMP-SMX as the first-line treatment of melioidosis in Thailand. First, according to national surveillance on antimicrobial susceptibility to *B. pseudomallei* during 2000–2005, more than 99% of *B. pseudomallei* isolates were susceptible to ceftazidime.[2] Second, although several antibiotics have been studied for the treatment of melioidosis, none have shown superiority to ceftazidime with or without TMP-SMX.[3–5] Third, ceftazidime and TMP-SMX are inexpensive relative to alternative regimens. Carbapenems have some speculative benefits over ceftazidime, given that they are more active in vitro,[6,7] display a post-antibiotic effect[8] and have been associated with decreased endotoxin release.[6] In a time-kill study, carbapenems Exhibit 99% bactericidal activity within four hours.7 In this case, switch to a carbapenem was associated with clinical improvement after six days of failed ceftazidime therapy. The addition of TMP-SMX to ceftazidime was well tolerated, but was not shown to reduce mortality in a recent study.[9] Although controversial, the potential advantages of combining TMP-SMX with ceftazidime include the intracellular activity of TMP-SMX and the potential for reduced risk of emergence of antimicrobial resistance.[2] We acknowledge that the potential benefit of granulocyte colony-stimulating factor (GCSF) in this case remains speculative. A recent study in Australia suggested a reduction in mortality associated with GCSF treatment of patients in septic shock due to melioidosis, whereas an earlier clinical trial in Thailand showed no survival benefit.[10]

In conclusion, we suggest that patients with melioidosis who do not respond to ceftazidime with or without TMP-SMZ should undergo a thorough work-up inclusive of abdominal ultrasound, echocardiogram and MIC values of selected antibiotics. If there is no evidence of specific organ infection or abscess, an alternative antibiotic should be considered based on MIC results. This case of disseminated melioidosis

1201-9712/$36.00
doi:10.1016/j.ijid.2008.11.018

occurred while the patient was on ceftazidime with TMP-SMX, highlighting the role of carbapenems as an alternative in patients who are allergic or not responding to ceftazidime with or without TMP-SMZ.

Acknowledgements

This study was supported, in part, by the Thai American Physician Foundation (to A.A.) and, in part, by Thammasat University Fund to the Infectious Disease and Hospital Epidemiology Research Unit (to A.A.).

Conflict of interest: No conflict of interest to declare.

References

1. Clinical and Laboratory Standards Institute (CLSI), 2008. Performance standards for antimicrobial susceptibility testing; eighteenth informational supplement. CLSI document M100-S18. CLSI, Pennsylvania, USA.
2. Paveenkittiporn W, Apisarnthanarak A, Trakoolsomboon S, Dejsirilert S. Five years surveillance for *Burkholderia pseudomallei* in Thailand, 2000—2004: prevalence, clinical epidemiology and antimicrobial susceptibility. *J Med Assoc Thai* 2009 (In press).
3. Suputtamongkol Y, Rajchanuwong A, Chaowagul W, Dance DA, Smith MD, Wuthiekanun V, et al. Ceftazidime vs. amoxicillin/clavulanate in the treatment of severe melioidosis. *Clin Infect Dis* 1994;**19**:846—53.
4. Simpson AJ, Suputtamongkol Y, Smith MD, Angus BJ, Rajanuwong A, Wuthiekanun V, et al. Comparison of imipenem and ceftazidime as therapy for severe melioidosis. *Clin Infect Dis* 1999;**29**:381—7.
5. Chetchotisakd P, Porramatikul S, Mootsikapun P, Anunnatsiri S, Thinkhamrop B. Randomized, double-blind, controlled study of cefoperazone-sulbactam plus cotrimoxazole versus ceftazidime plus cotrimoxazole for the treatment of severe melioidosis. *Clin Infect Dis* 2001;**33**:29—34.
6. Simpson AJ, Opal SM, Angus BJ, Prins JM, Palardy JE, Parejo NA, et al. Differential antibiotic-induced endotoxin release in severe melioidosis. *J Infect Dis* 2000;**181**:1014—9.
7. Smith MD, Wuthiekanun V, Walsh AL, White NJ. Susceptibility of *Pseudomonas pseudomallei* to some newer beta-lactam antibiotics and antibiotic combinations using time-kill studies. *J Antimicrob Chemother* 1994;**33**:145—9.
8. Walsh AL, Smith MD, Wuthiekanun V, White NJ. Postantibiotic effects and *Burkholderia (Pseudomonas) pseudomallei*: evaluation of current treatment. *Antimicrob Agents Chemother* 1995;**39**:2356—8.
9. Chierakul W, Anunnatsiri S, Short JM, Maharjan B, Mootsikapun P, Simpson AJ, et al. Two randomized controlled trials of ceftazidime alone versus ceftazidime in combination with trimethoprim-sulfamethoxazole for the treatment of severe melioidosis. *Clin Infect Dis* 2005;**41**:1105—13.
10. Cheng AC, Stephens DP, Anstey NM, Currie BJ. Adjunctive granulocyte colony-stimulating factor for treatment of septic shock due to melioidosis. *Clin Infect Dis* 2004;**38**:32—7.

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Corresponding Editor: William Cameron

12 October 2008