MAJOR ARTICLE

An Open, Randomized, Controlled Trial of Penicillin, Doxycycline, and Cefotaxime for Patients with Severe Leptospirosis

Yupin Suputtamongkol,[1] Kanigar Niwattayakul,[3] Chuanpit Suttinont,[4] Kitti Losuwanaluk,[5] Roongroeng Limpaiboon,[6] Wirongrong Chierakul,[2] Vanaporn Wuthiekanun,[2] Surapee Triengrim,[1] Mongkol Chenchittikul,[7] and Nicholas J. White[2,8]

[1]Department of Medicine, Faculty of Medicine at Siriraj Hospital, Mahidol University, and [2]Wellcome Trust–Mahidol University Oxford Tropical Medicine Research Programme, Faculty of Tropical Medicine, Mahidol University, Bangkok, [3]Department of Medicine, Loei Hospital, Loei Province, [4]Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima Province, [5]Banmai Chaiyapod Hospital, Bureerum Province, [6]Department of Medicine, Udonthani Hospital, Udonthani, and [7]National Institute of Health, Ministry of Public Health Thailand, Nondhaburi, Thailand; and [8]Centre for Vaccinology and Tropical Medicine, Nuffield Department of Medicine, Churchill Hospital, Oxford, United Kingdom

Background. Leptospirosis is an important cause of fever in the rural tropics. Since 1996, there has been a marked increase in the incidence of leptospirosis in northeastern Thailand. Although leptospirosis generally is susceptible to antibiotics, there is no consensus regarding the optimal treatment for severe leptospirosis.

Methods. An open-label, randomized comparison of parenteral cefotaxime, penicillin G sodium (hereafter known as "penicillin G"), and doxycycline for the treatment of suspected severe leptospirosis was conducted. The study involved 540 patients admitted to 4 hospitals in northeastern Thailand.

Results. A total of 264 patients (48.9%) had leptospirosis confirmed by serologic testing or culture. The overall mortality rate was 5%. There were no significant differences between the antibiotics with regard to associated mortality, defervescence, or time to resolution of abnormal findings of laboratory tests either among all study participants or among the subgroup of patients with confirmed leptospirosis. A total of 132 patients had rickettsial infection diagnosed, and, for these patients, treatment with doxycycline was superior to treatment with penicillin G.

Conclusions. Doxycycline or cefotaxime is a satisfactory alternative to penicillin G for the treatment of severe leptospirosis.

Leptospirosis is an acute febrile illness caused by infection with pathogenic spirochetes of the genus *Leptospira*. Leptospirosis is considered to be an emerging infectious disease in many countries, including Thailand [1–4]. Since 1996, there has been a marked increase in the number of reported leptospirosis cases and leptospirosis-associated deaths occurring annually in this country [4]. The clinical manifestations of leptospirosis are nonspecific and vary from subclinical infection [5, 6], a self-limited febrile illness, to a potentially lethal multisystem illness characterized by jaundice, renal failure, and pulmonary hemorrhage (known as "Weil syndrome"). The mortality rate associated with severe leptospirosis may be as high as 22% [7]. The manifestations of severe leptospirosis initially are similar to those of other community-acquired septicemias or to severe manifestations of other common tropical infections, including scrub typhus and malaria. The lack of a widely available, sensitive, and rapid method of laboratory confirmation has been an important impediment to both diagnosis and the selection of appropriate treatment.

There remains uncertainty regarding the optimal treatment for severe leptospirosis [8–14]. Penicillin G sodium (hereafter known as "penicillin G") is the generally recommended treatment for severe leptospirosis. However, antibiotic resistance has compromised the efficacy of penicillin G against many important bacterial pathogens, and the agent is intrinsically inactive against other organisms (e.g., *Rickettsia* organisms) that are major causes of systemic illness in tropical areas, such

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Reprints or correspondence: Dr. Yupin Suputtamongkol, Dept. of Medicine, Faculty of Medicine at Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand (siysp@mahidol.ac.th).

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as northeastern Thailand. Ceftriaxone was recently reported to be as effective as penicillin G in the treatment of severe leptospirosis [13]. Cefotaxime, another broad-spectrum third-generation cephalosporin, is widely available and has also been found to be highly active against leptospires in vitro and in an animal study [15]. Doxycycline, which has been recommended and used widely for the prophylaxis and treatment of leptospirosis of mild severity [16, 17], is also active against *Rickettsia* organisms. Both cefotaxime and doxycycline are well-tolerated and potentially alternative treatments for severe leptospirosis. We report the results of a multicenter, open, randomized, controlled study in which we compared the efficacy and tolerability of cefotaxime, parenteral doxycycline, and penicillin G in the treatment of patients with suspected leptospirosis.

PATIENTS AND METHODS

Study site and patients. The present study was conducted from July 2001 through December 2002 at 4 hospitals in northeastern Thailand: Udonthani Hospital (Udonthani Province), Maharat Nakhon Ratchasima Hospital (Nakhon Ratchasima Province), Loei Hospital (Loei Province), and Banmai Chaiyapod Hospital (Bureerum Province). Included in the trial were adult patients with suspected severe leptospirosis—that is, patients who presented with acute fever (duration, <15 days) in the absence of an obvious focus of infection. Criteria for exclusion from the trial included pregnancy or lactation, diabetes, known allergy to any of the study medications, and a definite history of receipt of treatment active against leptospirosis for >48 h. The study protocol was approved by the ethics review subcommittee of the Ministry of Public Health Thailand. Written, informed consent was obtained from all patients or their guardians before the patients entered the study.

Randomization and study protocol. The independent, computer-generated, random allocation sequences were prepared for each study hospital by the team of investigators in Bangkok, Thailand. The sequences were then sealed in an opaque envelope, and the envelopes were numbered. The investigator at each study hospital assigned study participants to their treatment groups after opening the sealed envelope and reviewing the allocation sequences. Patients were randomly allocated to receive 1 of the 3 study drugs. The patients who received penicillin G (hereafter known as "group P") were given penicillin G (provided by the Government Pharmaceutical Organization in Thailand), 1.5 million U iv q6h. The patients who received cefotaxime (hereafter known as "group C") were given cefotaxime (Siam Pharmaceuticals), 1 g iv q6h. The patients who received doxycycline (hereafter known as "group D") were given doxycycline (Pfizer International), 200 mg infused for 30 min, followed by infusion of 100 mg q12h. Gentamicin was administered, at the discretion of individual investigators, when gram-negative sepsis could not be excluded as a differential diagnosis. Gentamicin therapy was discontinued within 72 h of the report of an initial negative blood culture result. Parenteral study treatment was continued until the patient was afebrile and was well enough to have treatment switched to oral therapy. Treatment was then switched to either oral amoxicillin, 2 g/day (for group P and group C), or oral doxycycline, 200 mg/day (for group D). The total duration of treatment was 7 days. Other aspects of fluid-balance management and patient care were similar among the 3 treatment groups.

A detailed history and the findings of physical examinations and laboratory investigations were recorded on a standard form. Investigations performed at baseline included a full blood cell count and platelet count; 2 blood cultures for detection of common aerobic bacteria; leptospiral culture of 5 mL of blood collected in a sterile heparinized bottle and placed in Ellinghausen-McCullough medium as modified by Johnson and Harrison (EMJH); determination of plasma glucose, electrolyte, serum urea, and creatinine levels; liver function tests; urinalysis; and chest radiography. At least 2 serum samples, which were obtained at admission and at the outpatient visit occurring at 2–4 weeks of follow-up, were stored at −20°C until serologic testing was performed. All serum samples underwent serologic tests for the diagnosis of leptospirosis, scrub typhus, murine typhus, and dengue infection, as described elsewhere [1, 18–23].

Diagnostic tests. The 4 hospitals that participated in the study are located outside the area where malaria is endemic, but a diagnosis of malaria was excluded if the patients had a history of recent travel. The diagnostic tests for leptospirosis included culture in EMJH medium, and serologic tests for leptospirosis included the microagglutination test (MAT), the indirect immunofluorescent antibody test (IFAT), and the microcapsule agglutination test (MCAT). A definite serologic diagnosis of leptospirosis was indicated by (1) the isolation of leptospires from blood or (2) a 4-fold or greater increase in the agglutinin antibody titer (to ⩾1:200; as determined by MAT) or the specific IgG and IgM antibody titers (to ⩾1:200; as determined by IFAT) or (3) a single titer or stable antibody titer of ⩾1:400 [18, 19]. When the results of MAT and IFAT were negative, patients were also classified as having a confirmed case of leptospirosis if the MCAT result was positive and if there was no evidence of other infections [20]. All leptospires isolated from the present study were confirmed and serotyped at the World Health Organization/Food and Agricultural Organization of the United Nations/Office International des Epizooties Collaborating Centre for Reference and Research on Leptospirosis (Brisbane, Australia). Criteria for the diagnosis of rickettsial infection (e.g., scrub typhus, murine typhus, and spotted fever group rickettsiae) were (1) at least a 4-fold increase in the specific antirickettsial IgG or IgM titer (to ⩾1:200; as determined by IFAT) between paired serum samples, or (2) a single titer or stable IFA titer of ⩾1:400 [21, 22].

Table 1. Demographic characteristics and clinical presentations of and final diagnoses for patients with clinically suspected severe leptospirosis, according to treatment group.

Analysis status, finding	Patients given penicillin G sodium (n = 181)	Patients given doxycycline (n = 172)	Patients given cefotaxime (n = 187)	P
Excluded from analysis				
No. of patients	9	5	6	
Reason for exclusion, no. of patients				
Died within 48 h after admission	5	3	3	
Inappropriate randomization	2	2	2	
Uncertain outcome	2	…	1	
Inclusion in intent-to-treat analysis				
No. of patients	172	167	181	
Demographic or clinical characteristic				
No. of males/no. of females	154/18	144/23	151/30	.53
Age, median years (range)	36 (13–92)	35 (15–75)	37 (15–71)	.80
Duration of illness, median days (range)	3 (1–11)	3 (1–15)	4 (1–15)	.07
Final diagnosis, no. (%) of patients				.52
Leptospirosis				
Only	87 (50.6)	81 (48.5)	88 (48.6)	
Plus rickettsioses	23 (13.4)	21 (12.6)	18 (9.9)	
Plus other bacteremia	1 (0.6)	1 (0.6)	…	
Rickettsioses	18 (10.5)	26 (15.6)	27 (14.9)	
Other				
Other bacterial infection	5 (2.9)	8 (4.8)	9 (5.0)	
Viral infection	11 (6.4)	3 (1.8)	5 (2.8)	
Unknown	27 (15.7)	27 (16.2)	34 (18.8)	

Patients with confirmed leptospirosis were prospectively classified according to organ-system involvement manifested by hypotension (i.e., a systolic blood pressure of <90 mm Hg or a sustained decrease in systolic blood pressure of ⩾40 mm Hg), jaundice (an increase in the total bilirubin level to ⩾50 μmol/L [range considered to be normal, 5–17 μmol/L]), renal dysfunction (either oliguria [i.e., a urine output of <0.5 mL/kg/h for at least 1 h] or azotemia [a serum creatinine level of ⩾265 μmol/L), pulmonary involvement (abnormal findings on a chest radiograph or the need for mechanical ventilation at admission to the hospital), a decreased level of consciousness, or hemorrhagic complications (e.g., hemoptysis or gastrointestinal bleeding).

Statistical analysis. The incidence of leptospirosis was predicted to be 30%–40% among patients with acute febrile illness in whom leptospirosis was suspected. In a previous study, the mean duration of defervescence ($\pm$SD) was 4.7 $\pm$ 4.2 days [9]. Thus, the study required that 160 patients with suspected leptospirosis be included in each group to detect a 40% reduction in time to clearance of fever (from 5 days to 3 days) in either group D or group C, compared with group P, with 95% confidence and 90% power. Descriptive statistics were used to summarize the demographic characteristics of and data at baseline for patients in each study group. Differences between groups were analyzed using the χ^2 test, for categorized variables, and the Kruskal-Wallis H test, for continuous variables. Outcomes were compared between each treatment group, and multivariate analysis was used to compare the efficacy of the 3 antibiotic treatments.

The efficacy of the 3 study drugs was analyzed both for the treatment groups overall (i.e., on an intent-to-treat basis) as well as for 2 subgroups of patients (i.e., patients who had serologically confirmed leptospirosis and patients who had rickettsial infections with or without leptospirosis coinfection). Patients who died within the first 48 h after admission to the hospital were excluded from all analyses of clearance of fever. Body temperature was recorded every 4 h during hospitalization. The duration of fever was measured from the time of administration of the first dose of antimicrobial therapy to the time that the last temperature of >37.5°C was recorded. The resolution of fever in each treatment group was compared using Kaplan-Meier plot and log-rank tests. The duration of the increase in the serum creatinine level was measured, among patients with renal dysfunction, as the time from the day of entry into the study until the time that the last abnormal serum creatinine level (>133 μmol/L) was recorded. The duration of

Table 2. Clinical manifestations and findings of laboratory investigations at the time of admission to the hospital for 520 patients with clinically suspected severe leptospirosis, according to study group.

Finding	Patients given penicillin G sodium (n = 172)	Patients given doxycycline (n = 167)	Patients given cefotaxime (n = 181)	P
Clinical manifestation				
Acute febrile illness	41 (23.8)	41 (24.6)	45 (24.9)	.66
Jaundice	52 (30.2)	49 (29.3)	53 (29.3)	.98
Renal dysfunction	65 (37.8)	49 (29.3)	68 (37.6)	.18
Hypotension	24 (14)	21 (12.6)	27 (15)	.81
Lung involvement	37 (21.5)	36 (21.6)	38 (21)	.97
Bleeding complication	28 (16.3)	19 (11.4)	16 (8.8)	.21
WBC count >12,000 cells/mm^3	56 (32.6)	61 (36.5)	66 (36.5)	.62
Thrombocytopenia	59 (34.3)	58 (34.7)	72 (39.8)	.52
Laboratory value, median (range)				
Serum creatinine level,[a] μmol/L	133 (62–1197)	115 (62–1153)	133 (44–1117)	.08
Total bilirubin level,[b] μmol/L	22.1 (1.7–890.8)	20.4 (1.7–744.6)	23.8 (3.4–642.6)	.49
Aspartate aminotransferase level,[c] U/L	60 (13–568)	59 (10–5865)	48 (13–627)	.37
Alanine aminotransferase level,[d] U/L	44 (3–2750)	43 (2–4695)	41 (6–478)	.25
Alkaline phosphatase level,[e] U/L	122 (21–1156)	126 (20–965)	136 (20–1082)	.98
Treatment before admission to the hospital				.82
None	108 (62.8)	98 (58.7)	109 (60.2)	
Penicillin G sodium or ceftriaxone	23/9	25/13	35/12	
Doxycycline or chloramphenicol	8/2	5/1	4/0	
Penicillin G sodium or ceftriaxone				
Plus doxycycline	16	20	17	
Plus gentamicin	6	5	4	

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

[a] Level considered to be normal, <133 μmol/L.
[b] Level considered to be normal, <17 μmol/L.
[c] Range considered to be normal, 1–40 U/L.
[d] Range considered to be normal, 1–40 U/L.
[e] Level considered to be normal, <117 U/L.

the increases in the serum total bilirubin and/or aminotransferase levels and/or the alkaline phosphatase levels was measured, among patients with hepatic dysfunction, as the time from the day of entry into the study until the time that the last abnormal level was recorded.

RESULTS

Overall, 540 patients were enrolled in the study. For 264 patients (48.9%), a diagnosis of leptospirosis was confirmed by isolation of leptospires from blood samples (for 49 patients [18.6%]), by MAT (for 110 patients [41.7%]), by IFAT (for 78 patients [29.5%]), and by MCAT (for 27 patients [10.2%]). Use of the cross-adsorption test for serogroup identification of the leptospire isolates identified *Leptospira interrogans* serogroups Autumnalis (31 isolates), Pyrogenese (7 isolates), and Icterohaemorrhagia, Javanica, and Grippotyphosa (1 isolate each). Serogroup identification remains ongoing for 8 isolates, for which, meanwhile, the presumptive serogroups determined by MAT were mixed Copenhegeni and Australis (2 isolates) or Australis, Autumnalis, and Ballico (1 isolate each); the MAT result was negative for 3 isolates. For culture-negative patients, the presumptive serogroup of the isolates was determined by MAT for 110 patients; the serogroups were determined to be Australis (for 52 patients [47.3%]), mixed (for 28 [25.5%]), Louisiana (for 6 [5.5%]), Shermani and Bataviae (for 5 each [4.5% each]), Autumnalis and Cynopteri (for 3 each [2.7% each]), Hebdomadis, Icterohaemorrhagia, and Sejroe (for 2 each [1.8% each]), and Ballum and Pomona (for 1 each [1.0% each]).

The proportion of patients with coincident rickettsioses—mainly, scrub typhus—was similar in the 3 study groups. Two patients had leptospirosis and concomitant bacteremia due to gram-negative bacilli (one patient had both leptospiremia and *Salmonella* group D bacteremia, and the other patient had a 4-fold increase in agglutinin antibody to *L. interrogans* serogroup Grippotyphosa [to a titer of 1:400] and bacteremia due to *Klebsiella pneumoniae*). Overall, 27 patients (5%) died in the present study. Twenty patients were excluded from the subsequent efficacy analysis. Demographic characteristics, reasons for

Table 3. Demographic and clinical characteristics of and laboratory test findings for patients with laboratory-confirmed leptospirosis, according to study group.

Finding	Patients given penicillin G sodium (n = 87)	Patients given doxycycline (n = 81)	Patients given cefotaxime (n = 88)	P
Demographic characteristic				
No. of males/no. of females	77/10	73/8	74/14	.47
Age, median years (range)	35 (13–70)	33 (15–61)	35 (16–70)	.51
Clinical characteristic				
Duration of illness, median days (range)	3 (1–11)	3 (1–10)	3 (1–14)	.85
Previous antimicrobial therapy				.84
None	52 (59.8)	53 (65.4)	59 (67.0)	
Penicillin G sodium or ceftriaxone	18 (20.7)	14 (17.3)	22 (25)	
Doxycycline or chloramphenicol	5 (5.7)	3 (4)	3 (3.4)	
Penicillin G sodium or ceftriaxone				
Plus doxycycline	8 (9.2)	9 (11.1)	3 (3.4)	
Plus gentamicin	4 (4.6)	2 (2.4)	1 (1.1)	
Clinical manifestation				
Acute febrile illness	15 (17.3)	18 (22.2)	15 (17.0)	.47
Renal dysfunction	36 (41.4)	23 (28.4)	35 (39.8)	.17
Jaundice	28 (32.2)	20 (24.7)	31 (35.2)	.32
Hypotension	14 (16.1)	10 (12.3)	13 (14.8)	.78
Lung involvement	21 (24.1)	22 (27.2)	19 (22.0)	.91
Bleeding complication	16 (18.4)	14 (17.3)	10 (11.4)	.09
WBC count >12,000 cells/mm^3	23 (26.4)	30 (39)	31 (36.9)	.62
Thrombocytopenia	30 (34.5)	28 (37.3)	35 (43.8)	.66
Laboratory value				
Serum creatinine level, median μmol/L (range)	133 (62–1197)	124 (71–763)	142 (44–1020)	.39
Total bilirubin level, median μmol/L (range)	27.4 (1.7–890.5)	21.3 (3.4–743.8)	22.6 (2.9–642.6)	.76
Aspartate aminotransferase level, median U/L (range)	62 (13–554)	59 (10–560)	47 (17–627)	.57
Alanine aminotransferase level, median U/L (range)	42 (4–1184)	44 (6–567)	41 (6–478)	.70
Alkaline phosphatase level, median U/L (range)	119 (21–593)	115 (27–793)	135 (36–630)	.98

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

exclusion from the study, and distribution of diagnoses, as compared between the 3 study groups, are shown in table 1. Clinical presentations, results of laboratory investigations, and details regarding antimicrobial treatment administered before randomization of patients to treatment with the study drugs are shown in tables 2 and 3 for 520 patients who were included in the intent-to-treat analysis and for patients with laboratory-confirmed leptospirosis, respectively. Fifteen patients received concomitant treatment with gentamicin (8 patients in group P, 4 patients in group D, and 3 patients in group C; $P = .34$).

Outcomes of treatment for all randomized patients. Overall outcomes of treatment (i.e., death and clinical treatment failure, duration of fever, and duration of organ dysfunction after treatment) were similar among the 3 treatment groups. There were 10 patients enrolled in the study who had community-acquired bacteremia due to other bacteria (i.e., *Escherichia coli* [2 patients], *K. pneumoniae* [2 patients], *Salmonella* group D [2 patients], *Burkholderia pseudomallei* [2 patients], and streptococcal species [2 patients]). Four of these 10 patients died. Overall, for 69 patients, treatment was switched to other antimicrobial treatment (table 4). After initiation of the study drug, complications developed in 75 patients (31 patients [18%] in group P, 24 patients [14.4%] in group D, and 20 patients [11%] in group C; $P = .18$). Of these patients, 25% developed dysfunction in $\geq$2 vital organ systems. The major complications that developed were respiratory failure, including pulmonary hemorrhage (in 41 patients); hypotension or acute myocarditis (in 18 patients); hepatic dysfunction (in 9 patients); multiorgan dysfunction (defined as dysfunction of $\geq$3 vital organ systems; in 5 patients); and renal dysfunction (in 3 patients).

Outcomes of treatment for patients with confirmed leptospirosis. Of 256 patients with confirmed leptospirosis, 182 patients (71.1%) had fever for <5 days before admission to the hospital (65 patients [74.7%] in group P, 57 patients [70.4%] in group D, and 60 patients [68.2%] in group C; $P = .37$). However, 208 patients (81.3%) had evidence of dysfunction of

Table 4. Outcomes of treatment for 520 patients.

Patient group, outcome	Patients given penicillin G sodium	Patients given doxycycline	Patients given cefotaxime	*P*
All patients ($N = 520$)				
Death at ⩾48 h after treatment	5 (2.9)	4 (2.4)	7 (3.9)	.72
Time to defervescence, median h (range)	72 (8–512)	72 (12–264)	60 (8–200)	.42
Duration of hospitalization, median days (range)	6 (2–38)	6 (2–29)	5 (2–37)	.30
Reason for subsequent antimicrobial treatment				.08
Inadequate clinical response[a]	16 (9.3)	11 (6.6)	12 (6.6)	
Other diagnosis[b]	9 (5.2)	5 (3.0)	4 (2.2)	
Nosocomial infection	3 (1.7)	5 (3.0)	1 (.6)	
Adverse event	2 (1.2)	1 (.6)	…	
Patients with confirmed leptospirosis ($n = 256$)				
Death at ⩾48 h after treatment	2 (1.2)	2 (1.2)	…	
Time to defervescence, median h (range)				
For all patients	72 (12–240)	72 (12–264)	60 (8–192)	.56
For patients with no previous or concomitant antimicrobial treatment[c]	70 (16–240)	58 (12–216)	56 (12–192)	.43
Duration of hospitalization, median days (range)	6 (2–21)	5 (2–28)	5.5 (3–37)	.93
Reason for subsequent antimicrobial treatment	9 (10.3)	9 (11.1)	2 (2.3)	.19
Inadequate clinical response[a]	6 (7.0)	6 (7.4)	0	
Nosocomial infection	2 (2.2)	3 (3.7)	2 (2.3)	
Adverse event	1 (1.1)	…	…	

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

[a] Continued to have high fever or deterioration of vital signs after ⩾48 h of treatment with study drug.

[b] Diagnosis other than leptospirosis was obtained after entry into the study.

[c] $N = 164$.

⩾1 vital organ, and 54 patients (21.1%) developed multiorgan dysfunction at the time of admission to the hospital. A total of 164 patients did not receive any antimicrobial treatment before they entered the study (52 patients in group P, 53 patients in group D, and 59 patients in group C), and 1 patient in each study group received concomitant treatment with gentamicin. Four patients died. The causes of death were multiorgan failure (3 patients) and respiratory failure (1 patient). Details regarding treatment outcomes (for all patients and for patients with confirmed leptospirosis) are shown in table 4.

The median duration of fever after treatment was significantly associated with the extent of organ dysfunction at admission: 48 h (range, 12–128 h), for patients without any organ dysfunction; 60 h (range, 8–264 h), for patients with dysfunction of 1 vital organ system; 84 h (range, 12–264 h), for patients with dysfunction of 2 vital organ systems; and 96 h (range, 12–240 h), for patients with multiorgan dysfunction ($P < .001$). The median duration of fever after each treatment was similar in the 3 treatment groups. The Kaplan-Meier plot comparing the clearance of fever in the 3 treatment groups is shown in figure 1. There also was no statistical difference in the duration of renal and/or hepatic dysfunction among patients who were treated with either penicillin G, doxycycline, or cefotaxime. Subsequent switching of treatment to antimicrobial therapy occurred because of inadequate clinical responses in 11 patients (4 patients in group P, 6 patients in group D, and 1 patient in group C) and because of nosocomial infection in 6 patients (2 patients in group P, 3 patients in group D, and 1 patient in group C). In group P, 3 additional patients had treatment switched to other antimicrobial treatment because they were suspected of having coinfection with scrub typhus, and 1 patient had treatment switched to another treatment because of an adverse reaction (i.e., skin rash).

Multivariate analysis was used to predict the duration of fever after treatment, adjusted for onset (i.e., early onset [<5 days before treatment] or late onset [5–14 days before treatment]), severity of leptospirosis at admission (based on the number of vital organ systems with dysfunction), and antimicrobial treatment. Dysfunction of ⩾2 organ systems at admission was significantly associated with a longer duration of fever after treatment ($P < .001$). Antimicrobial therapy ($P = .56$) and onset of disease ($P = .83$) were not associated with the duration of fever after treatment in this model.

Outcomes of treatment for patients with rickettsioses. A total of 132 patients with rickettsioses with or without leptospirosis coinfection were enrolled in the present study (40 patients in group P, 47 patients in group D, and 45 patients in group C). The distributions of patients with combined lepto-

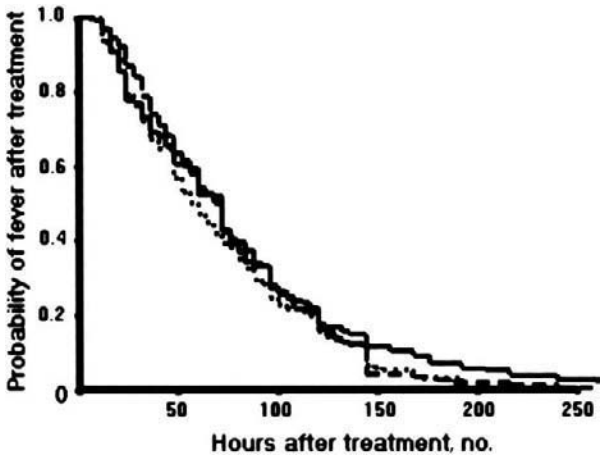

Figure 1. Kaplan-Meier plot of the duration of fever after treatment among patients with leptospirosis. *Solid line,* patients who received penicillin G sodium; *broken line,* patients who received doxycycline; *dotted line,* patients who received cefotaxime.

spirosis and any rickettsial infection (45.3% of group P, 39.1% of group D, and 34.1% of group C), scrub typhus (19% of group P, 32.6% of group D, and 38.6% of group C), murine typhus (14.3% of group P, 8.7% of group D, and 6.8% of group C), and spotted fever group rickettsiae (21.4% of group P, 19.6% of group D, and 20.5% of group C) were similar in the 3 treatment groups ($P = .56$).

In this subgroup analysis, penicillin was significantly less effective than doxycycline or cefotaxime for the treatment of patients with rickettsioses. The rates of treatment failure were 32.5%, 10.6%, and 11.1% for patients in group P, group D, and group C, respectively ($P = .01$).

DISCUSSION

There has been an epidemic of leptospirosis in Thailand since 1996 [3]. Although the clinical investigators in the present study were all very familiar with leptospirosis, which has become a major cause of admission to the hospital during the rainy season in the endemic areas of north and northeast Thailand, the present study clearly demonstrates the difficulty of making a correct clinical diagnosis of this infection, even when experienced clinicians are involved. Approximately one-half of the patients who had clinically suspected leptospirosis received laboratory confirmation of their diagnosis. Coinfection with leptospirosis and rickettsioses was also confirmed to be common in rural Thailand [24]. This is not surprising, because wet rice paddies provide a suitable habitat for these organisms and their hosts. Two documented cases of dual infection with leptospirosis and another bacterial septicemia were found in the present study. A definite diagnosis could not be determined for ~20% of the patients in the present study, despite extensive laboratory investigations.

Laboratory diagnosis of leptospirosis is still problematic. The sensitivity and specificity of serologic testing in areas of endemicity are uncertain. False-negative results of antibody tests, obtained using any currently available genus-specific test, are well recognized. Most patients in the present study arrived at the hospital while leptospirosis was in its early stage, because the patients were aware of the epidemic of leptospirosis in the region; this increased the opportunity for antimicrobial treatment to prevent progression to fatal disease, and it probably also contributed to a relatively low overall mortality rate [8, 12]. In very few places are results of diagnostic tests available on the day of admission to the hospital. Limitations associated with both the clinical and laboratory diagnosis of leptospirosis among patients admitted to the hospital with potentially life-threatening infection prompted us to conduct the present study to evaluate empirical antimicrobial therapies for patients with suspected leptospirosis. In addition to ceftriaxone, which recently has been shown to have efficacy against severe leptospirosis [13], cefotaxime and doxycycline were each as effective as penicillin G for the treatment of leptospirosis, as demonstrated by the results of the present study. The mortality rate, duration of fever, and progression of dysfunction of vital organs were similar among the 3 study groups, both for patients with suspected leptospirosis and for patients with confirmed leptospirosis. The 3 treatments were equally well tolerated. The main determinant of the duration of fever and illness in the present study was the severity of disease at presentation, not the antibiotic treatment or the stage of illness (early or late presentation).

Empirical treatment with doxycycline provided the additional benefit of efficacy in patients with rickettsioses who initially had suspected leptospirosis diagnosed. Penicillin G remains an effective treatment for leptospirosis, but its use as an initial empirical treatment for patients with suspected leptospirosis may not be appropriate for patients for whom a definite diagnosis cannot be made rapidly. In these circumstances, especially for patients for whom the result of serologic diagnostic testing for leptospirosis was negative at admission, antimicrobial therapy with either doxycycline or cefotaxime (or ceftriaxone) would be preferable. For severely ill patients for whom the diagnosis would be in doubt, use of doxycycline and cefotaxime combined would probably be best. More clinical studies to evaluate simple clinical and laboratory parameters for the differentiation of rickettsial infections from leptospirosis are urgently needed.

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