Ceftriaxone Compared with Sodium Penicillin G for Treatment of Severe Leptospirosis

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A prospective, open-label, randomized trial at Khon Kaen Hospital (Thailand) was conducted from July 2000 through December 2001 to compare the clinical efficacies of ceftriaxone and sodium penicillin G for the treatment of severe leptospirosis. A total of 173 patients with severe leptospirosis were randomly assigned to be treated with either intravenous ceftriaxone (1 g daily for 7 days; n = 87) or intravenous sodium penicillin G (1.5 million U every 6 h for 7 days; n = 86). The primary outcome was time to fever resolution. Survival analysis demonstrated that the median duration of fever was 3 days for both groups. Ten patients (5 in each group) died of leptospirosis infection. There were no statistically significant differences in the duration of organ dysfunction. Ceftriaxone and sodium penicillin G were equally effective for the treatment of severe leptospirosis. Once-daily administration and the extended spectrum of ceftriaxone against bacteria provide additional benefits over intravenous penicillin.

Leptospirosis has become a reemerging disease worldwide. The incidence is increasing, as is the proportion of patients who experience severe manifestations of leptospirosis or who die. Data concerning the efficacy of antimicrobial agents for the treatment of leptospirosis in humans are limited. A controlled trial of intravenous penicillin demonstrated a shortening of the duration of fever, impaired renal function, hospitalization, and leptospiruria in late-phase, advanced leptospirosis [1]; other controlled trials have failed to demonstrate a difference in the time to defervescence, recovery of organ dysfunction, or mortality [2]. Oral doxycycline has also demonstrated efficacy in shortening the duration of most symptoms and of leptospiruria in mild cases of leptospirosis [3, 4]. However, there was no definite proof of its efficacy. Until now, sodium penicillin G has been recommended as the standard antimicrobial agent for the treatment of moderate-to-severe leptospirosis [4, 5].

Ceftriaxone is a third-generation cephalosporin that has potential activity against leptospirosis [6]. The Department of Microbiology, Ramathibodi Hospital, Bangkok (Dr. Malai Worachit, personal communication), reported the in vitro susceptibility, determined using the tube dilution method [7], to ceftriaxone for L. interrogans serovar Bataviae and icterohaemorrhagiae at the MIC and minimal bactericidal concentration of <0.06 μg/mL in 10 serum samples (8 obtained from rodents and 2 obtained from humans). There were few reported cases of successful treatment with ceftriaxone for anicteric patients or patients with aseptic meningitis caused by the L. interrogans serovar Australis [8]. Its ability to be administered once daily for the
treatment of various infections, especially spirochetes [9, 10], and its reasonable cost make this antibiotic very popular. Early in the course of the disease, when the definite diagnosis of leptospirosis is pending, the prescription of an antibiotic that has activity against gram-negative bacteria is usually required because of the similarity of both conditions.

Panaphut and Susaengrat [6] conducted an open-label trial of a 7-day course of intravenous ceftriaxone administered to 16 consecutive adult patients with moderate-to-severe leptospirosis and demonstrated its efficacy: an average of 3.7 days passed before the resolution of fever, 5.3 days passed before recovery from renal failure (serum creatinine level, >180 μmol/L), and no mortality resulted from leptospirosis infection. However, no well-controlled study has demonstrated the efficacy of ceftriaxone in human leptospirosis. Therefore, we conducted this large-scale, randomized, controlled trial to compare the efficacy of ceftriaxone with that of sodium penicillin G for the treatment of severe leptospirosis in humans.

**PATIENTS AND METHODS**

**Study population.** We recruited patients from July 2000 through December 2001 at Khon Kaen Hospital, a tertiary care hospital in northeastern Thailand. To be eligible, patients (1) had to be aged ≥16 years; (2) had to have severe leptospirosis, defined by the presence of jaundice, a serum creatinine level of >180 μmol/L, or a mean arterial pressure of <70 mm Hg after receipt of appropriate fluid resuscitation; (3) had to have received no parenteral or oral antibiotics for <1 day; (4) had to have no history of allergy to penicillin or cephalosporin; (5) had to have experienced no cardiopulmonary resuscitation before admission; and (6) could not be stuporous or comatose.

Patients who had concurrent infection with other organisms at hospital admission were excluded from the study. Patients who presented with hemocoagulation (hematocrit, >45%) in the first 48 h after hospital admission or for whom atypical lymphocytes were noted on a peripheral blood smear were also excluded, to exclude dengue infection.

The diagnosis of leptospirosis was made on the basis of the World Health Organization criteria for leptospirosis diagnosis [11], and the diagnosis was serologically proven using the IgM-specific LEPTO dipstick assay (Organon Teknika; sensitivity of 60.1% and specificity of 94.1% for acute-phase serum samples) [12]. One hundred twenty-six (72.8%) of 173 patients had no evidence of other tropical infections, including melioidosis, malaria, and rickettsial infection, confirmed by microscopic agglutination test. Blood and urine cultures for detection of leptospirosis and demonstrated its efficacy: an average of 3.7 days passed before the resolution of fever, 5.3 days passed before recovery from renal failure (serum creatinine level, >180 μmol/L), and no mortality resulted from leptospirosis infection. However, no well-controlled study has demonstrated the efficacy of ceftriaxone in human leptospirosis. Therefore, we conducted this large-scale, randomized, controlled trial to compare the efficacy of ceftriaxone with that of sodium penicillin G for the treatment of severe leptospirosis in humans.

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**Randomization and study protocol.** After providing informed consent, patients were randomly allocated into 2 groups by stratified-block randomization. A random code was generated by computer via the block-of-4 technique, and each label was enclosed in a sealed, opaque envelope. The ceftriaxone group (group C) received 1 g of intravenous ceftriaxone (Cef-3; Siam Pharmaceutical) once per day. The penicillin G group (group P) received 1.5 million U of intravenous sodium penicillin G (M&H Manufacturing) every 6 h. Gentamicin was also administered for patients in group P for whom septicemia due to gram-negative pathogens could not be initially excluded. Gentamicin therapy was terminated as soon as the blood and urine cultures were negative for gram-negative bacteria (<3 days).

Supportive care, including intravenous fluid infusion, blood component transfusions, vasopressors, dialysis, respiratory support, and administration of other medications, was provided according to prospectively designed indications and regimens in both groups (Appendix) by the same groups of physicians and nurses. Patients were discharged from the hospital (1) if all 28 injections of penicillin or 7 injections of ceftriaxone had been completed, (2) if the oral temperature remained <37.6°C for at least 48 h, and (3) if the serum creatinine level was <180 μmol/L. Patients underwent a follow-up examination 1 week after discharge.

Patient characteristics, symptoms, and physical findings were recorded at hospital admission by use of standardized code sheets. Vital signs were measured every 1–4 h. In addition, urinalysis, chest radiography, and biochemical and hematological tests were performed at admission. All serum samples were obtained for performance of LEPTO dipstick assay, hemoculture, thick and thin blood films (for assessment of malaria), indirect immunofluorescent antibody test (IFA) for *Rickettsia tsutsugamushi*, and IFA for *Rickettsia typhi*. Serial measurements for complete blood cell count and determination of serum creatinine, aspartate aminotransferase, and total bilirubin levels were performed every other day until the patient was discharged from the hospital. Additional laboratory tests were performed as necessary for patient management. The severity of the disease in the first 24 h of hospitalization was assessed using the modified APACHE II scoring system [13], which was the same as the original APACHE II [14] except that information on the arterial oxygen pressure was not included, because such assessment was not performed routinely at hospital admission unless there was a particular indication.

An IgM-specific LEPTO dipstick test that used saprophytic genus-specific antigen (*Leptospira biflexa*) was chosen for serologic screening. Eligible patients were enrolled if the IgM-specific LEPTO dipstick test result was positive at a titer of ≥1:100. Serum samples obtained from every patient were also tested by microscopic agglutination test (MAT) [15], which was performed at the Regional Medical Sciences Center (Muang District, Khon Kaen Province, Thailand) against a panel of *Leptospira* serovars recommended by the World Health Organ-
ization [11]. Paired serum samples were also tested against rickettsial disease by IFA for *R. tsutsugamushi* and for *R. typhi*.

**Assessment of end points.** The primary end point was the time to the resolution of fever after commencement of treatment. Resolution of fever was defined as oral temperature of <37.6°C. The assessment for the resolution of fever was performed independently by 2 nurses who did not know the patients’ study group assignments. The agreement of the assessors was evaluated and calibrated. Secondary end points included hospital mortality and time to resolution of organ dysfunction. Organ dysfunctions were defined as a serum creatinine level of >180 μmol/L for renal failure, a serum aspartate aminotransferase level of >100 IU/L or a total bilirubin level of >100 μmol/L for hepatic dysfunction, and a platelet count of <100 × 10⁹ cells/L for thrombocytopenia.

This study protocol was approved by the ethics committee of Khon Kaen Hospital, Khon Kaen Province, Thailand.

**Sample size calculation.** A total of 87 patients for each group was planned for this 2-treatment, parallel-design study. This sample size would result in a probability of 90% to detect a treatment difference at a 2-sided 5% significance level if the true hazard ratio was 2. This was based on assumptions that were derived from a previous trial of penicillin for treatment of leptospirosis [1] and from the data from our previous study of leptospirosis in Khon Kaen Province [13]. The accrual period, the follow-up period, and the median duration of survival should be 540, 14, and 4 days, respectively.

**Baseline comparison.** Baseline characteristics of patients in the 2 groups were compared. Percentages were calculated for categorical variables, and median and interquartile ranges were calculated for nonnormally distributed continuous variables. We considered *P* < 0.05 to be statistically significant. All statistical tests were 2-sided. STATA (StataCorp) computer software was used for all analysis.

**Analysis of primary outcome.** The efficacy of treatment was analyzed on an intention-to-treat basis and a per-protocol basis. For the former analysis, all patients were analyzed on the basis of the groups on randomization—87 patients versus 86 patients in groups C and P, respectively. For the latter analysis, 4 patients who died within the first 24 h of hospitalization and 7 patients who withdrew consent were excluded. Therefore, we assessed only 80 and 82 patients in groups C and P, respectively. We applied 2 main analytical methods. First, we compared the time to fever resolution by use of survival methods. Here, the median duration of fever and the survival curves of the 2 groups were obtained by Kaplan-Meier methods. The absolute difference and its 95% CI were estimated. The log-rank test was used to test for the difference between such survival curves. The unadjusted hazard ratio and its 95% CI were then estimated by Cox regression analysis. This method was also used to obtain the hazard ratio adjusted for hypotension and thrombocytopenia, because the 2 parameters looked incomparable at baseline (table 1).

Second, we ignored censoring but still allowed for observation time by using the incidence density method. With use of this method, incidences for the resolution of fever for each group were calculated, and the absolute difference, the incidence rate ratio, and its 95% CIs were estimated. The χ² test was used to test for the difference of the rates between the 2 groups. For the secondary outcomes, we also applied the incidence density method, as mentioned above.

**RESULTS**

**Characteristics of patients.** Three hundred seventy-two patients with suspected severe leptospirosis were admitted to Khon Kaen Hospital during the study period. Of these, 172 patients were not eligible for the study: 94 had negative results of the LEPTO dipstick assay at admission, 63 had been treated with antibiotics for >1 day, 9 patients refused to participate, 3 patients were in a coma, and 3 patients had a history of penicillin allergy. Twenty-seven patients were excluded (12 in group C and 15 in group P) because other infections were present (13 patients had scrub typhus, 4 had murine typhus, 5 had a combination of leptospirosis and scrub typhus, and 5 had bacterial infection [1 infection due to *Staphylococcus aureus* and 4 infections due to gram-negative bacilli]). No patients developed hemoconcentration during the first 48 h of hospitalization or were excluded because dengue infection was present. Thus, a total of 173 patients (87 in group C and 86 in group P) with leptospirosis were enrolled in the study. After randomization, 7 patients (5 in group C and 2 in group P) withdrew consent after fever subsided and were discharged from the hospital before the study was completed. Four patients (2 in each group) died during first 24 h of hospitalization. Therefore, only 162 patients were assessed via per-protocol analyses. All results presented are based on the intention-to-treat analysis.

At enrollment, the groups were similar with regard to the distributions of age, sex, clinical features, and severity of illness (table 1). A total of 135 (78%) of the patients (39.9% in group C and 38.1% in group P) were treated with antibiotics that had activity against leptospirosis before study entry (table 1). Among the 173 patients who had positive results for leptospirosis via the LEPTO dipstick test, 126 patients (72.8%) were confirmed to be positive by MAT. Paired serum samples were available for only 119 patients (10 patients died, 7 withdrew, 34 did not return for follow-up to provide paired serum samples after being discharged from the hospital, and the blood samples of 3 were accidentally lost). Among this group of patients, only 9 had negative MAT results. For those who did not return for follow-up after being discharged from the hospital, data regarding their physical conditions after discharge were
Table 1. Baseline characteristics of patients in Thailand with severe leptospirosis who were treated with either ceftriaxone (group C) or sodium penicillin G (group P).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group C (n = 87)</th>
<th>Group P (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (IQR)</td>
<td>42 (31–53)</td>
<td>41 (31–52)</td>
</tr>
<tr>
<td>No. of male patients/no. of female patients</td>
<td>79/8</td>
<td>80/6</td>
</tr>
<tr>
<td>Duration of symptoms before hospital admission, median days (IQR)</td>
<td>4 (3–5)</td>
<td>4 (3–5)</td>
</tr>
<tr>
<td>No. of patients who received antibiotics before hospital admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>69</td>
<td>66</td>
</tr>
<tr>
<td>Penicillin (1–4 million U)</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>Ampicillin (1–2 g)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Ceftriaxone or cefotaxime (1 g)</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Doxycycline (100–200 mg)</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Penicillin and doxycycline</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>World Health Organization score, median (IQR)</td>
<td>24 (21–26)</td>
<td>23 (20–25)</td>
</tr>
<tr>
<td>Modified APACHE II score, median (IQR)</td>
<td>12 (9–16)</td>
<td>11 (8–15)</td>
</tr>
<tr>
<td>Symptom, no. (%) of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>72 (82.8)</td>
<td>68 (79.1)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>6 (6.9)</td>
<td>8 (9.3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75 (86.2)</td>
<td>66 (76.7)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>64 (73.6)</td>
<td>58 (67.4)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>38 (43.7)</td>
<td>41 (47.7)</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>34 (39.1)</td>
<td>33 (38.4)</td>
</tr>
<tr>
<td>WBC count, median cells × 10⁹/L (IQR)</td>
<td>12.3 (9.8–15.9)</td>
<td>12.6 (10.3–16.2)</td>
</tr>
<tr>
<td>Platelet count, median platelets × 10⁹/L (IQR)</td>
<td>37 (18–71)</td>
<td>42.5 (21–85)</td>
</tr>
<tr>
<td>Creatinine, median μmol/L (IQR)</td>
<td>371 (221–592)</td>
<td>380 (186–557)</td>
</tr>
<tr>
<td>Albumin, median g/L (IQR)</td>
<td>29 (25–32)</td>
<td>29 (24–32)</td>
</tr>
<tr>
<td>Aspartate aminotransferase, median IU/L (IQR)</td>
<td>69 (49–110)</td>
<td>74 (55–111)</td>
</tr>
<tr>
<td>Total bilirubin, median μmol/L (IQR)</td>
<td>77 (32–164)</td>
<td>60 (26–166)</td>
</tr>
</tbody>
</table>

NOTE. IQR, interquartile range.

obtained individually by direct contact of local health care personnel. All of the patients completely recovered from the illness.

Efficacy. The median duration of follow-up was 8 days for group C and 7 days for group P. The median duration of fever for each group was 3 days, and the absolute difference was 0 (95% CI, −0.2 to 0.2). Kaplan-Meier survival curves for the 2 groups were almost identical (P = .42; figure 1). Hazard ratios for the rate of fever abatement were 0.9 (95% CI, 0.7–1.2) for the unadjusted analysis and 0.9 (95% CI, 0.7–1.3) after adjustment for hypotension and thrombocytopenia, thus indicating comparable treatment outcome for patients in groups C and P. Similarly, the rate of difference of fever abatement per 100 patient-days (−3.0; 95% CI, −10 to 4.2), the unadjusted OR (1.2; 95% CI, 0.6–2.3), and the adjusted OR (1.0; 95% CI, 0.4–2.4) were comparable. The per-protocol analyses provided similar results (data not shown).

There was no statistical difference in the duration of organ dysfunction, including renal failure (relative risk [RR], 1.0; 95% CI, 0.7–1.4), elevated serum aspartate aminotransferase level (>100 IU/L; RR, 1.3; 95% CI, 0.7–2.2), jaundice (RR, 1.3; 95% CI, 0.7–2.4), and thrombocytopenia (RR, 0.9; 95% CI, 0.7–1.3). Kaplan-Meier survival curves of renal failure for the 2 groups are shown in figure 2. Ten patients (5 in each group) died, for an overall case mortality rate, 5.8%; all deaths occurred ≤5 days after hospital admission. The cause of death included pulmonary hemorrhage (5 patients), multiorgan failure (2 patients), severe hyperkalemia (1 patient), uremic encephalopathy (1 patient), and acute respiratory distress syndrome (1 patient). No patient in either group developed hypersensitivity reaction or any side effects directly related to the antibiotic therapy.

DISCUSSION

This study demonstrated that intravenous ceftriaxone was equivalent to intravenous sodium penicillin G for the treatment of severe leptospirosis. Both regimens could shorten the du-
ration of fever to 3 days. Their effects on other complications associated with leptospirosis, including renal failure, respiratory failure, liver impairment, and thrombocytopenia, were also comparable. These conclusions were made on the basis of our assumption that the absolute difference of <15% and the relative measure of effect of <2.5 were not clinically meaningful. In our study, the 95% CIs for all of the measured effects lay within this limit.

Although there were no differences in patient characteristics, initial presentations, and modified APACHE II scores between both groups, which indicates that randomization was successful in our study, it should be pointed out that our study was an unblinded trial. The colors of the 2 antibiotic preparations and the timing of antibiotic administrations were different. There was no sham infusion provided to patients in the ceftriaxone group because we wanted to avoid the mistake of providing
only placebo to severely infected patients and because of the tremendous workload during the epidemic period, which made the ethics committee reluctant to accept a double-blind, controlled protocol in severe cases of leptospirosis. In this study, however, the predetermined identical therapeutic schemes and the analyses made by the biostatistician, who did not know the patients’ therapeutic regimens, should minimize bias.

Concurrent infection with other organisms in our subjects was unlikely as a result of the initial screening for other infections, such as malaria or rickettsial infection. Although determination of dengue titer was not performed for our subjects, the possibility of dengue infection was very low as a result of the exclusion of patients with hemocoagulation or with the presence of atypical lymphocytes noted on peripheral blood smears. Moreover, the incidence of dengue infection for the adult population in Khon Kaen Province is very low (1.4 cases per 100,000 persons) [16], and the rate of hospital admission for adult dengue hemorrhagic fever at Khon Kaen Hospital was only 0.2 cases per 1000 admissions in 1999–2000 [17].

In our study, the majority of patients had been treated with some antibiotics that had activity against leptospirosis. However, this should have had little effect on the outcomes of our study, because we excluded patients who had received antibiotic therapy for >1 day. Moreover, both groups had comparable numbers of patients who had been treated with antibiotics before hospital admission.

There were no hypersensitivity reactions or side effects related directly to the antibiotic therapies in either group. Physicians and nurses accepted the prescription of a once-daily dose of intravenous ceftriaxone well. It greatly reduced the nurses’ workload during the time of the leptospirosis epidemic, when admissions due to other severe infections were overwhelming the hospital. From the physicians’ point of view, prescription of ceftriaxone has additional benefit in that it also provides coverage for sepsis due to gram-negative organisms, which is sometimes hard to differentiate from leptospirosis during the initial phase of infection. The total costs of 7-day courses of intravenous ceftriaxone and penicillin were US$26.40 and US$21.60, respectively. When the cost of the intravenous setup required for slow infusion of penicillin (US$4 per set) and the cost of the work required for every 6-h infusion were added to the cost of penicillin, the cost per day was comparable for both antibiotics. Therefore, prescription of ceftriaxone for severe cases of leptospirosis may be more cost-effective than penicillin.

Intravenous penicillin has been the standard treatment for severe leptospirosis [4]. A placebo-controlled trial of a 7-day course of intravenous penicillin for severe and late-phase leptospirosis was conducted by Watt et al. [1] in 1988 and demonstrated significant reductions in the durations of fever, elevated serum creatinine level, and hospitalization. Compared with the study by Watt et al. [1], our patients tended to experience more-severe infections. There was an overall case mortality rate of 5.8%, 10.4% of patients required dialysis, and 21.9% of patients experienced respiratory failure. In contrast, there was no mortality or need of dialysis in the study by Watt et al. [1]. The median modified APACHE II score was 12 in our study, indicating rather severe infection [13]. Delay in diagnosis or treatment was an unlikely cause of the high morbidity and mortality rates in our study, because the duration of fever before hospital admission was less than one-half of what was reported by Watt et al. [1]. The mortality rate in this study, however, was lower than the mortality rate reported in our previous study (14.1%) [13]. This might have resulted from the initial exclusion of patients with very severe cases of leptospirosis, including patients in a stupor or coma and patients who experienced cardiopulmonary resuscitation before enrollment in the study.

In conclusion, a 7-day course of 1 g of intravenous ceftriaxone per day is as effective against severe leptospirosis as intravenous penicillin. In addition, ceftriaxone therapy is easier for health care personnel to administer, is cost effective, and results in broader antimicrobial activity. Therefore, intravenous ceftriaxone should be an antibiotic of choice for the treatment of severe leptospirosis.

Acknowledgments

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APPENDIX

Definition of organ dysfunction.

1. Acute renal failure was defined by the presence of a serum creatinine level of >180 µmol/L.
2. Oliguria was defined by the presence of a first 24-h urine volume of <400 mL.
3. Pulmonary hemorrhage was defined as frank blood from endotracheal tube with ≥2 of the following characteristics: decrease in the hematocrit of ≥3% without another explainable source of bleeding, no clinical signs of volume overload (jugal venous pulsation of ≤5 cm above the sternal angle or central venous pressure of <12 cm), and a chest radiograph revealing unilateral or bilateral alveolar infiltration with normal cardiothoracic ratio.
4. Congestive heart failure was defined by the presence of ≥2 of the following characteristics: clinical signs of left-side...
ventricular dysfunction (jugular venous pulsation of >6 cm above the sternal angle, pulmonary rales, and hepatic pulsation or third heart sound [S3] galloping), central venous pressure of >15 cm (if indicated to perform), and a chest radiograph revealing diffuse alveolar pattern and increased cardiothoracic ratio.

5. Acute respiratory distress syndrome was defined by the presence of all of the following criteria: no clinical signs of congestive heart failure, as defined above; arterial gas exchange index of partial pressure of oxygen/fraction of inspired oxygen of <200; a chest radiograph revealing diffuse alveolar process with normal cardiothoracic ratio; and pulmonary capillary wedge pressure of <18 mm Hg (if possible).

6. Significant jaundice was defined as frank icteric sclera or a total serum bilirubin level of >100 μmol/L.

7. Cardiovascular collapse (hypotension) was defined as a mean arterial blood pressure of <70 mm Hg and the need for vasopressors to maintain blood pressure

**Indications for treatment.**

1. Dialysis was initiated when one of the following conditions was present: intractable hyperkalemia (potassium level, >6.5 mmol/L), intractable acidemia, clinically significant pulmonary edema, uremic encephalopathy, uremic pericarditis, and oliguria (urine output, <200 mL per 12 h) or a blood urea nitrogen level of >7072 μmol/L.

2. Ventilatory support (intubation and respirator) was initiated when one of the following conditions was present: respiratory rate of >30 breaths/min or arterial oxygen saturation of <90% when a patient was undergoing ventilation with a face mask and 8–10 L/min of 100% oxygen, deterioration of consciousness with respiratory rate of >30 breaths/min, and cyanosis.

3. Vasopressor (dopamine infusion) was initiated as needed to maintain vital signs when a patient experienced hypotension after fluid resuscitation

**References**


