

## CASE REPORT

### Scrub typhus infection in pregnancy: the dilemma of diagnosis and treatment in a resource-limited setting

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## Introduction

Scrub typhus caused by *Orientia tsutsugamushi*, an obligate intracellular gram-negative bacteria, transmitted by larval trombiculid mites (chiggers), is a zoonosis endemic in the rural areas of South-east Asia and remains a leading cause of acute undifferentiated fever (AUF) [1]. Contracted during pregnancy, it may lead to adverse maternal and newborn outcomes, including an unknown burden of maternal and newborn mortality [2].

Clinical diagnosis is poor, due to the similarity in presentation with other infections commonly seen in the tropics such as typhoid, leptospirosis, and dengue fever [3, 4]. In addition, a lack of sensitive and specific diagnostic tools available to rural clinics, where the disease is mostly seen, often results in under or misdiagnosis [5]. The presence of co-infection has also been reported in South-east Asia, which may contribute further to under diagnosis of scrub typhus [6].

#### Key Clinical Message

To save the life of both mother and fetus, the risks and benefits of the few antibiotics considered effective in the treatment of severe scrub typhus require consideration. In this case, chloramphenicol treatment averted maternal but not fetal mortality. Evidence-based guidelines appropriate for resource-limited endemic areas are required.

#### Keywords

Acute undifferentiated fever, maternal mortality, *Orientia tsutsugamushi*, scrub typhus, sepsis, stillbirth.

The clinical course is variable, ranging from spontaneous recovery without treatment to multiple organ failure with mortality ranging from 0 to 30% [7]. The *Orientia* bacteria, inoculated via chigger saliva during feeding, infect dendritic cells and macrophages in the dermis underlying the characteristic eschar that can develop. This leads to local lymphogenous and subsequent hematogenous dissemination, involving endothelial cells and macrophages, which release soluble cell-specific adhesion molecules and causes focal or disseminated vasculitis [5].

A review of scrub typhus in pregnancy reported on the total world literature: <100 cases with the pregnancy outcome reported in 18 years [2]. Prospective cohort data suggests [8, 9] the adverse consequences are significant and include: maternal death 2.4% (2/82), miscarriage 17.3% (14/81), and poor neonatal outcomes (including stillbirth, preterm labor, small for gestational age, or low birth weight) 41.8% (28/67) [2]. A recent systematic

review reported a median mortality of 6.0% (range 0–70%) in 19,644 untreated patients, but specifically recommended the requirement for more data to clarify mortality in vulnerable mother–child populations [10].

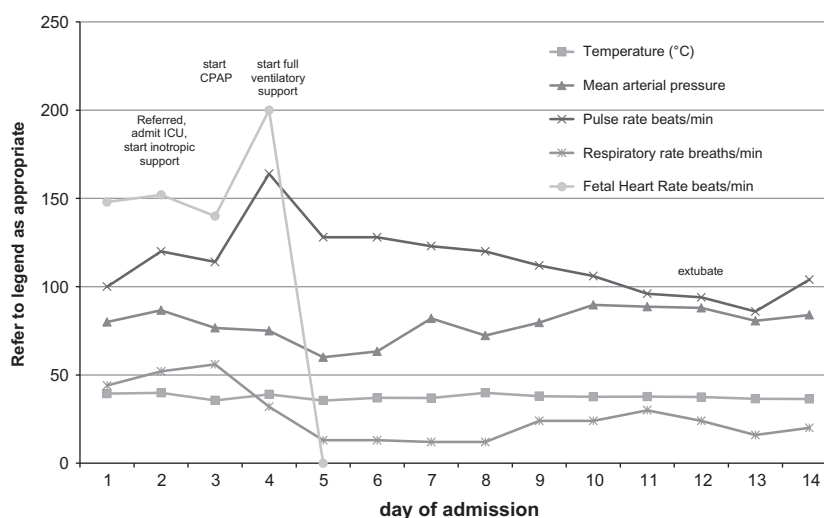
## Case Report

In December 2014, a 35-year-old woman, gravida 7, para 5, presented in the 31st gestational week to the clinic of Shoklo Malaria Research Unit (SMRU) in Maela refugee camp on the Thailand–Myanmar border. She complained of 6 days of fever, chills, rigors, headaches, nausea, cough, myalgia, joint pain, epigastric pain, and constipation for which she had self-medicated with intravenous vitamin injections but denied taking antibiotics. Fever, tachycardia, and tachypnea were noted on admission (Fig. 1) and no other abnormalities were detected on a systems physical examination, specifically no hepatomegaly, eschar, rash, jaundice, or lymphadenopathy, and fetal growth was appropriate for gestation week. Her first antenatal visit in the 23rd gestational week had confirmed a viable pregnancy and no significant medical or obstetric problems.

At the refugee camp, the patient was treated for AUF with 1 g of intravenous ceftriaxone and fluid replacement, but mistakenly azithromycin was omitted. Before commencing antibiotics, a venipuncture sample of blood was taken for the analysis in the Mae Sot laboratory 60 km away and the results became available the same evening (Table 1). Confidence in the scrub typhus results were low as 1 year of field experience with this test in pregnancy at SMRU suggested the possibility of over diagnosis: 13.6% (3/22) RDT-positive cases had a fourfold rise in IgM titer and none were PCR positive for scrub typhus

[2]. Initial clinical improvement was not maintained and at 24 h, persistent high-grade fever, worsening dyspnea and the onset of bilateral crepitations and peripheral edema were thought to be due to pulmonary edema. Intravenous fluids were stopped, IV furosemide 40 mg was given, and antibiotic therapy was modified to ceftriaxone 2 g every 12 h, with oral azithromycin 500 mg once daily and oral metronidazole 500 mg every 8 h, being added. Due to the limited facilities at the field site, the patient was transferred to a higher level of care.

In the Provincial Government Hospital in Mae Sot, Thailand, initial laboratory results were consistent with a severe mixed metabolic acidosis with respiratory alkalosis (Table 1). A provisional diagnosis of septic shock was given. Adjunctive therapy with dopamine, ceftriaxone at a higher dose (2 g every 12 h), and chloramphenicol (1 g every 8 h) were commenced to cover rickettsial infection. On day 3, continuous positive pressure ventilation was required, severe hypoglycemia (which remained persistent) and bleeding per vagina also occurred. In the early afternoon, the obstetrician prescribed hydrocortisone 100 mg 8 hourly for fetal lung maturation. On day 4, respiratory support was elevated to intubation and mechanical ventilation with a fraction of inspired oxygen FiO<sub>2</sub> up to 100%, and further inotropic support with norepinephrine initiated. Unfortunately, further vaginal bleeding, decreased platelet count and coagulopathy ensued, and the fetal heart rate deteriorated with fetal death in utero occurring on day 4. Infusion with packed red blood cells and two units of fresh frozen plasma were given before labor induction with misoprostol and amniotomy. A stillborn baby was delivered vaginally on day 5. No autopsy of the neonate or placental pathology was done.



**Figure 1.** Vital signs during admission.

**Table 1.** Patient laboratory results [normal range, NR] as they emerged.

	Abnormal results	Normal/Negative results
Admission Refugee Camp Day 1	<ul style="list-style-type: none"> <li>–Urine stick: pH 6, glucose negative, ketones 2+, white blood cells (WBC) 1+, nitrite negative, protein 1+, hemoglobin 4+</li> <li>–Urine sediment microscopy: WBC 5.0/HPF, red blood cells 8.0/HPF, bacteria 1+, epithelial cells 0.5/HPF and uric acid crystals 1+, no WBC or RBC casts.</li> <li>–Kidney ultrasound: dilation of the right renal pelvis, left kidney normal.</li> <li>–Platelet count 125 × 10<sup>9</sup>/L</li> <li>–C-reactive protein concentration &gt;200 mg/L</li> <li>–Creatinine kinase 199 [NR 26–140] units/L</li> <li>–SD Bioline Tsutsugamushi rapid detection test: positive</li> </ul>	<ul style="list-style-type: none"> <li>–Malaria smear, hematocrit (32%)</li> <li>–White blood cells count 5.1 × 10<sup>9</sup>/L</li> <li>–Differential count: neutrophils 4.3 × 10<sup>9</sup>/L (84%); lymphocytes 0.4 × 10<sup>9</sup>/L (8.0%); monocytes 0.4 × 10<sup>9</sup>/L (8.0%)</li> <li>–Hemoglobin 11.6 g/dL</li> <li>–Hematocrit 32.9%</li> </ul>
Admission Mae Sot Hospital (MSH) Day 2	<ul style="list-style-type: none"> <li>–Arterial blood gas: pH 7.420, PaCO<sub>2</sub> 19.0 mmHg, base excess -12.3</li> <li>–Potassium 3.3 [NR 3.3–5.1] mmol/L</li> <li>–Sodium 133 [NR 130–148] mmol/L</li> <li>–Platelets 74 [NR 140–450] × 10<sup>9</sup>/L</li> <li>–Scrub typhus IgM and IgG antibody: positive</li> </ul>	<ul style="list-style-type: none"> <li>–SaO<sub>2</sub> 99% on 3L O<sub>2</sub> (nasal cannula)</li> <li>–Serum aspartate transaminase 66 [NR 4–32] IU/L</li> <li>–Alanine aminotransferase 61 [2–25] IU/L</li> <li>–Alkaline phosphatase 184 [38–299] IU/L</li> <li>–Protein total 5.4 [5.6–6.7] g/dL</li> <li>–Albumin 2.7 g/dL [2.3–4.2] g/dL</li> <li>–Creatinine 0.8 [NR 0.4–0.9] mg/dL</li> <li>–Urea 8.54 [NR 3–11] mg/dL</li> <li>–Blood dextrose: 78 mg/dL</li> <li>–Urine culture: No significant growth</li> <li>–Blood culture: No significant growth</li> </ul>
MSH Day 3	<ul style="list-style-type: none"> <li>–Dextrose 34 mg/dL</li> </ul>	
MSH Day 4	<ul style="list-style-type: none"> <li>–Platelets 14 [NR 140–450] × 10<sup>9</sup>/L</li> <li>–INR 1.25 [NR 0.9–1.2]</li> </ul>	
5 weeks	<ul style="list-style-type: none"> <li>–Scrub typhus PCR: positive</li> </ul>	

After delivery, the patient improved and could be weaned from noradrenaline within 24 h. Repeated transfusions of packed red blood cells and platelets were required with the nadir of platelet count occurring on day 4. Ceftriaxone was continued for 10 days, chloramphenicol was switched after 5 days to doxycycline (100 mg every 12 h) and prescribed for 10 days. Due to bronchial spasticity, the patient was only extubated after 11 days of ventilatory support and therapy with dexamethasone and beta-2-mimetics. Three days after extubation, the patient was discharged back to SMRU.

Severe sacral ulceration (stage 4) required dressings and debridement over the next 2 weeks by which stage her eldest daughter had learnt how to do the dressings. She had made a full recovery. Five weeks after the patient had first presented the admission blood test for the PCR targeting gene that encodes the 47-kDa outer-membrane antigen highly specific for *O. tsutsugamushi* was reported as positive (the test is not routinely available).

## Discussion

Prolonged intensive care avoided a third trimester near miss maternal mortality but not fetal loss at 31+4 weeks gestation, after late presentation, misdiagnosis, and

inappropriate first-line antimicrobials. The hospital costs for this patient were equivalent to saving 10 lives by providing life-saving cesarean section for five women. This typifies previous case reports of mortality from scrub typhus in pregnancy [5, 8].

Rapid clinical improvement after antibiotic administration is characteristic with doxycycline, the drug of choice for AUF in nonpregnant patients from settings endemic for scrub typhus and would favor a diagnosis of *O. tsutsugamushi* infection [6]. For this case, rapid diagnostic tests (RDT) were employed for diagnosis and later confirmed by PCR. Although RDTs are simple to perform, they are expensive and not accurate enough to be relied upon [11]. For definitive diagnosis, serology using paired sera is used. Although a PCR-positive result is regarded as reliable, specimens must be obtained early in the course of the infection and such techniques are usually unavailable in resource-limited settings in a clinically useful timeframe [12]. Accurate, simple, and cost-effective diagnostics for scrub typhus are therefore required. While they are ideal and may one day become available in rural clinics for scrub typhus, they remain experimental and expensive, so that even the tertiary referral hospital relied upon acute scrub typhus serology to diagnose this case [13].

Guidelines for nonmalaria AUF in pregnant women in low and middle income countries are lacking. Streamlining the treatment of AUF with short-course doxycycline including in pregnancy is likely to be feasible in terms of cost and availability, although safety data is weak [5, 10, 14, 15]. Availability of intravenous azithromycin is limited by cost, although good outcomes with intravenous treatments have been reported in pregnancy in two series [16, 17]. Intravenous chloramphenicol, the antimicrobial most likely responsible for the acute recovery from infection, was correctly administered to save the mother's life notwithstanding concerns for gray baby syndrome [18]. The cause of death in the neonate could not be established, but maternal multiorgan failure and/or *O. tsutsugamushi* vasculitis-associated pathology of the placenta, possibly associated with thrombotic occlusions and/or coagulopathy cannot be excluded [19].

AUF in pregnant women is potentially life-threatening and sepsis protocols are required for scrub typhus endemic settings. Treatment protocols for AUF in areas where scrub typhus is endemic should include: oral azithromycin (or doxycycline if azithromycin is unavailable [15]) in uncomplicated AUF to prevent progress to severe disease; and preferably intravenous azithromycin (or chloramphenicol if azithromycin is unavailable) in severe disease. The aim of treatment in this case of scrub typhus was to save the mother and the fetus based on disease severity and gestation and the risks and benefits of the antibiotic. Evidence-based guidelines for AUF in pregnant women in settings where the burden of vector-borne disease is high are required. There is an urgent need for reliable field-based RDTs for scrub typhus.

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## Ethical Approval

Ethical approval to review SMRU hospital records was given by the Oxford Tropical Research Ethics Committee (OXTREC 28–09).

## Conflict of Interest

None declared.

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