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The Characteristics and Clinical Course of Patients with Scrub Typhus and Queensland Tick Typhus Infection Requiring Intensive Care Unit Admission: A 23-year Case Series from Queensland, Tropical Australia

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Abstract. Scrub typhus and Queensland tick typhus (QTT)—rickettsial infections endemic to tropical Australia—can cause life-threatening disease. This retrospective study examined the clinical course of all patients with laboratory-confirmed scrub typhus or QTT admitted to the intensive care unit (ICU) of a tertiary referral hospital in tropical Australia between 1997 and 2019. Of the 22 patients, 13 had scrub typhus and nine had QTT. The patients' median (interquartile range [IQR]) age was 50 (38–67) years; 14/22 (64%) had no comorbidity. Patients presented a median (IQR) of seven (5–10) days after symptom onset. Median (IQR) Acute Physiology and Chronic Health Evaluation II scores were 13 (9–17) for scrub typhus and 13 (10–15) for QTT cases (P = 0.61). Following hospital admission, the median (IQR) time to ICU admission was five (2–19) hours. The median (IQR, range) length of ICU stay was 4.4 (2.9–15.9, 0.8–33.8) days. Multi-organ support was required in 11/22 (50%), 5/22 (22%) required only vasopressor support, 2/22 (9%) required only invasive ventilation, and 4/22 (18%) were admitted for monitoring. Patients were ventilated using protective lung strategies, and fluid management was conservative. Standard vasopressors were used, indications for renal replacement therapy were conventional, and blood product usage was restrictive; 9/22 (41%) received corticosteroids. One patient with QTT died, and two (8%) additional patients with QTT developed purpura fulminans requiring digital amputation. Death or permanent disability occurred in 3/9 (33%) QTT and 0/13 scrub typhus cases (P = 0.055). Queensland tick typhus and scrub typhus can cause multi-organ failure requiring ICU care in otherwise well individuals. Queensland tick typhus appears to have a more severe clinical phenotype than previously believed.

INTRODUCTION

Rickettsial infections are found on every continent, except Antarctica.[1,2] In Australia, the most important rickettsial infections are caused by *Orientia tsutsugamushi* (which causes scrub typhus) and *Rickettsia australis* (which causes Queensland tick typhus [QTT]), and their incidence is increasing.[1,3] Rickettsial infections were responsible for 6% of undifferentiated febrile illness in one inpatient series from tropical Australia.[4]

Scrub typhus—a common and well-described pathogen in Southeast Asia—often causes a mild, self-limiting illness, but it can also lead to multi-organ failure if untreated.[5,6] There are fewer data describing the clinical course of QTT. It had been believed to cause only mild symptoms,[7] but recent reports suggest that it can also cause disabling and lethal disease.[3,8,9]

Scrub typhus and QTT are uncommon causes of critical illness in Australia. However, a high index of suspicion for the infections is important, as diagnosis requires specific testing,[1] and effective antibacterial therapy is often not included in empirical regimens for patients with sepsis.[10–12]

Although there are series from India,[13] South Korea,[14] Nepal,[15] and China[16] that have described the clinical course of rickettsial infection admitted to the ICU, none, to our knowledge, have been published from Australia.

MATERIALS AND METHODS

This retrospective study was performed at Cairns Hospital, a 531-bed tertiary referral center in Far North Queensland, tropical Australia. Patients were eligible for inclusion if they were admitted to the hospital's ICU between January 1997 and December 2019 with a laboratory-confirmed diagnosis of scrub typhus or QTT. Definite infection was defined as a positive blood PCR or a 4-fold increase in titers of paired serological samples. Probable infection was defined as a single serological titer ≥ 128 with a clinically compatible syndrome (≥ 2 of fever, rash, eschar, myalgia, or headache). Patients were excluded if, on chart review, a non-rickettsial diagnosis was determined to be more likely.

Patients' medical records were reviewed to collect demographic and epidemiological data, and details of their clinical presentation, comorbidities, and management. The patients' Acute Physiology and Chronic Health Evaluation II (APACHE-II) and Sequential Organ Failure Assessment (SOFA) scores were calculated.[17,18] Acute respiratory distress syndrome (ARDS) severity was graded using the Berlin definition.[19] Appropriate anti-rickettsial therapy was defined as at least 7 days of doxycycline, or 5 days of azithromycin.[11]

Statistical analysis. Data were de-identified, entered into an electronic database (Microsoft Excel 2016, Microsoft Corp., Redmond, WA), and analyzed with statistical software (Stata version 14.2, StataCorp, College Station, TX). Groups were compared with the Kruskal–Wallis test or Fisher's exact test, where appropriate. Correlation coefficients were determined using Spearman's method.

Ethics statement. The Far North Queensland Human Research Ethics Committee provided ethical approval for the study (HREC/17/QCH/66–1148 QA). As the data were retrospective and de-identified, the committee waived the requirement for informed consent.

RESULTS

Twenty-two patients were admitted to the ICU with a laboratory-confirmed diagnosis of rickettsial infection during

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TABLE 1
Selected demographic and epidemiological characteristics of the 22 patients at the time of presentation to hospital

Demographic	
Male gender	12 (55%)
Age (years)	51 (38–67, 22–77)
Interhospital transfer from a rural facility	14 (64%)
Rural residential address	16 (73%)
Duration of symptoms before presentation (days)	7 (5–10, 0–14)
Significant comorbidity*	8 (36%)

All values represent the absolute number (%) and the median (interquartile range, range).
* Significant comorbidity: chronic cardiovascular disease (receiving any ongoing treatment for a cardiovascular condition), chronic lung disease (receiving any ongoing treatment for a chronic lung condition), chronic renal disease (a serum creatinine ≥ 150 μmol/L documented before the presentation), immunosuppression (the use of immunosuppressive agents, including corticosteroids, chemotherapy, or immunomodulatory therapies), an active malignancy, or a diagnosis of diabetes mellitus.

TABLE 2
Symptoms and signs documented in the 22 patients at the time of presentation to hospital

Symptom	
Subjective fevers	22 (100%)
Myalgia	15 (68%)
Cough	11 (50%)
Fatigue/lethargy	10 (45%)
Rash	10 (45%)
Headache	10 (45%)
Nausea/vomiting	10 (45%)
Rigors	6 (27%)
Dyspnea	6 (27%)
Confusion	4 (18%)
Easy bleeding/bruising	14 (5%)
Clinical findings	
Tachypnea (respiratory rate > 22 breaths/minute)	19 (86%)
Hypoxia (oxygen saturations < 95% on room air)	18 (82%)
Tachycardia (heart rate > 100 beats/minute)	18 (82%)
Hypotension (mean arterial pressure < 65 mmHg)	16 (72%)
Temperature > 38.0°C	14 (63%)
Eschar	6 (27%)
Glasgow Coma Scale score < 15	4 (18%)
Abnormal bleeding	2 (9%)
Lymphadenopathy	2 (9%)
Hepatomegaly	2 (9%)
Splenomegaly	1 (5%)

the study period. This included 13 (64%, five definite, eight probable) patients with scrub typhus and 9 (36%, four definite, five probable) patients with QTT. Almost two-thirds (14/22; 64%) had no comorbidity. No patient received anti-rickettsial antibiotics before their hospital admission. The patients' other demographic and epidemiological characteristics are presented in Table 1.

Clinical presentation. The median (interquartile range [IQR]) duration of symptoms before hospital presentation was 7 (5–10) days. Rickettsial infection was considered in the initial differential diagnosis of 9/22 (41%). The most common alternatively considered diagnoses were pneumonia (9/22 40%) and leptospirosis (9/22 40%). The patients' symptoms and signs documented at the time of hospital presentation are detailed in Table 2.

ICU admission and management. Following hospital admission, the median (IQR) time to ICU admission was five (2–19) hours; only 4/22 (18%) were admitted > 24 hours after presentation. The median (IQR) length of ICU stay was 4.4 (2.9–15.9) days (Figure 1). The reason for ICU admission was multi-organ support in 11/22 (50%), vasopressor support in 5/22 (22%), mechanical ventilation in 2/22 (9%), and continuous monitoring in 4/22 (18%). The patients' median (IQR) APACHE-II score at ICU admission was 13 (9–16); their median (IQR) SOFA score on admission was eight (7–12).

Laboratory findings. The patients' laboratory findings at their hospital admission and during their hospitalization are presented in Table 3. There were 9/22 patients (40%) with simultaneously prolonged clotting times and low fibrinogen—consistent with disseminated intravascular coagulation,[20] five (56%) of whom had abnormal bleeding. Two of these patients developed purpura fulminans.[21]

Radiological findings. All patients had at least one chest X-ray (CXR) performed: 4/22 (18%) showed single lobe consolidation, 6/22 (27%) had multi-lobar consolidation, 5/22 (22%) demonstrated interstitial changes, and in 1/22 (4%), bilateral pleural effusions were also present. The CXR was normal in 7/22 (31%) (Figure 2).

Antibiotic therapy. All patients received appropriate anti-rickettsial antibiotic therapy; 15/22 (68%) received doxycycline, 6/22 (27%) received both doxycycline and azithromycin, and 1/22 (4%) received azithromycin alone. In 17/22 (72%), anti-rickettsial therapy was administered within the first 24 hours of their hospitalization; the median (range) delay was 1 (1–4) days in the remainder.

Respiratory support. A similar number of patients with scrub typhus and QTT required intubation (Table 4). A further 8/22 patients (36%) required high-flow oxygen; only 2/22 did not require supplemental oxygen. The median (IQR) PaO_2/FiO_2 ratio in the 20 patients in whom it could be calculated was

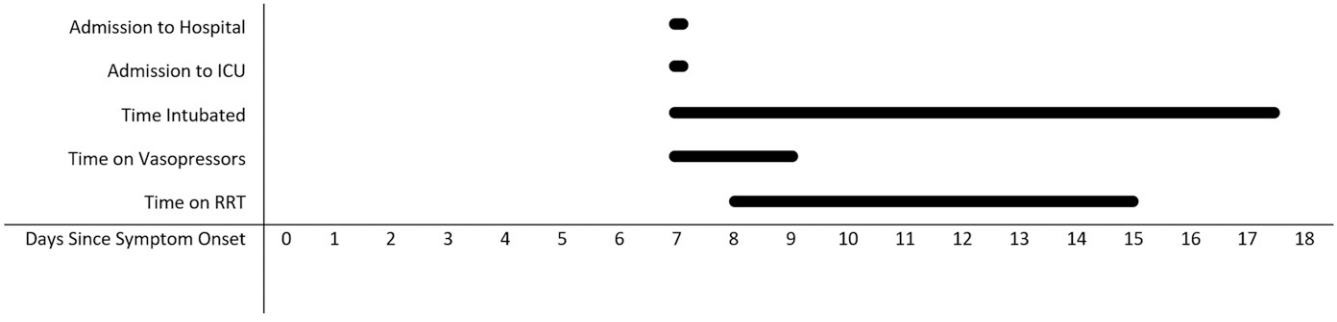

FIGURE 1. Median timing of initiation and duration of supportive therapies provided in the ICU.

TABLE 3
Laboratory findings at the time of hospital presentation of the 22 patients

		Value at hospital admission					Most deranged value (throughout hospitalization)				
Variable	Reference range*	Measured	Median	IQR	Range	Abnormal* (%)	Measured†	Median	IQR	Range	Abnormal* (%)
Hemoglobin (g/L)	135–180	22/22	134	122–145	91–180	14	22/22	88	74–108	66–139	82
White cell count ($\times 10^9$/L)	4.0–11.0	22/22	10.6	6.4–13.6	1.6–29.4	41	22/22	14	10.6–19.2	1.6–45.9	73
Neutrophils ($\times 10^9$/L)	2.00–8.00	21/22	8.4	4.6–11.8	1.1–26.5	52	22/22	11.4	8.2–16.9	1.1–39.9	77
Lymphocytes ($\times 10^9$/L)	1.00–4.00	21/22	0.63	0.36–1.1	0.15–4.1	62	22/22	0.54	0.36–0.95	0.05–11.2	77
Platelets ($\times 10^9$/L)	140–400	21/22	153	92–167	36–556	43	22/22	93	29–126	6–358	77
Sodium (mmol/L)	135–145	22/22	131	129–134	112–139	77	22/22	131	129–133	112–138	82
Potassium (mmol/L)	3.5–5.2	22/22	3.8	3.6–4.1	2.1–4.9	5	22/22	4.8	4.4–5.2	2.1–5.8	41
Urea (mmol/L)	2.1–7.1	22/22	8.0	5.1–16.9	3.8–31.1	50	22/22	14.1	7.4–20.0	4.8–34	64
Creatinine (μmol/L)	60–110	22/22	105	85–185	61–530	59	22/22	120	94–222	69–530	68
Albumin (g/L)	35–50	21/22	26	25–32	17–50	90	22/22	19	16–21	15–34	100
Total bilirubin (μmol/L)	< 20	21/22	25	16–41	9–77	57	22/22	28	17–72	12–131	68
Alkaline phosphatase (U/L)	30–110	21/22	147	91–237	54–587	52	22/22	230	155–508	60–1,350	82
Gamma glutamyl transpeptidase (U/L)	< 55	21/22	100	58–186	18–887	81	22/22	199	75–392	53–2,270	100
Alanine transaminase (U/L)	< 45	21/22	89	74–206	25–404	95	22/22	133	81–241	37–3,880	100
Aspartate transaminase (U/L)	< 35	21/22	143	99–309	24–864	95	22/22	183	131–356	60–18,100	100
Lactate dehydrogenase (U/L)	120–250	9/22	703	414–965	343–1,370	100	17/22	476	428–899	345–26,600	100
Creatinine kinase (U/L)	46–171	7/22	869	202–2,545	51–16,200	71	14/22	309	80–1,244	10–25,000	57
Prothrombin time (seconds)	9–13	12/22	13	12–16	11–23	42	22/22	16	13–20	11–100	73
Activated partial thromboplastin time (seconds)	24–39	12/22	36	32–40	24–70	33	22/22	40	36–61	28–150	68
Fibrinogen (g/L)	1.7–4.5	11/22	3.8	2.2–4.5	1.8–10	0	22/22	2.5	1.3–3.6	0.5–7.8	32
C-reactive protein (mg/L)	< 5.0	11/22	206	179–289	2–498	82	15/22	219	179–302	5–500	87

IQR = interquartile range. The most deranged values (range) during the patient's hospitalization are also presented.
* Outside of the reference range provided by the reporting laboratory (Queensland Pathology).
† Number of patients with this laboratory value measured on at least one occasion during their hospitalization.

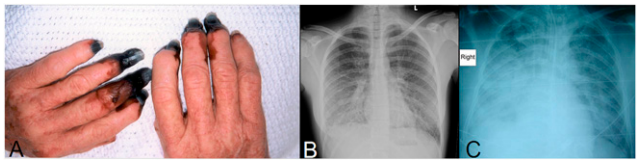

FIGURE 2. (**A**) Digital necrosis complicating histologically proven purpura fulminans in a 69-year-old woman without comorbidity. She had a 4-fold increase in serology for Queensland tick typhus (QTT) infection; her fingers later required digital amputation. (**B**) Chest X-ray demonstrating bilateral patchy non-confluent alveolar opacification in a 26-year-old woman without comorbidities who presented with a maculopapular rash, deranged liver function tests, thrombocytopenia, and a prolonged prothrombin time; she had a single serological titer of 1:1,024 for QTT. She required ICU admission for vasopressor support but required only supplemental oxygen by a Hudson mask and made a complete recovery. (**C**) Chest X-ray demonstrating right middle and lower lobe pneumonia and early left lower lobe consolidation in a 45-year-old male patient with a history of tick bite and a 4-fold increase in serology for QTT infection. He required intubation and ventilation for 16 days but made a complete recovery. These images have been published previously.[3] This figure appears in color at www.ajtmh.org.

140 (106–190). There were four (18%) patients with severe and six (27%) with moderate ARDS.

The median (IQR) duration of intubation was 10.3 (4.5–15.4) days. Intubated patients had more severe disease than those not requiring intubation (median [IQR] APACHE-II score: 15 [13–18] versus nine [8–12], $P = 0.0006$). Patients requiring intubation had a greater fluid balance over the first 72 hours of their ICU stay than those who did not (median [IQR] 3,823 [3,061–6,344] mL versus −24 [−89 to 852] mL, $P = 0.0002$).

Other supportive therapies. Vasopressor support was required in 15/22 (68%) for a median (IQR) duration of 2.1 (0.6–3.5) days. Noradrenaline (10/15; 67%) was the most frequently used vasopressor. Renal replacement therapy (RRT) was required in 5/22 (23%) and was initiated in all cases for oliguric or anuric renal failure with volume overload (Table 5). One patient requiring RRT died after 2.1 days; none of the remaining patients subsequently required long-term dialysis. Intravenous fluid therapy became more restrictive during the study period with the mean initial 72-hour fluid balance declining as the study proceeded (Spearman's rho = −0.62, $P = 0.003$) (Figure 3).

Red blood cell transfusion was delivered to 5/22 (23%) and fresh frozen plasma to 4/22 (18%). Despite the ubiquity of thrombocytopenia, no platelet transfusions were administered. Only 2/22 (9%) had a clinically significant hemorrhage—both upper gastrointestinal bleeds—but neither had thrombocytopenia or coagulopathy at the time.

Corticosteroids were prescribed in 9/22 (41%) for a median (IQR) duration of 4 (1–5) days. Nasogastric feeding, deep venous thrombosis, and stress ulcer prophylaxis were provided to all patients, unless there was a contraindication.

TABLE 4
Requirement of supportive therapies by type of rickettsial infection

Disease	Scrub typhus ($n = 13$)	Queensland tick typhus ($n = 9$)	P-value
Mechanical ventilation	8 (61%)	4 (44%)	0.67
Vasopressor support	9 (69%)	6 (67%)	1
Renal replacement therapy	2 (15%)	3 (33%)	0.61

Morbidity and mortality. The single death occurred in a previously well 55-year-old man with QTT, who presented with established multi-organ failure 7 days after symptom onset. Two patients with QTT and purpura fulminans required surgical amputation of necrotic digits (Figure 2). The remaining 19 patients (86%) recovered without permanent disability.

DISCUSSION

Australian patients admitted to the ICU with rickettsial infections have excellent outcomes in the country's well-resourced health system. The reported case fatality rate of ICU patients with scrub typhus in international studies varied from 10% to 24%,[13–16] but there were no deaths from scrub typhus in 22 years at this center and just one (1/9; 11%) from QTT. This is despite the cohort having APACHE-II and SOFA scores that would have predicted an overall case fatality rate of approximately 20%.[17,18]

In this small series, it is not possible to define which components of care were responsible for these encouraging outcomes; however, prompt anti-rickettsial antibiotic therapy and early access to sophisticated multimodal ICU support are likely to have contributed. Patients were ventilated using protective lung strategies, and fluid management was generally conservative. Standard vasopressors were used, indications for RRT were conventional, and blood product usage was restrictive. Over 40% of the patients had severe thrombocytopenia ($< 50 \times 10^9$/L) at some point during their hospitalization, but no platelet transfusions were administered, and no thrombocytopenic patient had major bleeding. Approximately 40% of the cohort received corticosteroids; however, this was usually delivered as only one of several concurrent interventions.

Pulmonary involvement heralded a more complicated course; despite this, 90% of patients with moderate to severe ARDS survived. Patients with a greater positive fluid balance were more likely to be intubated; it is therefore notable that fluid prescription became more restrictive over the course of the study, an approach which may have contributed to the good outcomes.[22]

Severe QTT has been thought to be rare.[7] However, in this series, nine patients with QTT required ICU support, including one who died and two who required digital amputation. The clinical findings of patients with QTT in this cohort are consistent with the pathophysiology described in a murine model of the disease.[23] Mice infected experimentally with *R. australis* developed a severe systemic vasculitis and multifocal hepatic necrosis and demonstrated extensive rickettsial invasion of the pulmonary alveolar septa, the renal glomeruli, and interstitium. Higher inoculums of *R. australis* were uniformly lethal.

Indeed, the pathophysiology of severe human QTT appears likely to be similar to that of scrub typhus and Rocky Mountain spotted fever, two rickettsial conditions whose pathological hallmark is also endothelial infection and inflammation.[24,25] This endothelial inflammation leads to microvascular dysfunction, increasing vascular permeability, which in turn increases the risk of shock and lung injury.[24,26] Endothelial activation may lead to widespread platelet adhesion and microvascular thrombosis, exacerbating the systemic microvascular dysfunction and increasing the likelihood of multi-organ failure.[27,28]

TABLE 5
Clinical and laboratory findings at the time of RRT commencement and subsequent duration of RRT

Age (years), gender	pH	Urea (mmol/L)	Potassium (mmol/L	Base excess (mmol/L)	Urine output	Clinically volume overloaded?	Total positive fluid balance (mL)	Duration of RRT (days)
53, Male	7.07	11.2	4	−16.7	Oliguric	Yes	20,483	3
44, Female	7.26	16.8	3.6	−12.3	Oliguric	Yes	16,995	3.9
69, Female	7.36	18.9	4.3	−3.4	Anuric	Yes	13,010	23
35, Male	7.35	33.1	3.9	−7.8	Oliguric	Yes	19,234	9.9
56, Male	7.34	19.8	4.9	−6.7	Anuric	No	4,937	2.1*

RRT = renal replacement therapy.
* Patient died at this point.

The patients in this cohort presented a median (IQR) of 7 (5–10) days after symptoms developed. Most had not sought medical advice before their presentation, and none had received anti-rickettsial antibiotic therapy, echoing findings from other studies that have shown that delayed antibiotic therapy increases the likelihood of severe rickettsial disease.[29]

It was notable that almost two-thirds of the patients in this ICU series had no comorbidity, highlighting the organisms' pathogenic potential. The absence of any pediatric cases—the youngest patient was 22 years—was also striking; this is despite local children presumably having a similar exposure risk.[30]

This retrospective study has limitations, with patients' symptoms and signs especially likely to be incompletely described. A minority had a PCR-confirmed diagnosis or a 4-fold increase in serology; although patients were only included if they satisfied prespecified criteria similar to those in the international literature. Patients with scrub typhus and QTT are presented together, and some may take issue with this approach. However, there are significant similarities in the infections' pathophysiology and management, and hence, we felt that it was reasonable to present them together.[3] The small sample precludes definitive conclusions about optimal management strategies; however, it provides hypothesis-generating data that might be tested in future prospective studies. The ability to deliver this care in the resource-limited settings—which bear the greatest global burden of rickettsial diseases—will be an essential consideration in this research.

In summary, rickettsial infections uncommonly require ICU admission in Australia but can cause critical illness in patients without comorbidity. Late presentation is likely to increase the risk of severe disease, but despite this, if patients can access prompt, multidisciplinary ICU support, their outcomes are usually excellent.

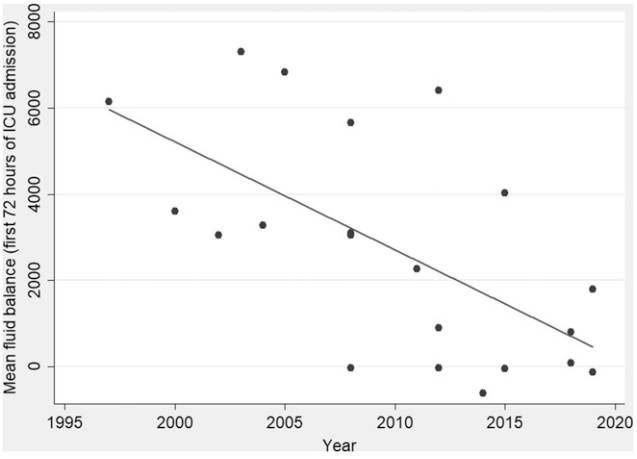

FIGURE 3. Mean fluid balance over the first 3 days of each patient's ICU admission over the course of the study.

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