Comparison of Imipenem and Ceftazidime as Therapy for Severe Melioidosis

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An open, prospective, randomized, comparative treatment trial was conducted to compare the therapeutic efficacy of high-dose intravenous imipenem and ceftazidime for acute severe melioidosis. Adult Thai patients with suspected acute, severe melioidosis were randomized to receive either imipenem, at a dosage of 50 mg/(kg · d), or ceftazidime, at a dosage of 120 mg/(kg · d), for a minimum of 10 days. The main outcome measures were death or treatment failure. Of the 296 patients enrolled, 214 had culture-confirmed melioidosis, and 132 (61.7%) of them had positive blood cultures. Mortality among patients with melioidosis was 36.9% overall. There were no differences in survival overall ($P = .96$) or after 48 hours ($P = .3$). Treatment failure after 48 hours was more common among patients treated with ceftazidime ($P = .011$). Both treatments were well tolerated. Imipenem is a safe and effective treatment for acute severe melioidosis and may be considered an alternative to ceftazidime.

Melioidosis, an infection caused by the environmental organism *Burkholderia pseudomallei,* is a major cause of human morbidity and mortality in northeast Thailand [1]. Only four trials of treatment for severe disease have been reported. In the first two, ceftazidime-including regimens reduced the mortality associated with severe melioidosis by half, compared with the mortality with use of a four-drug combination of chloramphenicol, doxycycline, and trimethoprim-sulfamethoxazole (TMP-SMZ) [2, 3]. Treatment with co-amoxiclav (amoxicillin–clavulanic acid) then proved to be effective, with a similar mortality (~40%) but an increased risk of treatment failure [4].

A recently reported trial suggests that cefoperazone-sulbactam plus TMP-SMZ may be effective, but the trial was too small to draw useful conclusions about the relative merits of this combination [5]. Ceftazidime therefore remains the drug of choice for severe melioidosis. Carbapenem antibiotics have been shown in vitro to be highly active against *B. pseudomallei* [6], and there is anecdotal evidence to suggest that imipenem may be effective for treatment of melioidosis [7]. We report the results of a large prospective, randomized, open treatment trial comparing the therapeutic efficacy of high-dose iv imipenem and ceftazidime in the acute treatment of severe melioidosis.

Patients and Methods

All adult patients (aged ⩾15 years) admitted to Sappasitprasong Hospital (Ubon Ratchathani, Thailand) with suspected severe melioidosis were eligible for enrollment in the trial if they or their attending relatives gave informed consent. Exclusion criteria included known hypersensitivity to penicillins, cephalosporins, or carbapenems; recent treatment with an antibiotic active against *B. pseudomallei*, along with clinical evidence of a response to treatment; and infection with a strain of *B. pseudomallei* already known to be resistant to either of the study drugs. Previous enrollment in the trial was not an exclusion criterion for reenrollment if the patient subsequently relapsed.

Melioidosis is a seasonal disease, with the majority of cases occurring during the rainy season and considerable variation in monthly incidence [8]. The study was performed during the rainy season of June to November in each study year. All patients enrolled in the trial were allocated by a restricted randomization method, in blocks of 10, to receive either iv imipenem/cilastatin sodium (Tienam; MSD Asia, Hong Kong), at a dosage of 50 mg/(kg · d) (usual adult dose, 1 g of imipenem three times daily by infusion), or iv ceftazidime (Fortum; Glaxo U.K., Greenford, U.K.), at a dosage of 120 mg/(kg · d) (usual adult dose, 2 g three times daily by bolus injection).

The treatment allocations were kept in sealed envelopes, which were not opened until after enrollment in the study. The attending physicians were not blinded as to drug therapy. The

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study site is a very busy general hospital and the two treatments are administered differently, so blinding was considered impractical. Both drugs were given every 8 hours. Dose adjustments were made for patients with renal failure, but the first dose was always either 1 g of imipenem or 2 g of ceftazidime.

The study endpoints were successful acute treatment (with a consequent switch to oral therapy), in-hospital death due to uncontrolled melioidosis (or patient taken home moribund), or treatment failure. Treatment failure was determined by members of the study team only, after discussion and mutual agreement. Treatment failure was defined as death in the hospital >48 hours after the start of treatment with the study antibiotic; development of septic shock (systolic blood pressure of <90 mm Hg, not responding to fluid replacement) at least 72 hours after the start of treatment with the study antibiotic; fever (temperature of >37.5°C) that persisted without signs of resolution for 14 days; or *B. pseudomallei* bacteremia that persisted for at least 7 days after the start of treatment. Persistent isolation of *B. pseudomallei* from other sites or persistence of radiographic abnormalities in the absence of definite clinical evidence of deterioration was not regarded as treatment failure, as our previous studies have clearly shown that both are common despite good clinical response [4]. The results were analyzed on an intention-to-treat basis.

Patients received parenteral therapy until they showed definite clinical evidence of improvement (usually a minimum of 10 days). Surviving patients were then switched to oral maintenance therapy (usually chloramphenicol, doxycycline, and TMP-SMZ in combination, doxycycline alone, or co-amoxiclav alone), to complete a total of 12–20 weeks of antibiotic therapy. All patients were offered follow-up, initially monthly and then yearly, dependent on clinical progress.

Surviving patients whose initial treatment failed or who had a serious adverse effect considered to be due to the study antibiotic were switched to the alternative treatment regimen.

Clinical and Laboratory Procedures

The trial was conducted with use of a protocol similar to that in our two previous trials [2, 4]. The study protocol is available on request. During enrollment in the study, a detailed history and physical examination findings were recorded on standardized forms. Admission APACHE II scores were calculated. Baseline investigations at study enrollment included a full blood cell count; determinations of plasma electrolyte, glucose, and lactate concentrations; renal and liver function tests; determination of clotting indices; and an indirect hemagglutination assay for antibodies to *B. pseudomallei.*

Baseline microbiological sampling included collection of three 5-mL blood culture specimens (inoculated into 50-mL brain-heart infusion broth medium), three 1-mL pour-plate blood culture specimens for quantification of bacteremia [9] (without added β-lactamase), and urine and throat swab samples for cultures. Wound swabs, sputum, and pus were also cultured if available. Chest radiography and abdominal ultrasonography were performed either before or as soon as possible after study enrollment, and further radiological investigations were performed as clinically indicated.

Vital signs were recorded every 4 hours. Appropriate supportive care was provided as clinically indicated. Abscesses were always drained when possible. All patients were seen at least once daily by one of the study team members, who performed a thorough examination. Detailed records of each patient's progress were kept. Further laboratory tests and radiological examinations were performed as indicated, together with repeated tests following any abnormal laboratory findings. Patients who were culture-negative for melioidosis after a minimum of 96 hours of treatment were removed from the study and switched to therapy with appropriate antibiotics.

Microbiology specimens were processed as described previously [10, 11]. Further blood cultures were performed after 24 and 72 hours for all patients, after 7 days of antibiotic treatment when enrollment blood cultures were positive, and weekly thereafter when appropriate. When cultures of other specimens were positive, such cultures were repeated weekly until negative or until the patient was discharged from the hospital.

Isolates of *B. pseudomallei* were identified as described previously [10]. Antimicrobial susceptibilities were determined initially by the Kirby-Bauer disk-diffusion method for all isolates. MICs of ceftazidime and imipenem were subsequently determined for representative isolates from each patient by an agar dilution method [12].

Drugs

Imipenem was donated by MSD Asia. Between 1994 and 1996, ceftazidime was donated by Glaxo U.K. After 1996, ceftazidime was purchased from Glaxo with the aid of financial support from the Thai Research Fund.

Sample Size

The trial was designed to detect a difference in treatment failure rates of 45% and 25% with 95% confidence and 80% power. In the original protocol an interim analysis was planned after enrollment of 200 culture-confirmed cases of melioidosis.

Statistical Analyses

Normally distributed continuous data were compared by means of Student's *t* test. Data not conforming to a normal distribution were compared with the Mann-Whitney *U* test. Proportions were compared with the χ^2 test with Yates' correction. Survival rates were plotted by the Kaplan-Meier method and compared with the log-rank test. All analyses were

Table 1. Baseline information on the 296 patients enrolled in the study.

Variable	No. (%) of patients: Melioidosis (n = 214)	Not melioidosis (n = 82)	P value
Male	118 (55.1)	35 (42.7)	.07
Age in years: median (range)	51 (18–82)	53 (16–85)	.18
Treatment received			
Imipenem	108 (50.5)	40 (48.8)	.80
Ceftazidime	106 (49.5)	42 (51.2)	
Underlying disease			
None	31 (14.5)	40 (48.8)	<.001
Any	183 (85.5)	42 (51.2)	
Diabetes mellitus	104 (48.6)	26 (31.7)	.009
Renal	42 (19.6)	8 (9.8)	.043
Diabetes mellitus and/or renal	132 (61.7)	26 (31.7)	<.001
Other	51 (23.8)	16 (19.5)	.14
More than one	63 (29.4)	9 (11.0)	.02
Blood-culture positive	132 (61.7)	13 (15.9)	<.001
Mortality	79 (36.9)	24 (29.3)	.22

performed with use of the statistical computing package SPSS for Windows, version 7.0 (SPSS, Chicago).

Ethical Approval

Ethical approval for the study was obtained from the Ethical and Scientific Review Subcommittee of the Thailand Ministry of Public Health.

Results

The study was performed between July 1994 and November 1997 at Sappasitprasong Hospital. The trial was stopped when the scheduled interim analysis point had been reached because of difficulties in ensuring continuation of the antibiotic supply. A total of 296 patients were enrolled, 148 patients in each study group (this includes 8 patients who were reenrolled in the study after relapsing). Of these, 214 (72.3%) had culture-confirmed melioidosis; 108 patients received imipenem and 106 received ceftazidime. Thus, melioidosis was either excluded or not confirmed for 82 patients; of these, 32 (39%) had a confirmed (other) infection, and 13 were bacteremic.

Baseline data were similar for the two groups of patients, as is shown in table 1. Significantly more of the patients with melioidosis had a preexisting underlying disease, particularly diabetes mellitus or renal disease. Only 14.5% of the patients with melioidosis had no identifiable underlying disease, compared with nearly half of the nonmelioidosis group. Five patients were receiving oral steroids and three were known to have HIV infection. Patients with melioidosis in the ceftazidime treatment group more frequently had skin or soft-tissue involvement (P = .02), and more had positive blood cultures than in the imipenem group. Baseline demographic, clinical, and laboratory data for the patients with melioidosis in the two antibiotic groups were otherwise similar (tables 2 and 3).

Mortality

Overall, 103 patients (34.8%) died. Outcomes for the 214 patients with melioidosis are shown in table 4. In-hospital mortality for all patients with melioidosis was 36.9% (79 died: 39 in the imipenem group and 40 in the ceftazidime group). Forty-nine patients with melioidosis died within 48 hours of enrollment in the study, including 27 (25.0%) in the imipenem group and 22 (20.8%) in the ceftazidime group (P = .56). A further 30 patients (14.0%) died after 48 hours, including 12 given imipenem and 18 given ceftazidime. Thus, the proportion of patients who died after 48 hours was 14.8% (12 of 81) among imipenem recipients and 21.4% (18 of 84) among ceftazidime recipients (P = .3).

Overall, the choice of parenteral treatment did not influence mortality (table 4). In a logistic regression analysis to adjust for differences in admission creatinine and albumin values, blood culture status, and systolic blood pressure (factors known to be associated with prognosis from our previous studies), choice of parenteral treatment was not a predictor of outcome (P = .81). A Kaplan-Meier survival plot is shown in figure 1.

Table 2. Baseline information and admission clinical data for all patients with melioidosis (n = 214).

Characteristic	No. (%) of recipients: Imipenem (n = 108)	Ceftazidime (n = 106)	P value
Male	61 (56.5)	57 (53.8)	.69
Age in years: median (range)	52 (18–82)	51 (21–76)	.91
Duration (d) of fever, median (range)	10 (1–90)	10 (1–150)	.32
Prior antibiotic therapy (this episode)	72 (66.7)	80 (75.5)	.16
Type/site of infection			
Septicemia	62 (57.4)	70 (66.0)	.25
Lung	60 (55.6)	59 (55.7)	1.0
Hepatic or splenic abscesses	29 (26.9)	30 (28.3)	.81
Skin or soft-tissue infection	21 (19.4)	36 (34.0)	.02
Bone or joint infection	11 (10.2)	10 (9.4)	.85
Positive pour-plate culture	28 (28.0)	34 (35.1)	.36
Fever (temperature of >37.5°C)	61 (56.5)	62 (58.5)	.77
Hypotension (systolic blood pressure of <90 mm Hg)	13 (12.0)	10 (9.4)	.54
Impaired consciousness level	22 (20.4)	21 (19.8)	.92
Dyspnea	43 (39.8)	45 (42.5)	.69
Jaundice	29 (26.9)	23 (21.7)	.38
Hepatomegaly	48 (44.4)	49 (46.2)	.79
Splenomegaly	15 (13.9)	13 (12.3)	.72

Table 3. Laboratory indices and APACHE II scores in all cases of melioidosis.

Variable	Median value (range), per treatment group		*P* value
	Imipenem	Ceftazidime	
Hematocrit (%)	32 (12–45)	33 (16–51)	.42
WBC count (no. × 10^6/L)	12,650 (500–35,800)	12,400 (800–32,000)	.24
Prothrombin time (seconds)	14 (10–88)	13 (9–61)	.17
Blood urea nitrogen (mg/dL)	31.5 (8–159)	29 (4–246)	.15
Creatinine (mg/dL)	2.0 (0.6–13.3)	1.7 (0.6–11.5)	.19
Alkaline phosphatase (IU/L)	148 (30–1,286)	159 (18–910)	.54
Aspartate aminotransferase (IU/L)	69 (14–3,892)	69 (11–1,178)	.32
Total bilirubin (mg/dL)	1.1 (0.3–16.6)	1.3 (0.3–12.3)	.52
Albumin (mg/dL)	2.6 (1.4–5.6)	2.6 (1.4–5.0)	.94
Bicarbonate (mmol/L)	16 (3–29)	18 (4–33)	.33
Glucose (mg/dL)	144 (6–875)	156 (33–931)	.60
APACHE II score	16 (1–38)	15 (0–33)	.19

Nineteen patients were excluded from further analysis (table 4), leaving 195 patients who fulfilled the prospectively determined criteria for evaluation of the treatment response. A more detailed analysis was limited to the 146 evaluable patients who survived >48 hours. Among these, 15.7% (11) of 70 imipenem recipients and 22.4% (17) of 76 ceftazidime recipients died ($P = .3$).

Treatment Failure

Of the 146 evaluable patients surviving >48 hours, two required a switch of treatment to the alternative agent because of possible side effects (a rash during use of ceftazidime and generalized convulsions possibly due to imipenem). These patients' responses to the second treatment were evaluable. Of the remaining 144 patients, the initial treatment for 45 was judged by the evaluating physicians to have failed (31 [41.3%] in the ceftazidime group and 14 [20.3%] in the imipenem group; $P = .011$). However, as there were more evaluable patients in the ceftazidime treatment group who were septicemic, a further analysis was performed to ensure that this potential confounding factor was not the cause of the difference in outcomes.

Logistic regression analysis showed that positivity of blood cultures at any time was the most important risk factor for treatment failure ($P < .001$; OR, 5.56; 95% CI, 2.32–13.37).

Table 4. Outcomes for all 214 patients with melioidosis.

Variable	No. (%) of recipients			*P* value
	Imipenem ($n = 108$)	Ceftazidime ($n = 106$)	All ($n = 214$)	
Survived	64 (59.3)	64 (60.4)	128 (59.8)	
Died	39 (36.1)	40 (37.7)	79 (36.9)	.96
Self-discharged	5	2	7	
Evaluable (survived >48 h)	70 (64.8)	76 (71.7)	146 (68.2)	.35
Died within 48 h of enrollment	27 (25.0)	22 (20.8)	49 (22.9)	
Not evaluable	11 (10.2)	8 (7.5)	19 (8.9)	
Died after ⩾48 h	12 (11.1)	18 (17.0)	30 (14.0)	.22
Switched to second agent	11 (10.2)	17 (16.0)	28 (13.1)	.20
Switched to third agent	2	2	4	
Duration of first treatment, median no. of days (range)	11 (0–34)	10 (0–30)	11 (0–34)	.95
Fever clearance: median no. of hours (range)	186 (24–912)	215 (6–924)	204 (6–924)	.87
Never febrile	15 (13.9)	9 (8.5)	24 (11.2)	.21
Never afebrile	38 (35.2)	39 (36.8)	77 (36.0)	.81
Overall success rate of first treatment (excluding nonevaluable cases)				
Success	55 (50.9)	44 (41.5)	99 (46.3)	.21
Failure	41 (38.0)	53 (50.0)	94 (43.9)	

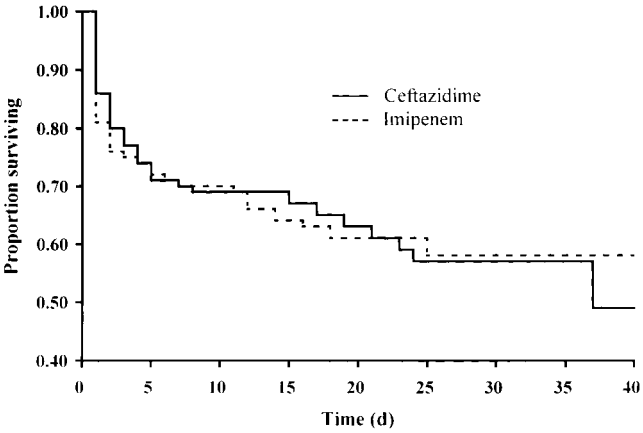

Figure 1. Kaplan-Meier survival plot showing proportions of patients surviving, against time since the start of parenteral therapy with ceftazidime or imipenem ($P = .95$, log-rank test). There are no patients remaining at the end of either curve.

However, ceftazidime as a first treatment was also significantly associated with treatment failure, in comparison with imipenem, independent of blood culture–positivity ($P = .025$; OR, 2.48; 95% CI, 1.12–5.49).

Twenty-eight of 146 patients were switched to the alternative antibiotic, 11 (15.7%) following use of imipenem as first treatment and 17 (22.4%) following use of ceftazidime; 26 patients (10 and 16, respectively) were switched because of primary treatment failure (table 4). Four imipenem-treated patients and 13 ceftazidime-treated patients died after ⩾48 hours, most of uncontrolled sepsis. A further two ceftazidime-treated patients were switched to oral conventional treatment but on review their initial treatment was considered to have failed.

Of the 11 patients switched from imipenem to ceftazidime, three were treated successfully and subsequently discharged from hospital. Seven patients' treatment failed; five died and two were switched to a third iv treatment regimen. One was given a combination of ceftazidime and ciprofloxacin, and the other a combination of ceftazidime and chloramphenicol; this latter patient died. One patient's response to ceftazidime as a second therapy was not evaluable.

Of the 17 patients switched from ceftazidime to imipenem, 11 were successfully treated. Six patients' second treatment failed, of whom 4 died and 2 required a switch to imipenem and ciprofloxacin in combination (1 died). Thus, there were 11 of 28 failures of second treatment (39.3%) overall. Success rates for second-agent therapy were 27.3% with ceftazidime and 64.7% with imipenem ($P = .12$).

Treatment failure resulting in a switch in therapy meant considerably longer hospital stays and courses of antibiotic treatment. The median total iv treatment duration for all patients with melioidosis who were not switched was 10 days (range, 1–34), whereas for those patients whose initial treatment failed and who were switched to the second agent, median treatment duration was 23 days (range, 12-47 days) ($P < .001$). The median stay for all patients with melioidosis who were not switched to a different therapy was 14 days (range, 1–73 days), whereas for those patients whose therapy failed and who were switched to the second agent, the median stay was 29 days (range, 12–73 days) ($P < .001$).

Clinical Responses to Treatment

Both of the treatment antibiotics were well tolerated despite the high doses used. One patient treated with imipenem had generalized convulsions possibly related to the drug, although other factors were potentially contributory. One patient developed a widespread erythematous rash during treatment with ceftazidime, which was sufficiently severe to warrant a switch of therapy. Most patients received a minimum of 10 days of total treatment, including those who required a switch of antibiotic. Among the 146 evaluable patients surviving >48 hours, the median total duration of therapy was 14 days (range, 5–43 days; interquartile range, 11–18 days) for patients receiving imipenem as first treatment and 15 days (range, 2–47 days; interquartile range, 10–20 days) for those receiving ceftazidime initially ($P = .88$). Fever clearance times were similar for both groups, with a median of 9 days for evaluable patients (range, <1–39 days; interquartile range, 4.5–15 days).

Complications of severe melioidosis were common. Sixty-four patients (29.9%) had septic shock, 123 (57.5%) became jaundiced or had biochemical evidence of impaired liver function, 34 (15.9%) had laboratory evidence of coagulopathy, and 54 (25.2%) had acute renal failure. There were no significant differences between the two groups for any of these variables.

The average per-patient antibiotic cost (in United States dollars) for a course of treatment for melioidosis was $1,000 for those patients treated with imipenem and $600 for those treated with ceftazidime. For survivors, the average cost of treatment was $1,450 for imipenem and $800 for ceftazidime.

Microbiology

Blood cultures were positive at any time for *B. pseudomallei* for 132 patients (61.7%). On the day of enrollment in the study, 117 patients had positive blood cultures, including 65 in the ceftazidime group and 52 in the imipenem group (61.3% vs. 48.1%; $P = .07$). Four patients' blood cultures were positive for *B. pseudomallei* on the second day of treatment but were previously negative.

For the 132 patients with positive blood cultures, *B. pseudomallei* was also isolated from the following specimens: sputum (48 patients); throat swab (53); sputum or throat swab (78); urine (51); pus or wound swab (40); liver or splenic pus (11); joint fluid (11); pericardial fluid (1); pleural fluid (5); peritoneal fluid (1); parotid pus (1); and others (3). Among septicemic patients, 58 (43.9%) had either a primary septicemic illness or had a single identifiable focus of infection. Another

74 had disseminated disease, i.e., more than one contiguous focus of infection was identified.

Among the 82 nonbacteremic patients, 67 (81.7%) had localized disease and 15 had multiple foci despite being blood culture–negative. Among these 82 patients, *B. pseudomallei* was isolated from the following specimens: sputum or throat swab (43); urine (9); pus or wound swab (23); liver or splenic pus (14); joint fluid (1); pleural fluid (4); and other (1).

For the 146 evaluable patients surviving >48 hours, blood cultures were positive at any time for *B. pseudomallei* for 83 patients (56.8%): 35 (50.0%) of the imipenem recipients and 48 (63.2%) of the ceftazidime recipients ($P = .15$). However, only 27 (38.6%) in the imipenem group, vs. 43 (56.6%) in the ceftazidime group, were blood culture–positive on the day of enrollment ($P = .04$). On day two, 16 of 57 patients (28.1%) in the imipenem group and 15 of 62 (24.1%) in the ceftazidime group were blood culture–positive. Three of the imipenem recipients who were blood culture–positive on day 2 had been negative on enrollment. However, by day 4, 5 of 48 patients (10.4%) in the imipenem group and 9 of 49 (18.4%) in the ceftazidime group were still blood culture–positive ($P = .4$). By day 7, 2 of 23 patients (8.7%) in the imipenem group and 7 of 33 (21.2%) in the ceftazidime group were blood culture–positive ($P = .28$). Five patients (4 who received ceftazidime initially) were still blood culture–positive at 14 days and 2 remained positive at 4 weeks (1 in each group). None of these patients had evidence of endocarditis.

On admission, 13 patients had isolates recovered that showed resistance, by disk-diffusion testing, to other antibiotics used routinely to treat melioidosis. Twelve patients' isolates were resistant to chloramphenicol; seven of these were resistant to fluoroquinolones, and one was resistant to doxycycline also. One patient's isolate was resistant to doxycycline alone. There were no isolates that were primarily resistant to ceftazidime, imipenem, or co-amoxiclav. Development of resistance to either ceftazidime or imipenem did not occur during treatment in any patients.

Long-Term Follow-Up

One hundred and twenty-eight patients were discharged from the hospital, 64 patients from each primary-treatment group. Forty-four (34.4%) of these patients received oral conventional four-drug therapy and 44 received oral doxycycline alone. Other oral maintenance regimens prescribed included co-amoxiclav (18 patients), doxycycline/TMP-SMZ (8), ciprofloxacin plus azithromycin (9), and ciprofloxacin alone (5). By March 1998, 16 patients (12.5%) had been readmitted because of suspected relapses; 12 (9.4%) of these were confirmed by culture. Five had been treated initially with imipenem and 11 with ceftazidime ($P = .18$).

Discussion

Melioidosis is endemic to Southeast Asia and northern Australia but is probably greatly underrecognized because diagnostic microbiology facilities are not available in many parts of the region [13]. Melioidosis is an important cause of community-acquired septicemia, and >60% of all cases may be bacteremic. In Ubon Ratchathani in northeastern Thailand, close to the borders of both Laos and Cambodia, melioidosis is the cause of 20% of cases of community-acquired septicemia and causes 40% of all deaths in this group of patients [14]. The annual disease incidence in this province has been estimated at 4.4 cases per 100,000 [8].

The treatment of melioidosis remains problematic. Before 1989, the conventional treatment for melioidosis was a combination of iv chloramphenicol, tetracycline, and TMP-SMZ. This four-drug regimen is bacteriostatic, and the components show mutual antagonism. The mortality associated with severe disease before 1989 was ~80%.

We have reported previously on two trials of iv treatment for severe melioidosis. The first study was a randomized, open trial comparing iv ceftazidime with conventional four-drug therapy. This study, completed in 1988, showed that ceftazidime was associated with a reduction in mortality of 50% among septicemic patients surviving at least 48 hours [2]. The second trial compared iv co-amoxiclav with ceftazidime for severe disease and was completed in 1992. Although the overall mortality was similar in the two treatment groups, there were more acute treatment failures in the co-amoxiclav group [4].

A third trial, also in northeastern Thailand, compared conventional therapy with a combination of iv ceftazidime and TMP-SMZ, with a substantial reduction in mortality with use of the latter regimen [3]. One further trial at the same center compared cefoperazone-sulbactam (Sulperazon; Pfizer, Groton, CT) plus TMP-SMZ with a combination of ceftazidime and TMP-SMZ [5]. This randomized study demonstrated that the cefoperazone-sulbactam regimen may be clinically useful, but only 38 evaluable patients were enrolled. A much larger trial is required before definite conclusions can be drawn. High-dose ceftazidime thus remains the drug of choice for severe melioidosis.

These four studies are the only reported randomized trials of therapy for severe melioidosis. However, despite these considerably improved treatment regimens, the mortality associated with severe melioidosis remains unacceptably high, at ~40%–45%. New, more effective drugs (or combinations) are desperately needed, as are studies of other therapeutic approaches.

B. pseudomallei is intrinsically antibiotic-resistant. Carbapenems are the most active antibiotics against *B. pseudomallei*, with MIC_{90} values of ~0.5 μg/mL. They also are active against strains of *B. pseudomallei* that are resistant to ceftazidime (MIC_{90}, ~4.0 μg/mL) [15]. In time-kill kinetic studies, ceftazidime exhibits very slow bactericidal activity, whereas imipenem is bactericidal (99.9% killing rate) within 4 hours [16]. The carbapenems bind preferentially to penicillin-binding pro-

tein 2 and induce formation of spheroplastic forms, whereas ceftazidime, which binds to penicillin-binding protein 3, leads to formation of long, filamentous forms of the organism, with the greater potential for endotoxin production [17].

The carbapenems also have a broader spectrum of activity than ceftazidime against the other common causes of community-acquired septicemia in this area of endemicity, so imipenem is an attractive candidate for empirical treatment of patients with suspected septicemic melioidosis. Early effective treatment is likely to improve the chance of survival.

This study has shown that imipenem is an effective acute treatment for severe melioidosis. Imipenem treatment did not result in an improved overall outcome when compared with ceftazidime therapy. As in previous studies, mortality during the first 48 hours of treatment was high. Many of these patients were moribund on admission and would be unlikely to benefit from improved antibiotic treatment. When patients who died in the first 48 hours were excluded from the analysis, there was still no difference in outcome ($P = .3$). However, there were significantly more treatment failures among patients receiving ceftazidime as first treatment (patients who either died after 48 hours or required a switch of treatment to imipenem).

A switch of treatment was associated with a considerably longer hospital stay. Thus, for a subgroup of patients, imipenem appears superior to ceftazidime. However, imipenem is more expensive, which may be a limiting factor in decisions regarding which drug to use in a particular setting. On the basis of current costs in the United Kingdom for the doses used in this study, the cost in United States dollars for ceftazidime treatment is ~$100 per day, vs. ~$150 for imipenem treatment. The two agents are comparable in terms of ease of administration and storage. These data suggest that imipenem may be considered an alternative to ceftazidime for the treatment of suspected or culture-confirmed melioidosis.

This trial also highlights a well known but seldom-discussed aspect of research in tropical infections: the difficulty of obtaining registered antibiotics for clinical trials. Despite their in vitro superiority over other compounds against *B. pseudomallei,* it has proved very difficult to obtain donations of carbapenem antibiotics for clinical trials of treatment for melioidosis. These studies are very costly to conduct, and if all drugs were purchased (at $100–$150 [U.S.] per patient per day), these trials would be prohibitively expensive.

This trial was stopped at the stage of interim analysis, when further supplies of antibiotic were not forthcoming. The results are suggestive but not conclusive. Melioidosis affects mainly poor rural people in the tropics, and there is little pharmaceutical industry interest in a "market" that is not considered sufficiently economically rewarding.

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