

Clinical indicators for severe prognosis of scrub typhus

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Background: The study explored clinical risk characteristics that may be used to forecast scrub typhus severity under routine clinical practices.

Methods: Retrospective data were collected from patients registered at two university-affiliated tertiary care hospitals in the north of Thailand, from 2004 to 2010. Key information was retrieved from in-patient records, out patient cards, laboratory reports and registers. Patients were classified into three severity groups: nonsevere, severe (those with at least one organ involvement), and deceased. Prognostic characteristics for scrub typhus severity were analyzed by a multivariable ordinal continuation ratio regression.

Results: A total of 526 patients were classified into nonsevere (n = 357), severe (n = 100), and deceased (n = 69). The significant multivariable prognostic characteristics for scrub typhus severity were increased body temperature (odds ratio [OR] = 0.58, 95% confidence interval [CI] = 0.45–0.74, $P < 0.001$), increased pulse rate (OR = 1.03, 95% CI = 1.01–1.05, $P < 0.001$), presence of crepitation (OR = 3.25, 95% CI = 1.52–6.96, $P = 0.001$), increased percentage of lymphocytes (OR = 0.97, 95% CI = 0.95–0.98, $P = 0.001$), increased aspartate aminotransferase (every 10 IU/L) (OR = 1.04, 95% CI = 1.02–1.06, $P < 0.001$), increased serum albumin (OR = 0.47, 95% CI = 0.27–0.80, $P = 0.001$), increased serum creatinine (OR = 1.83, 95% CI = 1.50–2.24, $P < 0.001$), and increased levels of positive urine albumin (OR = 1.43, 95% CI = 1.17–1.75, $P < 0.001$).

Conclusion: Patients suspicious of scrub typhus with low body temperature, rapid pulse rate, presence of crepitation, low percentage of lymphocyte, low serum albumin, elevated aspartate aminotransferase, elevated serum creatinine, and positive urine albumin should be monitored closely for severity progression.

Keywords: severe scrub typhus, risk factors, rickettsial infection, complications

Introduction

Scrub typhus, an infectious disease caused by *Orientia tsutsugamushi* from chigger bites, is common in Asia-Pacific countries.¹ In Thailand, there were 7,310 cases in 2011 and 9,000 cases in 2012, most prevalent in the northern region.² An infected person may show only low grade fever, which disappears in a few days, or severe manifestations caused by complications of various organs in the second week. Pneumonia, acute respiratory distress syndrome, myocarditis, liver failure, acute renal failure, encephalitis, and shock from focal vasculitis and perivasculitis are some examples. Severe complications were reported in 2%–36% of cases and were associated with organ involvement, different serotype, and patient immunity. Severe complications may cause death, and mortality reports, which may be as high as 30% without proper treatment, varied from place to place.^{3–10}

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An indirect immunofluorescence antibody test is the standard diagnostic test, but other methods, such as the indirect immunoperoxidase test and the polymerase chain reaction test, were developed later and are also used. However, these tests are still considered expensive in countries with limited health care resources. They require well-equipped laboratory settings, trained personnel, and may take many days to many weeks to provide results.^{1,11,12} The cheaper Weil–Felix test is, therefore, still used in the general hospitals of some countries; however, it has low sensitivity and specificity.^{7,12} The rapid immunochromatographic test is therefore used to help in making prompt treatment decisions in those countries, including Thailand. To make the test more specific, some countries developed their own tests utilizing the prevalent serotypes.¹²

In routine clinical practice, the disease is diagnosed from clinical signs and symptoms, the history of contact, and the initial laboratory tests in order to start treatment. Patients respond rapidly with early diagnosis and treatment, but when the diagnosis and treatment are delayed, complications are common and death may follow.^{3–5,13–15}

Studies of risk factors for severe scrub typhus and/or death reported somewhat similar results: mainly they include abnormalities of laboratory findings such as leukocytosis, thrombocytopenia, hyperbilirubinemia, hypoalbuminemia, elevated transaminase, serum creatinine levels and abnormal chest X-ray. Nonlaboratory risk factors related to severity were headache, presence of eschar, and age more than 60 years.^{5,7,13}

The present study aims to explore clinical risk characteristics that may be used to forecast disease severity under routine clinical practice. The findings may be incorporated into clinical evaluation, awareness, and prevention of disease complications, which may reduce case fatality.

Material and methods

Patients

Patients were those diagnosed with scrub typhus, registered in two university-affiliated tertiary care hospitals in Chiang Rai and Chiang Mai, in the north of Thailand, from 2004 to 2010. The guidelines for diagnosis used by the two hospitals followed the modified World Health Organization recommended surveillance standards (Table 1).⁹ Patients were categorized into three groups by their severity: (1) nonsevere, those without any complications; (2) severe, those with at least one organ involvement (Table 2); and (3) deceased, those who died of scrub typhus or complications following scrub typhus in the present admission. Patients were not included in the study if their discharge status was not stated, or if they were enrolled in another parallel study (a clinical trial on steroid treatment).

Table 1 Operational definitions of scrub typhus based on the World Health Organization

| Patients with both | Accompanied by at least one | Also accompanied with at least one |
|--|--|--|
| Exposed to chiggers (stayed or went into risk areas within 2 weeks before the onset of symptoms) | Headache Myalgia Profuse sweating | Presence of eschar Positive immunochromatographic test for scrub typhus |
| Reported acute fever (within 2 weeks of onset of symptoms) | Cough Conjunctival injection Lymphadenopathy Maculopapular rash | |

Note: Copyright © 2013. World Health Organization (WHO) 2013. Reproduced with permission World Health Organization. WHO recommended surveillance standards. 2004: 123–124. Available from: <http://www.who.int/csr/resources/publications/surveillance/whocdscsr92.pdf>. Accessed on July 21, 2013.⁹

Data collection

Retrospective data were used, and key information was retrieved from in-patient medical files, out patient cards, laboratory reports and registers.

Table 2 Definitions of severe scrub typhus

| System involvement | Characteristics |
|------------------------|--|
| Cardiovascular system | Presence of any of the following: Systolic blood pressure <90 mmHg Abnormal cardiac arrhythmia with no previous history of the following: 1. atrial fibrillation; 2. supraventricular tachycardia; 3. frequent premature ventricular tachycardia. Myocarditis: elevated CK-MB above base line. |
| Respiratory system | Presence of acute respiratory distress syndrome, defined as follows: 1. PaO ₂ /FiO ₂ (mmHg) <200 in room air; 2. with bilateral interstitial infiltration on chest X-ray; 3. with normal cardio/thoracic ratio or no volume overload of CVP from central venous catheter. |
| Central nervous system | Presence of any of the following: 1. GCS ≤ 12 without other causes; 2. seizure without other causes; 3. meningoencephalitis. |
| Hematology | Platelet count ≤ 20,000/mL |
| Urinary tract | Presence of acute renal failure defined as any of the following: 1. Creatinine ≥ 2 mg/dL 2. Creatinine change > 0.5 mg/dL/day |
| Gastrointestinal tract | Presence of hepatitis, as defined by the following: 1. elevated aspartate aminotransferase; 2. or alanine aminotransferase more than five-fold above baseline. |

Note: Adapted from Chiang Rai Prachanukroh Hospital expert agreements on categorizing scrub typhus severity (with permission).

Abbreviations: CK-MB, myocardial muscle creatine kinase; CVP, central venous pressure; GCS, Glasgow Coma Scale; PaO₂/FiO₂, ratio of partial pressure arterial oxygen and fraction of inspired oxygen.

Study characteristics

All of the following study characteristics were examined within the first day of admission:

- Demographic data: sex, age, underlying disease (diabetes, hypertension, chronic obstructive pulmonary disease, and liver cirrhosis).
- Clinical manifestations: headache, myalgia, cough, nausea, vomiting, abdominal pain, diarrhea, conjunctival injection, jaundice, eschar, maculopapular rash, lymphadenopathy, hepatomegaly, splenomegaly, stiff neck, seizure, crepitation, wheezing, and dyspnea.
- Vital signs: body temperature ($^{\circ}\text{C}$), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (beats per minute), and respiration (breaths per minute).
- Laboratory findings: hematological tests, liver function tests, renal function tests, electrolyte profiles, urine albumin, and urine glucose.

Data analysis

The different characteristics across the three groups were tested by using nonparametric trend testing across ordered groups. The characteristics related to disease severity (presented with odds ratios [OR]) were explored and tested with multivariable ordinal continuation ratio logistic regression. Type 1 errors were set at ≤ 0.001 .

Ethics statement

The study was approved by Chiang Rai Prachanukroh Hospital Ethics Committee for Research, the Ethics Committee for Research, Nakornping Hospital, and the Ethical Committee on Research in Patients, Faculty of Medicine, Chiang Mai University. All traceable individual data were kept confidential throughout all processes of analysis.

Results

A total of 526 eligible cases of scrub typhus were classified into nonsevere ($n = 357$), severe ($n = 100$), and deceased ($n = 69$). They were similar in sex, underlying disease, myalgia, cough, nausea/vomiting, abdominal pain, conjunctival injection, eschar, maculopapular rash, hepatomegaly, splenomegaly, respiration rate, hematocrit, hemoglobin, globulin, potassium, and chloride (Tables 3 and 4).

Different characteristics across groups were age, headache, diarrhea, jaundice, lymphadenopathy, stiff neck, seizure, crepitation, wheezing, dyspnea, vital signs (body temperature, systolic blood pressure, diastolic blood pressure, pulse rate), hematological tests (white blood cell count,

platelet count, neutrophils, lymphocytes, monocytes), liver function tests (aspartate aminotransferase [AST], alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, albumin), renal function test (blood urea nitrogen, creatinine), electrolyte profiles (sodium, carbon dioxide), and urine examinations (urine albumin, urine glucose) (Tables 3 and 4).

Under the multivariable ordinal continuation ratio logistic regression, the characteristics related to disease severity were increased body temperature (OR = 0.58, 95% confidence interval [CI] = 0.45–0.74, $P < 0.001$), increased pulse rate (OR = 1.03, 95% CI = 1.01–1.05, $P < 0.001$), presence of crepitation (OR = 3.25, 95% CI = 1.52–6.96, $P = 0.001$), increased percentage of lymphocytes (OR = 0.97, 95% CI = 0.95–0.98, $P = 0.001$), increased AST (every 10 IU/L) (OR = 1.04, 95% CI = 1.02–1.06, $P < 0.001$), increased serum albumin (OR = 0.47, 95% CI = 0.27–0.80, $P = 0.001$), increased serum creatinine (OR = 1.83, 95% CI = 1.50–2.24, $P < 0.001$), and increased levels of positive urine albumin (OR = 1.43, 95% CI = 1.17–1.75, $P < 0.001$) (Table 5).

Discussion

The present study confirmed some clinical profiles related to scrub typhus severity.

Vital signs

The present study demonstrated that a decline of 1°C , and a more rapid pulse rate, increased the risk of severe scrub typhus. Hypothermia (body temperature below 36°C) and a pulse rate >90 beats per minute were consequences of systemic inflammatory response syndrome in patients with systemic infections, which led to septic shock in severe infection.¹⁶ Septic shock was reported as a common complication and risk of death in scrub typhus.^{3–5,17} In patients with septic shock, hypothermia was a significant risk factor for organ dysfunction and death, compared to those with fever.¹⁸

Physical examinations

The presence of crepitation was associated with scrub typhus severity in our study. Studies in the past all reported complications involving pulmonary systems, with 11%–54% of the cases resulting as a consequence of vasculitis and perivasculitis in the lungs.^{5,13,14,19–22} Chest X-rays showed interstitial infiltration, plural edema, pulmonary congestion, plural effusion, or cardiomegaly in 10%–64% of the cases.^{19–21,22} Patients may experience coughing or difficulty in breathing, and crepitation was reported in 23%–28% of

Table 3 Demographic characteristics and clinical manifestations of patients with scrub typhus (n = 526)

| Characteristics | Nonsevere (n = 357) | Severe (n = 100) | Deceased (n = 69) | P-value |
|--------------------------------|------------------------|---------------------|----------------------|---------|
| Demographics | | | | |
| Male | 201 (56.3) | 55 (55.0) | 35 (50.7) | 0.413 |
| Age (years) | 25.0 ± 20.6 | 32.6 ± 21.8 | 46.7 ± 20.2 | <0.001 |
| Underlying diseases | 30 (8.4) | 14 (14.0) | 8 (11.6) | 0.186 |
| Clinical manifestations | | | | |
| Headache | 117 (32.8) | 29 (29.0) | 14 (20.3) | 0.041 |
| Myalgia | 69 (19.3) | 23 (23.0) | 13 (18.8) | 0.820 |
| Cough | 120 (33.6) | 32 (32.0) | 17 (24.6) | 0.172 |
| Nausea, vomiting | 83 (23.3) | 27 (27.0) | 12 (19.4) | 0.544 |
| Abdominal pain | 118 (33.1) | 35 (35.0) | 25 (36.2) | 0.565 |
| Diarrhea | 60 (16.8) | 25 (25.0) | 17 (24.6) | 0.047 |
| Conjunctival injection | 330 (92.4) | 90 (90.0) | 64 (92.8) | 0.823 |
| Jaundice | 11 (3.1) | 21 (21.0) | 17 (24.6) | <0.001 |
| Eschar | 192 (53.8) | 60 (60.0) | 38 (55.1) | 0.557 |
| Maculopapular rash | 324 (90.8) | 95 (95.0) | 66 (95.7) | 0.086 |
| Lymphadenopathy | 237 (66.4) | 73 (73.0) | 63 (91.0) | <0.001 |
| Hepatomegaly | 113 (31.7) | 36 (36.0) | 14 (20.3) | 0.198 |
| Splenomegaly | 40 (11.2) | 9 (9.0) | 4 (5.8) | 0.157 |
| Stiff neck | 6 (1.7) | 4 (4.0) | 4 (5.8) | 0.032 |
| Seizure | 4 (1.1) | 10 (10.0) | 12 (17.4) | <0.001 |
| Crepitation | 13 (3.6) | 18 (18.0) | 25 (36.2) | <0.001 |
| Wheezing | 2 (0.6) | 6 (6.0) | 7 (10.1) | <0.001 |
| Dyspnea | 7 (1.9) | 7 (7.0) | 25 (36.2) | <0.001 |
| Vital signs | | | | |
| Body temperature (°C) | 38.5 ± 1.1 | 38.0 ± 1.2 | 37.5 ± 0.9 | <0.001 |
| SBP (mmHg) | 105.8 ± 14.1 | 95.9 ± 19.8 | 99.9 ± 23.9 | <0.001 |
| DBP (mmHg) | 65.7 ± 9.5 | 58.8 ± 13.6 | 60.2 ± 16.5 | <0.001 |
| Pulse (beats/min) | 103 ± 21.3 | 104 ± 22.5 | 109.2 ± 24.7 | 0.049 |
| Respiration (breaths/min) | 25.2 ± 8.8 | 27.4 ± 10.7 | 23.5 ± 3.9 | 0.058 |

Notes: Values are n (%) or mean ± SD; P-values are from nonparametric trend testing across ordered groups.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

pediatric patients^{15,23} and 30.7% of adults.⁴ More severe pulmonary involvement may present with acute respiratory distress syndrome and death.⁴

Percentage of lymphocytes

All previous studies mentioned elevated white blood cell counts in severe scrub typhus, but there were no reports addressing the percentage of lymphocytes.^{5,7,13,15} Some studies reported insignificant atypical lymphocytes in young scrub typhus patients.^{14,24} A study on the role of lymphocytes in scrub typhus reported early reduction of lymphocytes (mean ± standard deviation 24.49% ± 12.73%), which was explained as the shifting of peripheral lymphocytes into the infected tissues.²⁵ The present study also reported a significant effect of the percentage of lymphocyte reduction. It may be inferred that antibiotics might be indicated, even in the absence of lymphocytosis.

Serum creatinine

Serum creatinine indicated impaired kidney function. Renal failure manifested by elevated serum creatinine was commonly reported in scrub typhus and may be life threatening.^{3,7,17,22} A study from India also reported serum creatinine >1.4 mg % as a risk predictor of death in scrub typhus.⁷

Aspartate aminotransferase

Elevated AST reflects hepatocellular involvement in most infectious diseases. In scrub typhus, 80% of the patients experienced significantly elevated AST.^{3,7,17,26,27} A study from Thailand in young scrub typhus patients reported 96.3% of patients with high AST. In patients with hepatic dysfunction, AST levels were as high as 197.7 ± 126.6 IU/L.²⁶ The present study reported elevated AST (every 10 IU/L) as risk of severe scrub typhus.

Table 4 Laboratory findings in patients with scrub typhus (n = 526)

| Characteristics | Nonsevere (n = 357) | Severe (n = 100) | Deceased (n = 69) | P-value |
|--|------------------------|---------------------|----------------------|---------|
| Hematological | | | | |
| WBC ($\times 1000/\text{mm}^3$) | 8.9 \pm 4.9 | 11.4 \pm 5.4 | 12.7 \pm 6.0 | <0.001 |
| Platelet ($\times 1000/\text{mm}^3$) | 150.0 \pm 107.7 | 111.9 \pm 110.7 | 76.6 \pm 76.1 | <0.001 |
| Hematocrit (%) | 35.2 \pm 6.3 | 34.3 \pm 5.4 | 36.2 \pm 6.8 | 0.805 |
| Hemoglobin (gm%) | 11.9 \pm 2.1 | 11.5 \pm 1.8 | 12.1 \pm 2.3 | 0.999 |
| Neutrophil (%) | 66.4 \pm 16.3 | 77.3 \pm 15.0 | 79.5 \pm 17.4 | <0.001 |
| Lymphocyte (%) | 24.7 \pm 14.7 | 14.7 \pm 11.7 | 11.6 \pm 12.7 | <0.001 |
| Monocyte (%) | 6.6 \pm 7.4 | 5.0 \pm 8.4 | 5.3 \pm 8.2 | <0.001 |
| Liver function | | | | |
| ALT (IU/L) | 94.5 \pm 94.5 | 121.5 \pm 102.2 | 253.7 \pm 606.8 | 0.001 |
| AST (IU/L) | 134.4 \pm 103.3 | 207.6 \pm 164.6 | 804.0 \pm 2,289.3 | <0.001 |
| ALP (IU/L) | 217.6 \pm 154.5 | 333.1 \pm 273.5 | 266.9 \pm 155.5 | <0.001 |
| Total bilirubin (mg/dL) | 1.3 \pm 1.7 | 3.9 \pm 4.7 | 5.9 \pm 7.9 | <0.001 |
| Direct bilirubin (mg/dL) | 0.5 \pm 1.0 | 2.1 \pm 2.4 | 3.4 \pm 3.9 | <0.001 |
| Albumin (g/dL) | 3.2 \pm 0.6 | 2.7 \pm 0.5 | 2.6 \pm 0.5 | <0.001 |
| Globulin (g/dL) | 3.3 \pm 0.7 | 3.1 \pm 0.7 | 3.3 \pm 0.7 | 0.199 |
| Renal function | | | | |
| BUN (mg/dL) | 15.5 \pm 12.1 | 38.0 \pm 28.3 | 55.0 \pm 34.0 | <0.001 |
| Creatinine (mg/dL) | 1.1 \pm 0.8 | 2.1 \pm 1.8 | 3.5 \pm 3.1 | <0.001 |
| Electrolyte profile | | | | |
| Na (mmol/L) | 133.8 \pm 3.9 | 132.6 \pm 5.2 | 132.6 \pm 6.1 | 0.034 |
| K (mmol/L) | 3.5 \pm 0.5 | 3.6 \pm 0.6 | 3.8 \pm 0.9 | 0.060 |
| Cl ₂ (mmol/L) | 101.1 \pm 4.6 | 100.6 \pm 6.2 | 100.0 \pm 7.7 | 0.365 |
| CO ₂ (mmol/L) | 22.8 \pm 3.7 | 20.2 \pm 4.5 | 16.4 \pm 5.0 | <0.001 |
| Urine albumin | | | | |
| Negative | 132 (44.4) | 25 (29.4) | 7 (1.5) | <0.001 |
| Trace | 58 (19.5) | 15 (17.7) | 5 (8.2) | |
| 1+ | 49 (16.5) | 17 (20.0) | 10 (16.4) | |
| 2+ | 45 (15.2) | 24 (28.2) | 20 (32.8) | |
| 3+ | 13 (4.4) | 4 (4.7) | 16 (28.2) | |
| 4+ | 0 (0) | 0 (0) | 3 (4.9) | |
| Urine glucose | | | | |
| Negative | 276 (92.9) | 78 (91.7) | 48 (78.7) | 0.002 |
| Trace | 16 (5.4) | 6 (7.1) | 11 (18.0) | |
| 1+ | 1 (0.3) | 0 (0) | 1 (1.6) | |
| 2+ | 1 (0.3) | 1 (1.2) | 0 (0) | |
| 3+ | 3 (1.0) | 0 (0) | 0 (0) | |
| 4+ | 0 (0) | 0 (0) | 1 (1.6) | |

Notes: Values are n (%) or mean \pm SD. For urine albumin, trace is 5–20 mg/dL; 1+, 30 mg/dL; 2+, 100 mg/dL; 3+, 300 mg/dL; 4+, 2,000 mg/dL. For urine glucose, trace is 100 mg/dL; 1+, 250 mg/dL; 2+, 500 mg/dL; 3+, 1,000 mg/dL; 4+, 2,000 mg/dL.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urine nitrogen; Cl₂, chloride; CO₂, carbon dioxide; K, potassium; Na, sodium; SD, standard deviation; WBC, white blood cell.

Serum albumin

Patients with severe scrub typhus may have liver impairment causing a decline in albumin production. When associated with albumin leakages from blood vessels, as caused by vasculitis, patients may develop severe hypoalbuminemia.^{13,17,26} However, a previous study reported no differences in mortality among patients with different albumin levels.²⁸ In our study, a decline in serum albumin, as measured in g/dL,

increased the risk of more severe scrub typhus, even after excluding patients with liver cirrhosis (data not shown).

Urine albumin

The presence of albumin in urine indicated renal pathology. Renal vasculitis, which causes leakage of albumin into the urine, was reported in scrub typhus patients with renal complications. Acute renal failure may cause shock; a study

Table 5 Multivariable analysis of prognostic indicators for scrub typhus severity (n = 526)

| Indicators | Multivariable odds ratio (95% CI) | P-value |
|--------------------------|-----------------------------------|---------|
| Body temperature (°C) | 0.58 (0.45–0.74) | <0.001 |
| Pulse rate (beats/min) | 1.03 (1.01–1.05) | <0.001 |
| Crepitation | 3.25 (1.52–6.96) | 0.001 |
| Lymphocyte (%) | 0.97 (0.95–0.98) | 0.001 |
| AST (×10 IU/L) | 1.04 (1.02–1.06) | <0.001 |
| Serum albumin (g/dL) | 0.47 (0.27–0.80) | 0.001 |
| Serum creatinine (mg/dL) | 1.83 (1.50–2.24) | <0.001 |
| Urine albumin* | 1.43 (1.17–1.75) | <0.001 |

Note: *Represents urine albumin levels from negative to 4+.

Abbreviations: AST, aspartate aminotransferase; CI, confidence interval.

in Thailand reported septic shock in 88.9% of patients with positive urine albumin.¹⁷ In India, the corresponding figure was 28.6% in adults²⁹ and 3%–17% in children.^{15,23} In the present study, higher levels of urine albumin significantly increased scrub typhus severity, even after excluding patients with diabetes, hypertension, and liver cirrhosis, all conditions in which positive urine albumin may already be present (data not shown).

The most important limitation of this report was the fact that the diagnosis of scrub typhus was based on routine practice as recommended by the World Health Organization for medical resource limited developing countries, where the indirect immunofluorescence antibody test, or more standard (and more complex) methods, were not readily available. Scrub typhus in this study, therefore, was actually suspected scrub typhus according to the World Health Organization's definition; however, we, the authors, believe that this is the more realistic situation currently occurring in poor developing countries.

Conclusion

Patients suspicious of scrub typhus with low body temperature, rapid pulse rate, crepitation, low percentage of lymphocytes, low serum albumin, elevated AST, elevated serum creatinine, and positive urine albumin may be at risk for more severe scrub typhus. Clinicians encountering such patients should be aware of disease progression to more severe states, and might consider early investigation or monitoring for systemic involvement to reduce or avoid further complications and death.

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Disclosure

The authors report no conflicts of interest in this work.

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