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Scrub Typhus With Multi-Organ Dysfunction in an Adolescent: A Narrative Review

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ABSTRACT

Scrub typhus, caused by *Orientia tsutsugamushi* and transmitted by the larvae of trombiculid mites, is a common but frequently unrecognised cause of fever across the Asia-Pacific region, and in a minority of patients it progresses to dysfunction of several organs at once. Adolescents sit awkwardly between paediatric and adult series. This narrative review brings together published work on the organism, on the vascular and inflammatory biology of severe disease, on the organ systems most often involved, and on diagnosis and treatment. It reports no patient data. The evidence suggests that endothelial injury and a strong cytokine response, rather than uncontrolled bacterial growth alone, underlie multi-organ dysfunction, that lung, kidney, liver, brain and circulation are the systems most often affected, and that delay in considering the diagnosis is a recurring theme. Doxycycline is the standard agent, yet the trials that support it enrolled mild illness, and no randomised evidence addresses severe disease. Case definitions and organ-dysfunction scores are not standardised for this infection.

Keywords: Scrub typhus; *Orientia tsutsugamushi*; Multi-organ dysfunction; Adolescent; Endothelial injury; Doxycycline; Narrative review

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Article Class: Narrative Review

1. Introduction

Scrub typhus is an old disease that keeps being rediscovered. It is caused by *Orientia tsutsugamushi*, an obligate intracellular bacterium transmitted by the larval stage of trombiculid mites, or chiggers (1, 2). The infection is widespread across a large arc of Asia and the western Pacific and has been described in many other settings (2, 3), and yet it is

still missed often enough that it has been called a seriously neglected life-threatening disease (4).

Most patients have a fever, headache and malaise that respond promptly to the right antibiotic. A smaller group deteriorates in the second week with failure of the lungs, kidneys, liver, brain or circulation, often several together (5, 6). That multi-organ dysfunction is the subject of this review.



The title of the article concerns an adolescent, and adolescents are a group the literature handles poorly. They are too old for most paediatric series and too young to be counted reliably in adult ones. We therefore draw on both bodies of work and say plainly when a statement comes from adults. The review reports no data from any patient or institution and does not describe a particular case. The aim is a fair account of what is known and what is merely repeated.

2. Literature Review

2.1 The Organism and Its Vector

The organism was moved from *Rickettsia* into its own genus, *Orientia*, in the 1990s on genetic and antigenic grounds (1). Its genome is unusual, with extensive repeated elements and many genes thought to support interaction with host cells (7, 8), and strains differ in antigenic type and distribution (3).

Humans are accidental hosts. The mite larva feeds once on a vertebrate, usually a small rodent, and the organism is maintained in the mite itself (2). Exposure is brief and painless, so many patients cannot recall a bite.

2.2 How Severe Disease Arises

After inoculation the organism multiplies at the bite site, and a black, crusted eschar may form there. How reliably it appears is debated; series report it in widely varying shares of patients, and it can lie in skin folds, the scalp or the groin where it is easily overlooked (9, 10). The organism then spreads through lymph and blood. Tissue studies show infected cells in many organs, endothelial cells and macrophages prominent among them (11), and eschar biopsies suggest that dendritic cells and monocytes are early targets (12).

The endothelium is the likeliest place where infection becomes organ

dysfunction. Infected endothelial cells release chemokines (13), blood monocytes show an altered gene expression programme in patients (14), and circulating cytokine concentrations track with severity. In one cohort, high interleukin-8 was associated with severe disease and death (15). Broader reviews of infection and the endothelium describe how injury of this layer produces leak, micro-thrombosis and loss of vascular tone (16), which is the same final common pathway described for sepsis from other causes (17, 18). Figure 1 sets out the sequence in simplified form.

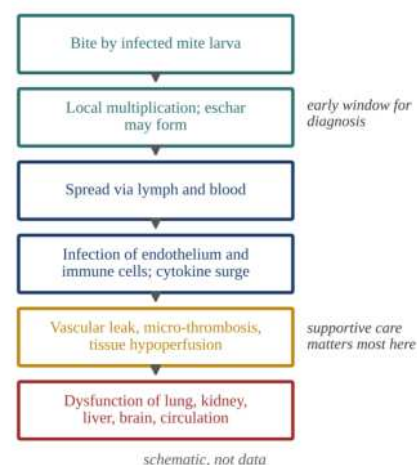


Figure 1. From mite bite to organ dysfunction: a commonly proposed sequence (schematic, not data).

There is a gap in this account: most mechanistic work comes from cell culture, animal models or small human studies, and the link from cytokines to a particular failing organ is inferred more than shown. The organism may act directly on some tissues, as argued for the kidney (19), and strain type may matter (20). Immune responses are reviewed elsewhere (21).

2.3 Organ Systems Involved

Table 1 summarises the systems most often described. Lung involvement ranges from interstitial change to respiratory failure; an interstitial pattern has been proposed as a marker of severity (22), and



the chest imaging findings have been reviewed (23). Acute kidney injury is well described, and one report linked tubular injury to direct invasion by the organism (19). Liver enzyme elevation is among the commonest findings, and jaundice appears in sicker patients (5, 6).

Table 1. Organ systems affected in severe scrub typhus and the mechanisms usually proposed.

System	Recognised problem	Proposed mechanism
Lung	Interstitial pneumonitis, respiratory failure (22)	Pulmonary vascular injury and leak (23)
Kidney	Acute kidney injury (19)	Tubular injury, perhaps direct, plus haemodynamic insult (19)
Liver	Raised transaminases, jaundice (5, 6)	Hepatic vascular and inflammatory involvement (16)
Brain	Meningitis, encephalopathy (24)	Perivascular inflammation, cerebral vasculopathy (5)
Circulatory	Hypotension, shock (5, 25)	Vasodilation and capillary leak (17, 18)
Blood	Low platelets, coagulopathy, rarely haemophagocytosis (6, 26)	Endothelial activation, cytokine excess (15)

Note: Qualitative summary of the cited literature. Frequencies differ widely between series and are deliberately not given.

Neurological involvement runs from headache to meningitis and encephalopathy (24). Circulatory failure is the least well characterised, partly because it overlaps so closely with septic shock from other causes. Haematological abnormalities include low platelets and, in some patients, a picture that fits haemophagocytic lymphohistiocytosis by published criteria (26). Each manifestation

has many competing causes in the tropics.

2.4 Diagnosis

The early illness looks like many others, and the tests are imperfect. Serology by indirect immunofluorescence is the usual reference, yet there is no consensus on cut-off titres, and a single acute-phase sample is often negative (27). The older Weil-Felix test lacks sensitivity (28). Molecular tests can confirm infection earlier (29), but are not available in many hospitals where patients are actually seen.

In practice the diagnosis rests on suspicion, exposure and an eschar if one is found, so the differential matters (Table 2). The condition shares features with leptospirosis, dengue, enteric fever, malaria and bacterial sepsis (2, 5).

Table 2. Conditions that can mimic severe scrub typhus in an endemic setting.

Condition	Overlap	Clue that may help
Rickettsioses	Fever, rash, organ involvement (2)	Exposure history; eschar pattern (9)
Leptospirosis	Fever, jaundice, renal injury (30)	Water or animal exposure
Dengue	Fever, low platelets, leak	Epidemic context; local testing
Enteric fever	Prolonged fever, hepatic upset	Culture; gradual onset
Malaria	Fever, organ failure	Parasite testing
Bacterial sepsis	Shock, multiple organ failure (31)	Cultures; focus of infection

Note: Clues are those emphasised in the cited reviews; none is reliable alone, and the eschar may be absent or hidden.

2.5 Treatment and Supportive Care

Doxycycline is the standard treatment and is rapidly effective in most patients (32).



The organism is susceptible to rifampicin in the laboratory (33), a trial in northern Thailand found doxycycline and rifampicin effective in mild disease (34), and a randomised comparison in adults found azithromycin comparable to doxycycline (30). Reports of infections slow to respond to antibiotics raised concern about reduced susceptibility, a question not fully resolved (35). None of these trials enrolled patients with organ failure, so for adolescents in that state recommendations rest on observational data and on extrapolation from sepsis research. That is no reason to doubt doxycycline, but it is a reason to be careful about claims of how well it works once organ dysfunction is established. Severe disease is otherwise managed on sepsis principles, with circulatory and respiratory support (25, 31, 36). Table 3 lists the options and caveats.

Table 3. Antimicrobial options for scrub typhus and the limits of the supporting evidence.

Agent	Role in the literature	Main caveat
Doxycycline	Standard first-line agent (32)	Trials enrolled mild disease (34)
Azithromycin	Comparable response in a trial in adults (30)	Little data in severe illness
Rifampicin	Studied for poorly responsive infections (34, 35)	Not a routine option
Chloramphenicol	Older alternative (32)	Toxicity; limited modern use
Supportive care	Fluids, ventilation, renal support (25, 36)	Borrowed from sepsis research

Note: Evidence statements are those of the cited reports; no dosing is given because this review offers no individual advice.

Supportive care follows the logic of sepsis management: fluid resuscitation, ventilatory support and renal replacement are used as in other critical illness (25), and paediatric critical care differs from adult practice in detail (36). None of these measures has been tested specifically in scrub typhus, so their use here is an extrapolation, a sensible one, but an extrapolation all the same.

3. Materials and Methods

3.1 Scope

This is a narrative review. It asks how scrub typhus causes multi-organ dysfunction, how that is recognised and managed, and how far the evidence supports what is commonly said. No patient is described. Scope is deliberately kept narrow, and no patient data are used.

3.2 Literature Assembly

We drew on peer-reviewed work on the microbiology and pathogenesis of *Orientia tsutsugamushi*, clinical series, diagnostic and treatment studies, and the paediatric and adult literature on sepsis. Only work up to 2014 was considered. We ran no formal systematic search, and the selection reflects the authors' judgement.

3.3 Appraisal Framework

To weigh a report we asked: were adolescents among the patients, how was scrub typhus defined, was organ dysfunction defined by a recognised standard (31, 37, 38), and did the design allow a statement about treatment or only a description of outcome? The organ-dysfunction scores in common use were derived in sepsis, not scrub typhus (39, 40).

4. Results

4.1 What the Evidence Describes

The literature on severe disease is dominated by hospital case series from



East and South Asia. Their weaknesses are selection, since the sickest patients reach tertiary hospitals, and heterogeneity, since each series uses its own definitions. Mortality appears to have fallen over time in one Indian centre (10), though the reason cannot be told from the data.

Paediatric and adolescent patients appear mainly as subgroups. Severe sepsis is a substantial cause of illness in children (41), but no organ-dysfunction score has been validated for scrub typhus, so inference from sepsis research is unavoidable. The picture is one of overlap, not of separate syndromes.

Geography matters too. Most of the evidence comes from countries where the disease is common and recognised, and much less has been written from regions where it is newly described, where the first clinical contact may involve clinicians who have never seen a case. Reports of this kind tend to describe the diagnostic puzzle more than the organ dysfunction.

4.2 Predictors of Severity

A Korean cohort identified clinical and laboratory findings at presentation that were associated with severe disease (6); the result is plausible but comes from one country. Cytokine markers may one day help (15), though none is used routinely.

	Reported	Mechanism suggested	Scoring unsettled
Lung	filled	filled	filled
Kidney	filled	filled	filled
Liver	filled		filled
Brain	filled		filled
Circulation	filled	filled	filled
Blood	filled		filled

filled = discussed in the literature (schematic, not data)

Figure 2. Qualitative matrix of organ systems and the complications reported for each (schematic, not data).

Figure 2 shows how unevenly the evidence is spread: lung, kidney and circulation have attracted mechanistic discussion, while liver, brain and blood are described more often than explained.

4.3 Diagnostic Delay

A recurring finding is that illness is recognised late. The causes are consistent: a non-specific early illness, a missing or hidden eschar, a negative early serology, and clinicians who do not think of the infection (4, 28). Figure 3 orders the questions a clinician might ask; it is a schematic, not a protocol.

5. Discussion

5.1 Interpretation

Read together, the literature describes an infection in which injury to the vascular lining and an exuberant inflammatory response, more than bacterial burden alone, drive organ failure (15, 16). That explains why unrelated organs fail together, and why measures developed in sepsis have a rationale here (17, 18).

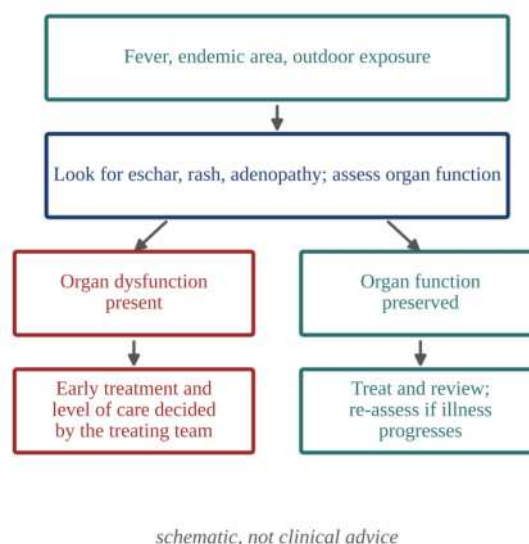


Figure 3. A stepwise way of thinking about a febrile adolescent in an endemic area (schematic, not clinical advice).

The adolescent sits between paediatric and adult practice, and cut-offs for organ



dysfunction differ by age (31, 39).

A shared mechanism does not guarantee a shared time course. Why one patient improves within a few days of treatment while another goes on to organ failure is not explained by the studies reviewed here; host factors and differences between strains have both been suggested, and neither question has been settled.

5.2 Limitations

The first limitation is the review itself: a narrative synthesis without a systematic search is open to selection bias, and a reader should treat its conclusions as a map, not a measurement. The second belongs to the evidence. Series are hospital based, definitions vary, serological cut-offs are contested (27), and most severe disease has been studied in adults. Mortality figures from different settings cannot be compared with confidence, so we quote none. Third, the mechanism is largely inferred from work in cells and animals (14, 21).

5.3 Future Work

Three needs stand out: shared case definitions and a validated organ-dysfunction approach for young people; treatment trials in moderate and severe disease; and diagnostic tests that work where patients first present, so that treatment need not wait for serology (28, 29).

Registries that record adolescents as a group of their own would help more than another small case series, and so would agreement on which organ-dysfunction criteria to report. Studies that follow patients after discharge are scarcer still; what becomes of kidney, lung and neurological function in the months after severe illness is hardly described, and a review of acute care alone cannot say.

6. Conclusion

Scrub typhus can cause multi-organ dysfunction through injury to the vascular lining and a strong inflammatory response. Recognition is often late. Doxycycline remains the standard treatment, but its evidence comes from milder disease, and what is known about severe illness in adolescents is largely inferred from adults and sepsis research.

The practical message is to keep the diagnosis in mind in any febrile adolescent from an endemic area, whether or not an eschar is found.

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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

E.V. conceived the review and wrote the sections on pathogenesis and organ involvement. E.W. wrote the sections on diagnosis and treatment. J.B. wrote the sections on paediatric and adolescent aspects. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No patients were studied and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.



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