Two Randomized Controlled Trials of Ceftazidime Alone versus Ceftazidime in Combination with Trimethoprim-Sulfamethoxazole for the Treatment of Severe Melioidosis

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Background. Two antibiotic regimens are used commonly in Thailand for the initial treatment of severe melioidosis: ceftazidime in combination with trimethoprim-sulfamethoxazole (TMP-SMX) and ceftazidime monotherapy. It is not known whether TMP-SMX provides an additional benefit.

Methods. Two prospective, randomized trials that compared these regimens for patients presenting with acute severe melioidosis were started independently at tertiary care hospitals in Ubon Ratchathani and Khon Kaen (in northeastern Thailand), and the results were analyzed together as a prospective, individual-patient data meta-analysis. The primary end point was in-hospital mortality rate.

Results. The in-hospital mortality rate among all enrolled patients (n = 449) was not significantly different between those randomized to ceftazidime alone (25.1%; 56 of 223 subjects) and those randomized to ceftazidime with TMP-SMX (26.6%; 60 of 226 subjects; odds ratio [OR], 1.08; 95% confidence interval [CI], 0.7–1.7; stratified P = .73). Of the 241 patients with culture-confirmed melioidosis, 51 (21.2%) died. Of these 241 patients, 31 (12.9%) died ≥48 h after the time of study entry. Among patients with melioidosis, there was no difference in death rate between the 2 treatment groups for either all deaths (OR, 0.88; 95% CI, 0.48–1.6; stratified P = .70) or for deaths that occurred ≥48 h after hospital admission (OR, 0.88; 95% CI, 0.41–1.9; stratified P = .73). Conditional logistic regression analysis revealed that bacteremia, respiratory failure, and renal failure were independently associated with death and treatment failure. Drug regimens were not associated with death or treatment failure in this model.

Conclusion. We conclude that the addition of TMP-SMX to ceftazidime therapy during initial treatment of severe melioidosis does not reduce the acute mortality rate.

Melioidosis is a serious bacterial infection caused by the gram-negative environmental organism Burkholderia pseudomallei. During the past 20 years, melioidosis has accounted for ~20% of cases of community-acquired septicemia in northeastern Thailand [1]. Clinical manifestations are protean, but the most frequent presenting clinical presentation among affected individuals in this region is a septicemic illness, which is often associated with bacterial dissemination to distant sites. B. pseudomallei is also an important pathogen in the Northern Territory of Australia, where it is the most common cause of fatal community-acquired pneumonia [2]. B. pseudomallei is listed as a category B disease/bioterrorist threat agent by the US Centers for Disease Control and Prevention.

Previous treatment trials have demonstrated the importance of the choice of antibiotic at the time of presentation. Studies that compared a 4-drug combination
of chloramphenicol, doxycycline, and trimethoprim-sulfa-
methoxazole (TMP-SMX; this was standard therapy in Thai-
land before 1988) with ceftazidime alone [3] or ceftazidime
plus TMP-SMX [4] demonstrated a 50% reduction in the mor-
tality rate for patients with severe melioidosis who received
either ceftazidime-containing regimen. It is unclear whether the
addition of TMP-SMX to ceftazidime therapy confers an addi-
tional benefit over ceftazidime monotherapy. The use of
TMP-SMX may lead to an increased number of adverse effects,
and there is in vitro evidence to suggest that TMP-SMX an-
tagonizes the bactericidal activity of ceftazidime [5]. Here, we
report the results of 2 large prospective, randomized treatment
trials comparing the therapeutic efficacy of ceftazidime alone
and ceftazidime with TMP-SMX for patients with acute, severe
melioidosis.

PATIENTS AND METHODS

Two prospective, randomized trials that compared ceftazidime
in combination with TMP-SMX and ceftazidime monotherapy
in patients who presented with acute, severe melioidosis were
started independently in 1999 at Sappasithiprasong Hospital
(Ubon Ratchathani, Thailand) and Srinagarind Hospital (Khon
Kaen, Thailand). The studies were continued until October
2003, with patient recruitment taking place during the rainy
season of June to November in each study year (a reflection
of disease seasonality). The studies were approved by the Min-
istry of Public Health, Royal Government of Thailand, and
Khon Kaen University Ethics Committee for Human Research.

The 2 studies were initiated independently and were both
designed to answer a question commonly under discussion in
the melioidosis research community. The protocols were sim-
ilar, because they were both based on the entry criteria and
study design used in previously published melioidosis trials
conducted in northeast Thailand. The decision to combine data
from the 2 trials in a prospective meta-analysis was made by
the principal investigators once the groups had discovered the
existence of each other’s studies. This decision was initiated by
the investigators; ethics committees and drug suppliers played
no role.

All adult patients (age, >14 years) with suspected severe me-
lioidosis were eligible for enrollment in the trials if they or their
attending relatives provided consent. Severe melioidosis was
declared as the presence of 2 of the following characteristics:
(1) temperature, >38°C or <36°C; (2) pulse rate, >90 beats/
min; (3) respiratory rate, >20 breaths/min, or partial pressure
of CO₂, arterial, <32 mm Hg; (4) WBC count, >12,000 × 10⁹
cells/L, or band forms, >10%; (5) organ dysfunction (as defined
by oliguria, mental change, or lactic acidosis); and (6) hypo-
tension (systolic blood pressure, <90 mm Hg). Exclusion cri-
teria in both trials were known hypersensitivity to penicillins,
cephalosporins, trimethoprim, or sulfa group drugs; receipt of
treatment for >24 h with an antibiotic active against B. pseu-
domallei, with clinical evidence of response to treatment; known
infection with an isolate of ceftazidime-resistant B. pseudom-
ellei; known HIV seropositivity; and pregnancy or lactation.
Patients with aplastic anemia or glucose-6-phosphate dehy-
drogenase deficiency and those with a serum creatinine level
of >530 μmol/L were also excluded from the study at Ubon
Ratchathani but not in Khon Kaen.

Detailed medical history and physical examination findings
were recorded at the time of hospital admission using stan-
dardized forms. Baseline investigations were complete blood
cell count; determination of plasma glucose, lactate, and elec-
trolyte concentrations; and renal and liver function tests. Mi-
crobiological samples obtained from all patients before the start
of antibiotic treatment were 2 blood samples (for culture) and
a throat swab specimen; urine, pus, and sputum samples were
obtained when available. Chest radiography was performed on
the day of hospital admission for all patients, and abdominal
ultrasonography was performed as clinically indicated.

All patients in both centers received ceftazidime (120 mg/kg
per day; 2 g t.i.d. by bolus intravenous injection or adjusted
for renal function). In Ubon Ratchathani, randomization was
performed in blocks of 10 using a computer-generated ran-
domized sequence, and the drugs were prepackaged in sealed
boxes labeled with the study code. Patients were randomly
allocated to receive either TMP-SMX (160/800 mg infused over
30 min every 8 h or adjusted for renal function) or placebo
(0.9% normal saline, identical in appearance to ampoules of
TMP-SMX). The study doctors and patients were blinded to
the treatment. In Khon Kaen, the study was performed as an
open-label trial with treatment allocations maintained in sealed
envelopes that were opened at the point of patient enrollment.
Dosing of TMP-SMX was identical to that used in Ubon
Ratchathani.

Vital signs were recorded every 4 h, and a detailed clinical
examination was performed daily. Supportive care and addi-
tional investigation was undertaken as clinically indicated. Ab-
scesses were drained wherever possible. Patients who were cul-
ture negative for melioidosis after a minimum of 5 days were
switched to an alternative antibiotic therapy, as appropriate,
and were observed to document study end points.

Patients received parenteral therapy until they showed def-
inite clinical evidence of improvement (usually after at least 10
days). Surviving patients in Ubon Ratchathani were then ran-
domized as part of an independent trial of oral therapy to
receive doxycycline and TMP-SMX, with or without chloram-
phenicol (total course, 20 weeks). Surviving patients in Khon
Kaen were treated with doxycycline and TMP-SMX or with
amoxicillin/clavulanate for at least 20 weeks.

The major end points were (1) in-hospital death (or dis-
charge of the patient while moribund at the request of the
Ceftazidime and TMP-SMX in Severe Melioidosis

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Figure 1. Flow chart describing patients recruited in the study. KK, Khon Kaen; TMP-SMX, trimethoprim-sulfamethoxazole; UR, Ubon Ratchathani.

Microbiological specimens were processed as described elsewhere [3]. Blood cultures were repeated after 24 h, 72 h, and 7 days for all patients and after 14 and 28 days of antibiotic treatment for patients with ≥1 positive blood culture result. Positive admission cultures of specimens from other sites were repeated weekly until negative or until the patient was discharged from hospital in Ubon Ratchathani but not in Khon Kaen. B. pseudomallei was identified as described elsewhere [6]. Antimicrobial susceptibilities were determined by the Kirby-Bauer disk diffusion method. TMP-SMX susceptibility testing by the disk diffusion method overestimates resistance [7], and patients were not excluded if the disk test indicated that the infecting isolate was drug resistant. TMP-SMX susceptibility has subsequently been determined by Etest for all Ubon Ratchathani isolates. Interpretive standards for this were based on NCCLS guidelines for B. pseudomallei [8], with TMP-SMX sensitivity defined as an MIC of ≤2/38 μg/mL and resistance defined as an MIC of ≥4/76 μg/mL.

The results were analyzed in both intention-to-treat and per-protocol analyses (for cases of culture-confirmed melioidosis) and are reported for each study site. Heterogeneity between the study sites was assessed for all variables to determine whether pooling of data was feasible. Homogeneous data were combined, and stratified $P$ values are shown, whereas $P$ values for each site are shown separately in brackets for heterogeneous data. Continuous data were compared using the Kruskal-Wallis test for each site, and conditional logistic regression was used for combined sites. Categorical data were compared using the $\chi^2$ test or Fisher’s exact test for each site, and the Mantel-Haenszel test was used for combined sites. Survival analysis was performed using the Kaplan-Meier method, with groups compared using the log-rank test, Wilcoxon test, or Cox regression, as appropriate. Multiple conditional logistic regression (forward
Table 1. Baseline characteristics of and mortality among 449 patients enrolled in a study of severe melioidosis, by study site.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Khon Kaen (n = 232)</th>
<th>Ubon Ratchathani (n = 217)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with</td>
<td>Patients without</td>
</tr>
<tr>
<td></td>
<td>melioidosis (n = 87)</td>
<td>melioidosis (n = 145)</td>
</tr>
<tr>
<td>Male sex</td>
<td>64 (73.6)</td>
<td>75 (51.7)</td>
</tr>
<tr>
<td>Age, median years (90% range)</td>
<td>51 (24–70)</td>
<td>60 (33–79)</td>
</tr>
<tr>
<td>Clinical characteristic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>16 (18.4)</td>
<td>33 (22.8)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>16 (18.4)</td>
<td>35 (24.1)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>27 (31.0)</td>
<td>38 (26.2)</td>
</tr>
<tr>
<td>Septicemia</td>
<td>52 (59.8)</td>
<td>22 (15.2)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>75 (36.2)</td>
<td>125 (86.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>50 (57.5)</td>
<td>86 (59.3)</td>
</tr>
<tr>
<td>Renal diseases</td>
<td>13 (14.9)</td>
<td>23 (15.9)</td>
</tr>
<tr>
<td>Steroid use</td>
<td>13 (14.9)</td>
<td>11 (7.6)</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>6 (6.9)</td>
<td>10 (6.9)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>8 (9.2)</td>
<td>16 (11.0)</td>
</tr>
<tr>
<td>Previous melioidosis</td>
<td>2 (2.3)</td>
<td>8 (5.5)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>6 (6.9)</td>
<td>7 (4.8)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>15 (17.2)</td>
<td>36 (24.8)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated.

* Determined by the Mantel-Haenszel test for heterogeneity; $P<.05$ denotes statistical significance.

$^a$ Determined by the Mantel-Haenszel test for categorical data and by conditional logistic regression for continuous data.

$^c$ $P$ value determined by the $\chi^2$ test for Khon Kaen and Ubon Ratchathani, respectively; no combined analysis was performed because the data from the 2 sites were heterogeneous.

The study was terminated when combined enrollment reached the higher of the intended enrollments calculated from a priori power calculations. At Ubon Ratchathani, the investigators intended to enroll 445 patients with suspected melioidosis, which would have 90% power to detect a reduction in the mortality rate among culture-positive patients from 35% to 17.5% (assuming that two-thirds of the enrolled patients were culture positive). At Khon Kaen, the investigators believed that 300 patients with suspected melioidosis should be enrolled, giving an 80% power to detect a reduction in the mortality rate among culture-positive patients from 40% to 20% (assuming that 60% of the enrolled patients were culture positive).

**RESULTS**

A total of 449 patients were enrolled, of which 232 were from Khon Kaen and 217 were from Ubon Ratchathani. A flow diagram of patient enrollment, diagnoses, and randomization selection was performed to evaluate factors associated with death and treatment failure for combined data. All analyses were performed using the statistical computing package Stata/SE, version 8.0 for Windows (Stata), and SPSS for Windows, version 11.0 (SPSS).

The study was terminated when combined enrollment reached the higher of the intended enrollments calculated from a priori power calculations. At Ubon Ratchathani, the investigators intended to enroll 445 patients with suspected melioidosis, which would have 90% power to detect a reduction in the mortality rate among culture-positive patients from 35% to 17.5% (assuming that two-thirds of the enrolled patients were culture positive). At Khon Kaen, the investigators believed that 300 patients with suspected melioidosis should be enrolled, giving an 80% power to detect a reduction in the mortality rate among culture-positive patients from 40% to 20% (assuming that 60% of the enrolled patients were culture positive).

Overall, 223 patients received ceftazidime alone (118 of whom had culture-confirmed melioidosis), and 226 patients received ceftazidime and TMP-SMX (123 of whom had culture-confirmed melioidosis). Baseline data for all patients are shown in table 1, and baseline data for patients with melioidosis are shown in tables 2 and 3. The distributions of underlying co-morbidities, physical examination findings, and most laboratory parameters were similar for patients in both treatment arms, with the exception that the median serum bicarbonate level was lower in the ceftazidime monotherapy group in Ubon Ratchathani but not in Khon Kaen (18 vs. 21 mmol/L [$P = .01$] and 19 vs. 20 mmol/L [$P = .49$], respectively).
### Table 2. Baseline characteristics and admission clinical data for 241 patients with melioidosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Khon Kaen (n = 87)</th>
<th>Ubon Ratchathani (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ceftazidime recipients (n = 46)</td>
<td>Ceftazidime–TMP-SMX recipients (n = 41)</td>
</tr>
<tr>
<td>Male sex</td>
<td>34 (73.9)</td>
<td>30 (73.2)</td>
</tr>
<tr>
<td>Age, median years (90% range)</td>
<td>54 (24–70)</td>
<td>50 (22–70)</td>
</tr>
<tr>
<td>Duration of fever, median days (90% range)</td>
<td>14 (2–90)</td>
<td>14 (3–90)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>39 (84.8)</td>
<td>36 (87.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31 (67.4)</td>
<td>19 (46.3)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>5 (10.9)</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>Steroid use</td>
<td>7 (15.2)</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>5 (10.9)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>3 (6.5)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Previous melioidosis</td>
<td>1 (2.2)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4 (8.7)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Type/site of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septicemia</td>
<td>30 (65.2)</td>
<td>24 (58.5)</td>
</tr>
<tr>
<td>Lung</td>
<td>23 (50.0)</td>
<td>23 (56.1)</td>
</tr>
<tr>
<td>Skin or soft tissue infection</td>
<td>18 (39.1)</td>
<td>12 (29.3)</td>
</tr>
<tr>
<td>Intra-abdominal abscess</td>
<td>14 (30.4)</td>
<td>13 (31.7)</td>
</tr>
<tr>
<td>Bone or joint infection</td>
<td>7 (15.2)</td>
<td>16 (39.0)</td>
</tr>
<tr>
<td>Source of <em>Burkholderia pseudomallei</em> isolate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>30 (65.2)</td>
<td>24 (58.5)</td>
</tr>
<tr>
<td>Sputum</td>
<td>12 (26.1)</td>
<td>9 (22.0)</td>
</tr>
<tr>
<td>Urine</td>
<td>5 (10.9)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Skin/soft-tissue pus</td>
<td>15 (32.6)</td>
<td>11 (26.8)</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>7 (15.2)</td>
<td>13 (31.7)</td>
</tr>
<tr>
<td>Other site</td>
<td>10 (21.7)</td>
<td>8 (19.5)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. TMP-SMX, trimethoprim-sulfamethoxazole.

<sup>a</sup> Determined by the Mantel-Haenszel test for heterogeneity; P<.05 denotes statistical significance.

<sup>b</sup> Determined by the Mantel-Haenszel test for categorical data and by conditional logistic regression for continuous data.

<sup>c</sup> P value determined by the χ² test for Khon Kaen and Ubon Ratchathani, respectively; no combined analysis was performed because the data from the 2 sites were heterogeneous.

Blood culture results were positive for 140 (58.1%) of the patients with melioidosis; a higher proportion of patients in the ceftazidime monotherapy group were bacteremic (65.3% vs. 51.2%; stratified P<.03). Eighty-one (34%) of 241 patients with culture-confirmed melioidosis had positive blood culture results in association with either a single or no identifiable focus of infection (i.e., septicemic disease), 59 (24%) had positive blood culture results with multiple noncontiguous foci of infection (i.e., disseminated disease), 72 (30%) had negative blood culture results and a single focus of infection (i.e., localized disease), and 29 (12%) had negative blood culture results with multiple noncontiguous foci of infection (i.e., multifocal disease). These patients were evenly distributed between treatment groups.

**Mortality.** Overall, 116 patients died (25.8%) (table 1). The in-hospital mortality rate among all patients treated with ceftazidime alone was 25.1% (56 of 223 patient), and for patients treated with ceftazidime and TMP-SMX, it was 26.6% (60 of 226 patients; stratified P=.75). The mortality rate for all patients did not differ between the ceftazidime monotherapy group and the ceftazidime–TMP-SMX group at either Khon Kaen (18% [21 of 117 patients] vs. 26.1% [30 of 115 patients]; P=.16) or Ubon Ratchathani (33% [35 of 106 patients] vs. 27% [30 of 111 patients]; P=.38). The difference in the survival rate between the 2 treatment groups was 10% (95% CI, 2%–18%). The mortality rate in the non-melioidosis group was higher than that in the melioidosis group (31.3% [65 of 208 patients] vs. 21.2% [51 of 241 patients]; stratified P=.001 (table 1).

Among the 241 patients with melioidosis, there was no dif-
Table 3. Laboratory findings at hospital admission for 241 patients with melioidosis.

<table>
<thead>
<tr>
<th>Laboratory value</th>
<th>Khon Kaen (n = 87)</th>
<th>Ubon Ratchathani (n = 154)</th>
<th>Heterogeneity P&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Stratified P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit, %</td>
<td>32 (21–42)</td>
<td>32 (21–41)</td>
<td>32 (19–41)</td>
<td>31 (18–41)</td>
</tr>
<tr>
<td>WBC count, x10&lt;sup&gt;9&lt;/sup&gt; cells/L</td>
<td>12.3 (4.7–34.4)</td>
<td>13.6 (2.3–24.2)</td>
<td>13.5 (5.5–30.1)</td>
<td>13.4 (5.8–26.7)</td>
</tr>
<tr>
<td>Blood urea nitrogen, mmol/L</td>
<td>7.5 (2.5–36.8)</td>
<td>6.8 (3.6–47.5)</td>
<td>7.5 (1.8–24.6)</td>
<td>7.1 (2.5–38.2)</td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>115 (62–389)</td>
<td>97 (71–937)</td>
<td>124 (62–380)</td>
<td>124 (71–469)</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>271 (61–832)</td>
<td>223 (72–767)</td>
<td>211 (64–1227)</td>
<td>186 (86–636)</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>59 (19–186)</td>
<td>64 (26–250)</td>
<td>63 (18–362)</td>
<td>75 (22–309)</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>59 (13–224)</td>
<td>65 (18–156)</td>
<td>42 (17–156)</td>
<td>54 (18–194)</td>
</tr>
<tr>
<td>Total bilirubin, µmol/L</td>
<td>27.4 (6.8–179.6)</td>
<td>22.2 (8.6–92.3)</td>
<td>22.2 (5.1–222.3)</td>
<td>17.1 (6.8–222.3)</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>29 (20–37)</td>
<td>27 (15–36)</td>
<td>26 (15–42)</td>
<td>27 (15–38)</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>19 (12–26)</td>
<td>20 (8–28)</td>
<td>18 (8–27)</td>
<td>21 (10–31)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>9.4 (5.8–34.3)</td>
<td>9.5 (3.2–29.2)</td>
<td>9.4 (2.5–34.9)</td>
<td>8.8 (2.4–25.1)</td>
</tr>
</tbody>
</table>

NOTE. TMP-SMX, trimethoprim-sulfamethoxazole.

<sup>a</sup> Determined by the Mantel-Haenszel test for heterogeneity; P<.05 denotes statistical significance.

<sup>b</sup> Determined by the Mantel-Haenszel test for categorical data and by conditional logistic regression for continuous data.

<sup>c</sup> P value determined by the χ² test for Khon Kaen and Ubon Ratchathani, respectively; no combined analysis was performed because the data from the 2 sites were heterogeneous.

Table 4. Outcomes for all 241 patients with melioidosis.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Khon Kaen (n = 87)</th>
<th>Ubon Ratchathani (n = 154)</th>
<th>Heterogeneity P&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Stratified P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived</td>
<td>39 (84.8)</td>
<td>53 (73.6)</td>
<td>35 (16.5)</td>
<td>45 (16.4)</td>
</tr>
<tr>
<td>Died</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All deaths</td>
<td>1 (2.3)</td>
<td>9 (12.5)</td>
<td>9 (6.1)</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>Died ≤48 h after enrollment</td>
<td>0 (0)</td>
<td>7 (9.7)</td>
<td>8 (9.8)</td>
<td>8 (6.5)</td>
</tr>
<tr>
<td>Died &gt;48 h after enrollment</td>
<td>0 (0)</td>
<td>12 (16.7)</td>
<td>9 (11.0)</td>
<td>12 (13.1)</td>
</tr>
<tr>
<td>Treatment failure among persons who survived the first 48 h&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock after 72 h of treatment</td>
<td>5 (11.6)</td>
<td>6 (16.2)</td>
<td>1 (1.4)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Persistent bacteremia for &gt;7 days</td>
<td>4 (8.7)</td>
<td>1 (2.4)</td>
<td>2 (2.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clinical failure requiring switch of therapy</td>
<td>8 (17.4)</td>
<td>5 (12.2)</td>
<td>8 (11.1)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Treatment failure and/or late death in among persons who survived the first 48 h&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined outcome of death or treatment failure</td>
<td>11 (23.9)</td>
<td>11 (26.8)</td>
<td>18 (25.0)</td>
<td>12 (14.6)</td>
</tr>
<tr>
<td>Duration of first treatment, median days (90% range)</td>
<td>14 (7–24)</td>
<td>14 (7–31)</td>
<td>15 (8–26)</td>
<td>12 (5–22)</td>
</tr>
<tr>
<td>Time to fever clearance, median days (90% range)</td>
<td>12 (3–24)</td>
<td>4 (1–30)</td>
<td>9 (2–26)</td>
<td>7 (1–23)</td>
</tr>
<tr>
<td>Duration of hospitalization, median days (90% range)</td>
<td>19 (1–35)</td>
<td>18 (3–43)</td>
<td>15 (1–34)</td>
<td>13 (1–29)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated. TMP-SMX, trimethoprim-sulfamethoxazole.

<sup>a</sup> Determined by the Mantel-Haenszel test for heterogeneity; P<.05 denotes statistical significance.

<sup>b</sup> Determined by the Mantel-Haenszel test for categorical data and by conditional logistic regression for continuous data.

<sup>c</sup> Total number of patients, some of whom died and some of whom also had ≥1 event that defined clinical failure.
2.48; 95% CI, 1.04–5.90; \( P = .041 \)), renal failure (OR, 5.3; 95% CI, 2.43–11.56; \( P < .001 \)), and respiratory failure (OR, 16.09; 95% CI, 5.25–49.30; \( P < .001 \)) were each independently associated with mortality.

**Treatment failure.** There were no differences between treatment groups with regard to the incidence of shock (stratified \( P = .45 \)) and of persistent bacteremia (stratified \( P = .06 \)). There were more switches in therapy in the ceftazidime monotherapy group than in the ceftazidime–TMP-SMX group (stratified \( P = .049 \)) (table 4). Survival analysis that censored patients who died confirmed this difference (stratified \( P = .05 \), by log rank test), but in Cox regression analysis, which adjusted for the presence of bacteremia at the time of hospital admission, there were no differences in treatment switches between the 2 groups (hazard ratio, 0.45; 95% CI, 0.19–1.11; stratified \( P = .08 \)).

There was no difference in the combined outcome of death and treatment failure between the 2 treatment groups (stratified...
P = .29, by the Wilcoxon test) (figure 3). Multiple conditional logistic regression analysis showed that the presence of bacte-
riaemia (OR, 2.89; 95% CI, 1.45–5.79; P = .03), respiratory failure
(OR, 6.74; 95% CI, 2.43–18.68; P < .001), and renal failure (OR,
3.08; 95% CI, 1.59–5.97; P = .001) were independently asso-
ciated with the combined outcome of mortality or treatment
failure.

Adverse events. Both treatments were well tolerated. Four
patients in the ceftazidime–TMP-SMX group and 2 patients in
the ceftazidime monotherapy group developed a widespread
erythematous rash during treatment (stratified P = .48). This
was sufficiently severe to warrant a switch of therapy for only
1 patient, who had received TMP-SMX. Hyperkalemia in asso-
ciation with renal impairment developed in a similar pro-
portion of patients in the ceftazidime–TMP-SMX group and
the ceftazidime monotherapy group (11 patients [8.9%] vs. 6
patients [5.2%]; stratified P = .17).

Complications of severe melioidosis were common: 52 pa-
tients (21%) developed septic shock, and 48 (19.9%) developed
acute renal failure. One hundred thirty-three patients (55.2%)
developed anemia (i.e., the hemoglobin level decreased by >1
g/dL from baseline), of whom 79 (32.8%) underwent transfu-
sion. There were no significant differences between the 2
treatment groups for any of these variables.

Antimicrobial susceptibility of B. pseudomallei. There
were 144 clinical isolates recovered from the 154 patients in
Ubon Ratchathani available for TMP-SMX susceptibility testing
by Etest; isolates from the Khon Kaen study were not stored.
Resistance to TMP-SMX was detected in 18 isolates (12.5%)
recovered from 18 patients, of whom 6 (8.6%) of 70 tested
strains were in the ceftazidime only group and 12 (16.2%) of
74 tested strains were in the ceftazidime–TMP-SMX group
( P = .17). When these patients were removed from the analysis,
there was no significant difference in treatment failure between
the 2 treatment groups (10 [16.7%] of 60 patients in the cefta-
zdime monotherapy group and 9 [14.5%] of 62 patients in the
ceftazidime–TMP-SMX group; P = .74). There were no differ-
ences in the percentages of drug-resistant strains between
subjects who experienced treatment failure or had a late death
and survivors who did not experience treatment failure when
considering both treatment arms (7 [20.6%] of 34 patients vs.
9 [9.4%] of 96 patients; P = .09) or the ceftazidime–TMP-
SMX group alone (3 [21.4%] of 14 patients vs. 8 [15.1%] of
53 patients; P = .69).

DISCUSSION
Several studies of severe melioidosis have been published in
which mortality data are available for either receipt of cefta-
zidime alone [3, 9, 10] or receipt of ceftazidime plus TMP-
SMX [4, 11]. It is difficult to extrapolate the best practice from
these findings, because the ceftazidime monotherapy studies
were performed at one center (in Ubon Ratchathani) and the
combined regimens were studied at another (in Khon Kaen).
A meta-analysis of previous data on the value of TMP-SMX
was not feasible because of differences in study design.

In this study, there was no mortality benefit associated with
the addition of TMP-SMX to the treatment regimen. With the
exception of a switch in therapy ( P = .049), other markers of
treatment failure were not significantly different between the 2
study groups. In a post-hoc analysis adjusting for bacte-
riaemia at hospital admission, the P value for a switch in therapy
was increased to .08, suggesting that a slight imbalance in initial
severity between the treatment groups may, in part, explain this
finding.

A prolonged course of oral antibiotic therapy is prescribed
after initial parenteral therapy for melioidosis, for a total treat-
ment duration of 12–20 weeks. The rationale for this is that
rates of recurrent infection are high (∼6% in the first year),
and a treatment duration of <12 weeks is associated with a
greater risk of relapse. One issue not addressed by this study
is whether the drugs used for initial therapy also affect rate of
relapse. It is possible that the drugs used in early disease in-
fluence bacterial clearance and the likelihood of persistence,
particularly because TMP-SMX has been used successfully in
Australia for oral eradication therapy. In view of this, follow-
up of patients in this study continues to define the relapse rate
in the 2 groups.

The addition of TMP-SMX to ceftazidime regimens is well
tolerated but does not affect mortality related to melioidosis.
In this study, the overall mortality rate for severe melioidosis
was 21%, which, although still high, is lower than has been
reported previously. This may result from general improve-
ments in supportive treatment and from the exclusion of pa-
tients with renal failure at one of the study sites. Much of this
mortality is due to early fulminant sepsis (40% of deaths oc-
curred within 48 h after commencement of specific antibiotic
treatment). Interventions directed at the complications of ful-
minant sepsis may improve outcomes in the future for patients
with melioidosis.

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