National Guideline on

Diagnosis, Management and Prevention of Scrub typhus in Nepal

2079 (2022)

Government of Nepal
Ministry of Health and Population
Department of Health Services
Epidemiology and Disease Control Division

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Foreword

I am pleased to note that the **National Guideline on Diagnosis, Management and Prevention of Scrub typhus in Nepal** has been developed through rigorous consultations among all related stakeholders. I believe this document serves as a guiding document for federal, provincial and local level to accelerate the efforts towards the control and prevention of Scrub typhus in Nepal.

The right to basic health services is enshrined in Constitution in Nepal and has been encompassed by the National Health Policy 2076. Moreover, Nepal is committed towards the Sustainable Development Goals (SDG) 3 of 'Ensuring Health lives and promoting wellbeing for all at all ages. The rise in scrub typhus cases in recent years along with a risk of mortality has informed the Ministry of Health and Population to develop a response towards the disease.

The development of this guideline is based on the learnings from previous interim guideline on prevention and control of scrub typhus issued by Epidemiology and Disease Control Division following the 2015 mega earthquake, experts' opinions & experience, and the collation of global and national evidence. This guideline will provide a current and robust guidance for scrub typhus prevention, diagnosis, management and control in Nepal to medical doctors, other healthcare workers and public health officers involved in the clinical management and prevention of scrub typhus in the country.

I acknowledge the efforts of all those who have contributed to develop this first ever guideline. I strongly believe that the joint efforts of federal, provincial and local levels as well as key stakeholders will adhere towards the guideline in prevention, diagnosis, management and control of scrub typhus in Nepal.

Dr Roshan Pokhrel

Secretary

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FOREWORD

It gives me an immense pleasure to present the first ever **National Guideline on Diagnosis, Management and Prevention of Scrub typhus in Nepal** with the technical support provided by World Health Organization Nepal Office.

Scrub typhus is a life-threatening infectious disease which presents as an acute undifferentiated febrile illness transmitted by the bite of chigger's mite. Globally, one million cases of scrub typhus occur each year with an estimate case fatality of 10% rate unless treated early and appropriately. The World Health Organization (WHO) has highlighted that Scrub typhus is probably one of the most underdiagnosed and underreported febrile illnesses requiring hospitalization in the South East Region.

This guideline intends to orient medical doctors, other health care workers and public health officers on epidemiology, clinical presentation, diagnostic approach, and evidence based clinical management and prevention and control of scrub typhus in Nepal. I sincerely hope this guideline will help local and provincial level in prevention and control of Scrub typhus and different level of hospitals in diagnosis and management of scrub typhus case in Nepal. Thus, I kindly request all health professional to adhere on this guideline in control of scrub typhus in Nepal.

Lastly, I would like to express my gratitude to Epidemiology and Disease Control Division, WHO country office Nepal, clinical specialist and all others who contributed to this guideline.

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FOREWORD

Scrub typhus is a vector-borne acute febrile illness caused by the bite of infected mites. The number of reported cases of scrub typhus are ever rising in Nepal with incidence higher among rural population especially farming communities. Various studies conducted within Nepal have reported prevalence of scrub typhus ranging from 1.6% to 52.4%.

In 2015, Nepal experienced a mega earthquake leading in massive destruction and economic losses. During the same period, there was increase in the number of febrile illnesses in Nepal with mortality as high as 8% which was later confirmed as Scrub typhus outbreak in Nepal. An interim guideline on prevention and control of scrub typhus was issued by Epidemiology and Disease Control Division following the earthquake, which was updated in 2016. However, the continuous rise in reported cases of scrub typhus in Nepal demanded a guideline for diagnosis, management, and prevention of scrub typhus in Nepal.

It is my pleasure to express that the first ever **"National guideline on diagnosis, management and prevention of Scrub typhus in Nepal"** has been developed. The guideline is intended to ensure the diagnosis and timely management of Scrub typhus cases, along with the surveillance of scrub typhus cases in Nepal. I sincerely hope this guideline will assist health workers to diagnosis, management of cases and helps in prevention and control of scrub typhus cases within Nepal.

Lastly, I would like to thank VBD/NTDs section for taking the lead on preparing this guideline and WHO country office, Nepal for their overall support in developing the guideline. I would like to thank all the experts, health professionals who actively contributed to developing and finalizing the guideline.

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ACKNOWLEDGEMENT

Scrub typhus is a vector borne disease that can sometimes be life threatening if not diagnosed and treated on time. Following the mega earthquake in Nepal in 2015, Nepal saw a large outbreak of scrub typhus. Scrub typhus cases are being reported each year in Nepal with outbreak reported in many areas. Epidemiology and Disease Control Division, DoHS had released an interim guidance on prevention and control of scrub typhus in 2015. There was a need to develop an updated national Guideline for scrub typhus prevention, diagnosis, management and control in Nepal.

The Director General, Department of Health Services, Ministry of Health and Population, Nepal expresses immense pleasure in developing and finalizing this national Guideline that will provide a current and robust guidance for scrub typhus prevention, diagnosis, management and control in Nepal. EDCD, DoHS would like to express sincere gratitude to the World Health Organization, Country Office for Nepal for the technical support provided to develop this national Guideline, specially to Professor Dr Shital Adhikari, WHO Consultant who prepared the first draft of this Guideline. DoHS is also thankful to all the reviewers and contributors who contributed to bring this guideline to this shape.

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CONTENTS

ACRONYMS

AKI	Acute Kidney Injury
ARDS	Acute Respiratory Distress Syndrome
AUFI	Acute Undifferentiated Febrile Illness
BiPAP	Bi-level Positive Airway Pressure
CPAP	Continuous Positive Airway Pressure
CNS	Central Nervous System
CRP	C-reactive Protein
CSF	Cerebrospinal Fluid
DEET	N, N-diethyl-meta-toluamide
EDCD	Epidemiology and Disease Control Division
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-linked Immunosorbent Assay
EWARS	Early Warning and Reporting System
FIG.	Figure
GCS	Glasgow Coma Scale
HDU	High Dependency Unit
HMIS	Health Management Information System
ICU	Intensive Care Unit
IFA	Immunofluorescence Assay
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMV	Invasive Mechanical Ventilation
IPA	Immunoperoxidase Assay
PCR	Polymerase Chain Reaction
PHCC	Primary Health Care Center
RDT	Rapid Diagnostic Test
SOFA	Sequential Organ Failure Assessment
WHO	World Health Organization

CHAPTER - 1

INTRODUCTION

Scrub typhus is a vector-borne disease caused by a bacteria *Orientia tsutsugamushi* and transmitted to humans through the bites of infected larval mites (chiggers). The causative organism, *Orientia tsutsugamushi* is an obligate intracellular gram-negative bacterium of the genus *Orientia*, order Rickettsiales within the Rickettsiaceae family. The recently identified *Orientia chuto* species in United Arab Emirates is another human pathogen causing scrub typhus.

It is mainly a zoonotic disease where human beings are accidentally involved in a chain of transmission between larval trombiculid mites (chiggers) and animals, most commonly rodents. The association of a febrile illness with mite transmission was recognized in 1810 in the Niigata Prefecture in Japan leading to the definition of tsutsugamushi (tsutsuga meaning illness and mushi means insect/creature) fever.

The World Health Organization (WHO) statement of 1999 on scrub typhus remains valid even today. "Scrub typhus is probably one of the most underdiagnosed and underreported febrile illnesses requiring hospitalization in the region (South-East Asia and areas bordering Central Asian Republics). The absence of definitive signs and symptoms combined with a general dependence upon serological tests make the differentiation of scrub typhus from other common febrile diseases such as murine typhus, typhoid fever and leptospirosis quite difficult. It is an emerging and re-emerging disease in the South-East Asia and South-Western Pacific region".

Clinical manifestations of scrub typhus range from mild to severe illness. It generally starts with flu-like (fever, headache, myalgia etc.) symptoms and sometimes severe infection can lead to pneumonia, acute respiratory failure, shock, meningoencephalitis and disseminated intravascular coagulation.

Scrub typhus is an important cause of febrile illness with multisystem involvement and probably the world's most important rickettsial disease based on its disease burden. Epidemiological data on scrub typhus are limited, though there is steady rise in scientific literature.

1.1 NATIONAL GUIDELINE

Although the surveillance system for scrub typhus is not well established in Nepal, increasing number of scrub typhus cases are reported each year. The guidance on prevention of scrub typhus and proper diagnosis and cases management is very

critical towards preventing morbidity and mortality associated with this disease. Epidemiology and Disease Control Division (EDCD) had published an interim guidance on prevention and control of scrub typhus in 2015, however, there is a need to provide an updated guidance on prevention, diagnosis and management of scrub typhus in Nepal.

This national Guideline aims to provide a current and robust guidance for scrub typhus prevention, diagnosis and management in Nepal. The intended target audience of this Guideline are medical doctors, other healthcare workers and public health officers involved in the clinical management and prevention of scrub typhus in Nepal.

Objectives of the Guideline

The objective of this Guideline is to orient medical doctors, other healthcare workers and public health officers about

- Epidemiology of scrub typhus
- Clinical presentation of scrub typhus
- Diagnostic approach to scrub typhus
- Evidence-based clinical management of scrub typhus
- Prevention and control of scrub typhus

1.2 EPIDEMIOLOGY

Scrub typhus is a mite-borne infectious disease caused by bacteria *Orientia tsutsugamushi*. The previous endemic region of scrub typhus was named "Tsutsugamushi Triangle" a geographical region of South East Asia and the Southwest Pacific (Figure 1.1). It is distributed throughout the Asia Pacific rim, being endemic in Korea, China, Taiwan, Japan, Pakistan, India, Thailand, Malaysia, Nepal and northern parts of Australia (Figure 1.2). It has also been reported from regions of Africa, Europe and South America suggesting global distribution in tropical and sub-tropical regions (Figure 1.3).

The habitat of chiggers are areas where scrub vegetation- consisting of low-lying trees and bushes are encountered such as banks of rivers, rice fields, poorly maintained kitchen gardens, grassy lawns. Once considered rural disease, scrub typhus has been reported in urban population too. The chiggers are not visible by the naked eyes and usually feed on rodents and accidentally on humans and transmit the infection during the prolonged feeding which can last 1-3 days.

Incidence of scrub typhus is higher among rural population especially farming communities. Scrub vegetation near the house, cooking outside the home, uncemented house floor, piling weeds in the house, living or recreational activities in the vicinity of the water body, all increase the risk of scrub typhus which expose them to risk of biting by chiggers. The disease is seasonal in many parts of India

and Nepal. Risk factors for acquiring scrub typhus among children in India were recent exposure to the outdoor environment, either while defecating or playing in agricultural fields, as well as visiting agricultural fields, storing firewood indoors, and handling fodder for cattle. Of these risk factors, defecation in the agricultural field was the most common exposure at the population level.

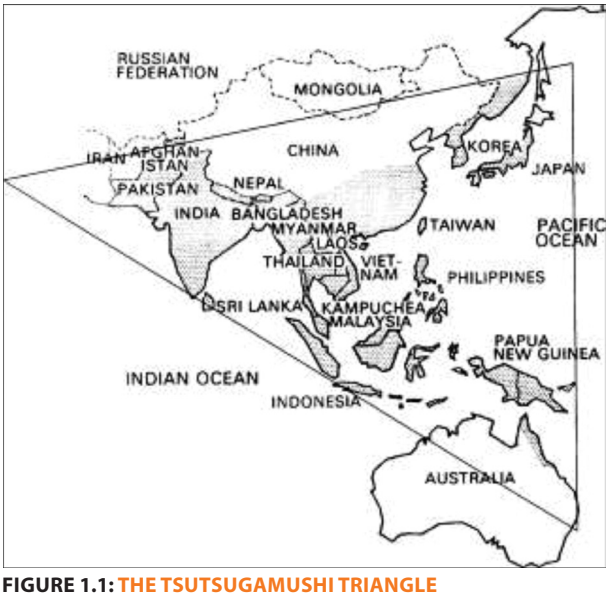


FIGURE 1.1: THE TSUTSUGAMUSHI TRIANGLE

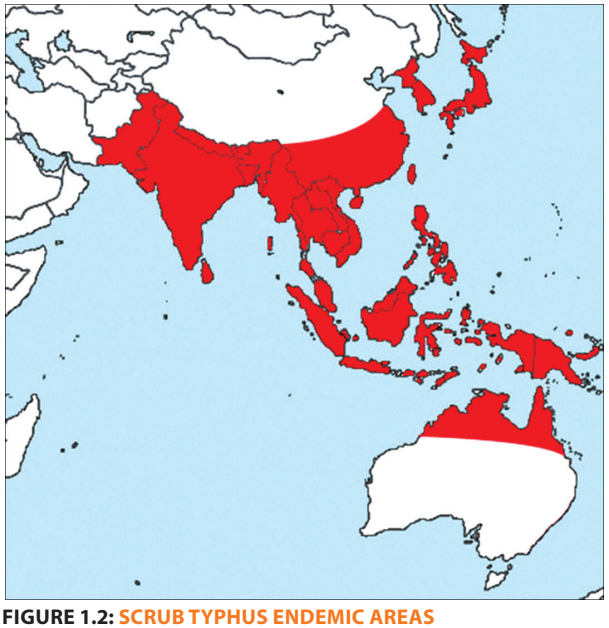


FIGURE 1.2: SCRUB TYPHUS ENDEMIC AREAS

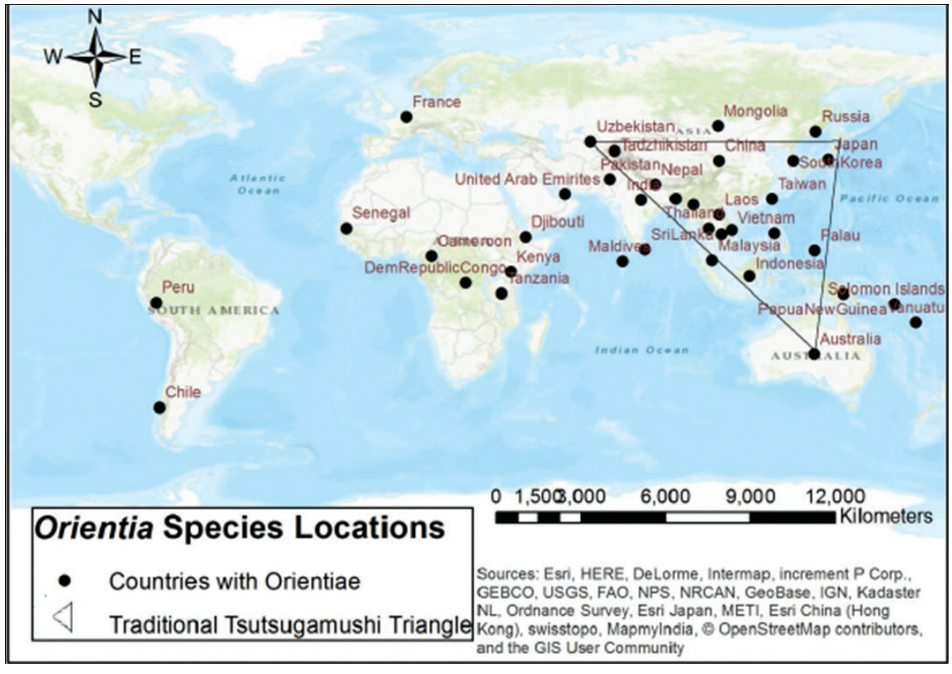


FIGURE 1.3: DISTRIBUTION OF ORIENTIA SPECIES BOTH WITHIN AND BEYOND THE ENDEMIC TSUTSUGAMUSHI TRIANGLE.

1.3 BURDEN OF DISEASE

Global and regional

Scrub typhus is a neglected tropical disease with approximately 1 million cases occurring per year worldwide with nearly one billion people at risk.

Seroprevalence studies from many Asian countries showed that the incidence per 100,000 population is the highest in Sri Lanka (26.3) followed by Bangladesh (23.7), Malaysia (17.9), South Korea (17.7), Taiwan (14.3) and Thailand (11.8). Cell culture/animal inoculation was done to detect pathogen in South Korea, Thailand and Taiwan but ELISA IgM/IgG was used in other countries for seroprevalence. Data from national surveillance from patients in China, Japan, Korea and Taiwan suggested that farmers and age group 60-69 years were most vulnerable, but in Thailand people of age group 45-54 years were the most commonly affected.

Scrub typhus is re-emerging disease in India and there are reports of outbreak from several states.

Nepal

Antibodies to scrub typhus were found in 19 people when 188 samples (100 healthy males recruited in British Army and 88 healthy male blood donors) from eastern

Nepal were analyzed in 1981. Analysis of blood samples from patient presenting with fever in Patan Hospital, Kathmandu valley, in 2004, found that 3.2% were positive for scrub typhus by serology. Enteric fever was the clinical diagnosis in half of them and many of them were farmers. After the devastating earthquake in 2015, outbreak of scrub typhus has been reported from across the country causing several morbidities and mortalities. Although the surveillance system for scrub typhus is not well established, 831, 670, 1098 and 1167 number of cases were reported from 2016-2019 through the early warning and reporting system (EWARS).

1.4 CAUSATIVE ORGANISM

Orientia spp. are obligate intracellular gram-negative coccobacillary bacteria. The typical constituents of gram-negative cell walls—peptidoglycan and lipopolysaccharide are absent. *O. tsutsugamushi* strains are antigenically diverse and divided into several serotypes, including Boryon, Gilliam, Karp, Kato and Kawazaki. A major outer surface protein, the 56-kDa type-specific antigen (TSA), containing four hypervariable regions, is mainly responsible for the organism's antigenic heterogeneity. Another species recently identified in UAE is *O. chuto*.

1.5 TRANSMISSION

Scrub typhus is transmitted to humans and rodents (Figure 1.4) by some species of trombiculid mites ("chiggers", *Leptotrombidium deliense* and others). There is no human to human transmission of scrub typhus. *Orientia tsutsugamushi* has been found in the salivary glands of these mites which act as a primary reservoir. Humans acquire the disease from the bite of an infected larval stage of the mite (Figure 1.5). The bite of the mite may leave a characteristic black eschar that is useful to make clinical diagnosis of scrub typhus.

FIGURE 1.4: CHIGGER MITES ON THE INNER'S EAR LOBE OF WILD-CAUGHT RAT (FAQ WHO, 2015)

FIGURE 1.5: CHIGGER MITE (FAQ WHO, 2015)

Biology and life cycle of the vector

Trombiculid mites, the vector of scrub typhus has a four-stage life cycle: egg, larva, nymph and adult (Figure 1.6). Adult trombiculid mites are about 1–2 mm in length, bright red or reddish-brown in color, and of velvety appearance. The nymph is similar to adult mite but smaller. The larvae, also called chiggers, are very small, being only 0.15–0.3 mm in length and can only be seen through a microscope or magnifying glass. Neither the adults nor the nymphs bite animals or humans; they live in the soil and feed on other mites, small insects and their eggs. The larvae, however, feed on skin tissue. The larva (chigger) is the only stage that can transmit the disease to humans and other vertebrates. After emerging from the eggs, the larvae crawl onto grasses or low-lying vegetation and leaf litter to wait for an animal or human host. They attach themselves to the skin of reptiles, birds, mammals and humans walking or resting in the habitat. On humans they seek out areas where clothing is tight against the skin, the waist and ankles being the parts most commonly attacked. The larvae remain attached to the skin of the host for between two days and a month, depending on the species. They then drop to the ground and enter the soil to develop into the harmless nymphal and adult stages.

Mites are both the vector and reservoir. Chigger mites, the primary reservoirs for *O. tsutsugamushi,* get infection in nature by feeding on the body fluid of small mammals, including the rodents. They maintain the infection throughout their life stages and, as adults, pass the infection on to their eggs (transovarial transmission which can be 100%). Similarly, the infection passes from the egg to the larva or adult, the process known as transstadial transmission. Thus, chigger mite populations can autonomously maintain their infectivity over long periods of time.

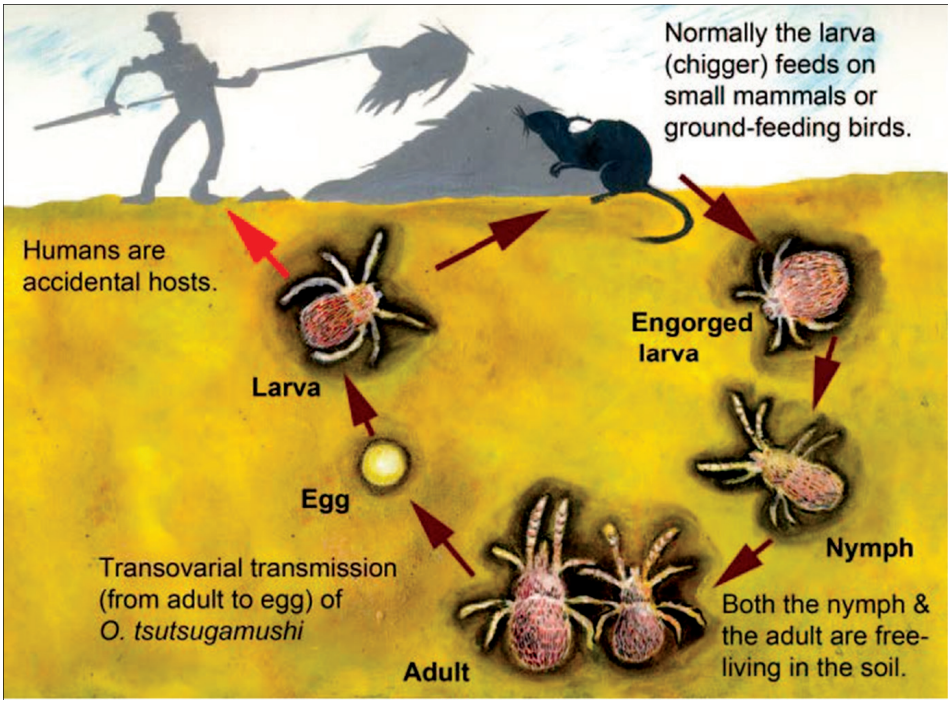


FIGURE 1.6: LIFE CYCLE OF TROMBICULID MITES (RADIOGRAPHICS. 2007 JAN-FEB; 27(1):161-72)

Distribution of the vector

Mites have a very patchy distribution over small areas because of their special requirements. The nymphs and adults need certain soil conditions for their survival and development while the larvae require host animals, such as wild rats, other small rodents and birds. Suitable habitats are found in grassy fields, shrubby areas, forests, abandoned rice fields and cleared forests. The mites are also found in parks, gardens, lawns and moist areas alongside lakes and streams. The larvae wait on leaves or dry grass stems until an animal or human passes by. People usually become infested after walking or standing in mite-infested areas. Bamboo bushes are favored by the mites in the tropics and subtropics.

1.6 PATHOGENESIS

Human infection is initiated via bite of an infected larval Leptotrombidium mite (also known as a chigger). The organism multiplies at the site of inoculation that progresses on to necrosis and evolves into an eschar with regional lymphadenopathy. Orientia-infected target cells include the endothelium and antigen-presenting cells, of which a subpopulation of infected monocytes has the propensity to enter the circulation and disseminate the pathogens (Figure 1.6). This bacteremia phase coincides with the onset of fever and lasts for approximately 10 days. Incubation

period of scrub typhus is 5 to 20 days (mean 10-12 days). The pathophysiological hallmark of scrub typhus is disseminated vasculitis with subsequent vascular injury that involves organs such as skin, liver, brain, lung, kidney, and meninges.

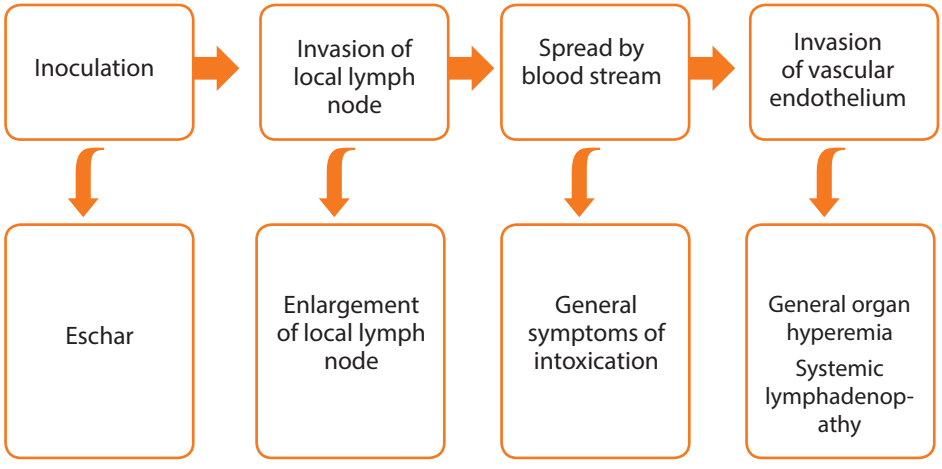


FIGURE 1.7: PATHOGENESIS OF SCRUB TYPHUS

Immune response

The IgM antibodies may appear 3-5 days of illness but reaches in detectable level after first week. IgG antibodies also begins to appear after the first week. The natural immune response against *Orientia* species is a combination of cellular and humoral components with relatively long period (over many years) of homologous protection but poor cross protection to other strains.

CHAPTER - 2

CLINICAL FEATURES

2.1 CLINICAL PRESENTATION

Scrub typhus can exhibit a pronounced seasonality, with high transmission peaks before and after the rainy season in regions of Southeast Asia, while a regular year-round transmission common in tropical and subtropical regions.

Acute undifferentiated febrile illness is the clinical presentation. The chigger bite is painless and may be noticed as a transient localized itch. Bites are often found on the groin, axillae, genitalia or neck. In some patients (7-97%), an eschar **(Figure 2.1, Figure 2.2)** may develop at the site of chigger bite. Eschar are painless up to 1 cm in size with black necrotic center resembling the mark of a cigarette burn. Eschar which represents localized cutaneous necrosis, is reported to be less frequent in South Asian patients than in East Asian. Studies from different parts of India showed presence of eschar in 13-55% of patients. Eschar on moist intertriginous surfaces (axilla, scrotum, perianal region) may be missed if not looked specifically because they may appear as shallow yellow based ulcers. Eschar is considered as pathognomonic of rickettsial diseases, but can be found in anthrax, bacterial ecthyma, spider bite and rat bite fever.

The illness begins suddenly with shaking chills, fever, severe headache, conjunctival infection and swelling of the lymph nodes. Fever is abrupt in onset, high grade, may be associated with headache, myalgia and arthralgia. The fever typically lasts longer period (median 14.4 days; range 9-19). A spotted rash on the trunk may be apparent after 3-5 days of onset of symptoms in a small proportion of patients. Initially, the rash is discrete, pink macular which later becomes maculopapular, petechial or hemorrhagic.

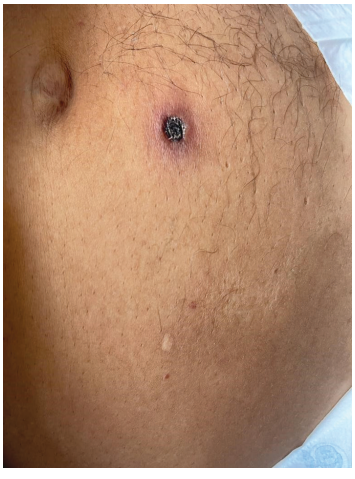


FIGURE 2.1: ESCHAR (PC: DR SHITAL ADHIKARI, CMC, CHITWAN)

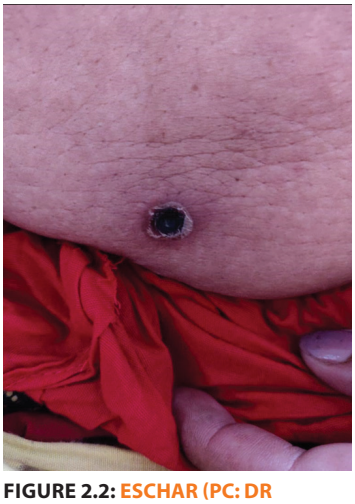


FIGURE 2.2: ESCHAR (PC: DR SHRAWAN KUMAR, STIDH, TEKU)

2.2 COMPLICATIONS

The complications of scrub typhus usually develop after the first week of illness. About a third of patients admitted to hospital have evidence of multi-organ dysfunction.

Respiratory symptoms like cough, shortness of breath are common in scrub typhus and need to be differentiated from the other causes of pneumonia. Signs of consolidation can be found on clinical examination. Pneumonia, acute respiratory distress syndrome (ARDS), pulmonary edema and hemorrhage are the pulmonary complications of scrub typhus.

Gastrointestinal symptoms like abdominal pain, vomiting and diarrhea can be presenting features. Presence of these symptoms along with respiratory symptoms should alert the clinician for consideration of scrub typhus in endemic areas (though COVID-19 also has similar presentation). Hepatosplenomegaly has been found in about 30 % of cases. Elevated hepatic transaminases, bilirubin and alkaline phosphatases are common laboratory abnormalities and need to keep leptospirosis and dengue as other differential diagnosis.

Patients with scrub typhus can present with fever with altered sensorium. Features of meningitis, meningoencephalitis or seizure are common neurological manifestations of scrub typhus. The pathological changes are in blood vessels and rapid improvement is expected with treatment.

Patient with scrub typhus may have various degree of renal abnormalities including acute kidney injury. Scrub typhus should be considered in endemic areas when patient presents with fever and renal impairment, though urosepsis may be more common with such presentation.

Myocardial involvement can be subclinical but conduction abnormalities like bradycardia, atrial flutter, ST-T changes can be seen. Myocarditis may lead to heart failure, cardiogenic shock and sudden cardiac death.

2.3 ASSESSMENT OF SEVERITY

A number of scoring systems have been validated to assess the severity. The Sequential Organ Failure Assessment (SOFA) score **(Figure 2.3)** is very useful to assess the organ dysfunction and predict outcome. Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection. The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction. A SOFA score of ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can

deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.

A rapid assessment of patient can be done with qSOFA which is also validated to be used in emergency unit and is a simple bed side test. It can be assessed quickly and repeatedly. Any 2 of 3 clinical variables— Glasgow Coma Scale (GCS) score of 13 or less, systolic blood pressure of 100 mm Hg or less, and respiratory rate 22/min or greater—offered predictive validity (AUROC = 0.81; 95% CI, 0.80-0.82) similar to that of the full SOFA score outside the ICU.

Following **red flag signs** have been also identified to assess the patients with acute undifferentiated febrile illness indicating need for hospitalization.

- **Prostration**- unable to stand, sit, or walk without support
- **Temperature**- hyperpyrexia (temperature > 41.5°C) or hypothermia (temperature < 36°C), or rigors
- **Respiration**- shortness of breath, respiratory rate >22breaths/minute, cyanosis, arterial oxygen saturation <92% on room air
- **Circulation**- systolic blood pressure <100 mmHg, cold clammy extremities, capillary refill time >3 seconds
- **Neurological**- altered mental status (GCS <13), convulsions, positive meningeal signs
- Abdominal pain, severe or persistent vomiting
- Petechial or purpuric rash
- Bleeding- from nose, gums or venipuncture sites

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

FIGURE 2.3: SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE

2.4 DIFFERENTIAL DIAGNOSIS

Differential diagnosis for scrub typhus based on presentation of acute undifferentiated febrile illness (AUFI) and based on syndromic approach is provided in the **Table 2.1** below:

TABLE 2.1: DIFFERENTIAL DIAGNOSIS OF SCRUB TYPHUS

Based on presentation of acute undifferentiated febrile illness	
Viral diseases	Dengue, SARS-CoV-2, influenza, measles
Bacterial	Typhoid, leptospirosis, meningococcemia, bacterial sepsis
Protozoal	Malaria
Based on syndromic approach	
Fever with rash/ thrombocytopenia	Dengue, meningococcal infection, malaria (usually falciparum), leptospirosis, measles, rubella and other viral exanthem.
Fever with ARDS	COVID-19 pneumonia, influenza including H1N1, leptospirosis, falciparum malaria, hantavirus infection, melioidosis, severe community acquired pneumonia, alveolar hemorrhage
AUFI with hepatic dysfunction	Leptospirosis, scrub typhus, dengue, COVID-19, bacterial sepsis, hepatitis A and E
AUFI with AKI	COVID-19 pneumonia, influenza including H1N1, leptospirosis, Falciparum malaria, hantavirus infection, melioidosis, severe community acquired pneumonia, alveolar hemorrhage
Febrile encephalopathy	Encephalitis (herpes simplex virus encephalitis, japanese and other viral encephalitis), meningitis (*S. pneumoniae*, *Neisseria meningitidis*, *Hemophilus influenzae*, *enteroviruses*), cerebral malaria, typhoid encephalopathy.
Fever with multiorgan dysfunction	Bacterial sepsis, falciparum malaria, leptospirosis, dengue, hepatitis A or E with fulminant hepatic failure and hepato-renal syndrome, Hanta virus infection

CHAPTER - 3

LABORATORY DIAGNOSIS

Clinical presentation of scrub typhus is non-specific and needs to be differentiated from other causes of acute febrile illnesses like dengue, malaria, typhoid, leptospirosis etc. Presence of eschar is highly specific (98.9%) but lacks the sensitivity (6-97%).

3.1 DIAGNOSTIC METHODS

Laboratory-based methods are required to diagnose scrub typhus and can be broadly classified as direct and indirect methods.

DIRECT METHOD

Molecular assay

Molecular detection using polymerase chain reaction (PCR) is possible from eschar swab, skin rash biopsies, lymph node biopsies or ethylenediaminetetraacetic acid (EDTA) blood. *O. tsutsugamushi* DNA can be demonstrated by standard or nested PCR. Realtime PCR assays are as sensitive as standard PCR but are more rapid and can give quantitative results. Common targeted genetic markers in PCR are 56 kDa tsa, 47 kDa HtrA, GroEL, and 16s rRNA. Eschar samples-based PCR has better sensitivity and specificity than isolates from whole blood, buffy coat and blood clot. When blood samples are used for PCR, the results are best within the first week of illness.

Advantage of PCR is early detection of infection with higher sensitivity and specificity where serology tests may not be helpful in the early stages of disease. However, requirement of biosafety level 3 facilities, higher costs and higher genetic diversity of the different serotypes are the major limitations.

Note: Culture of *Orientia* species in chicken embryo and cell lines from blood is difficult which can take several weeks owing to the fastidious nature of the bacteria and requires high containment facility. Hence, culture is not recommended as a diagnostic test for scrub typhus.

INDIRECT METHODS

Indirect laboratory methods of diagnosis include serological assays such as immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA), rapid diagnostic assays and Weil–Felix test.

Immunofluorescence assay (IFA) and immunoperoxidase assay (IPA)

Indirect IFA is considered the gold standard test for the detection of scrub typhus due to its higher sensitivity and specificity. However, due to lack of consensus for standardization of antigens and diagnostic positivity criteria in different population, fourfold rising immunoglobulin M (IgM) or immunoglobulin G (IgG) titers) taken at least 10 days apart is taken as a positivity criterion.

IPA is similar to IFA with substitution of fluorescein with a peroxidase enzyme which does not require expensive fluorescent microscope. These tests requires trained personnel with sophisticated equipment IFA/IPA and hence, it is being increasingly replaced by ELISA with similar sensitivity and specificity with lower cost.

Enzyme-linked immunosorbent assays (ELISAs)

ELISA is the most used method for the diagnosis of scrub typhus due to their better sensitivity and specificity using either culture-derived *O. tsutsugamushi* antigens or recombinant proteins to detect Orientia-specific antibodies IgM and IgG. IgM antibodies can be captured at the end of first week and IgG antibodies appear at the end of second week. The sensitivity and specificity is reported greater than 85%. False positivity can occur due to the presence of background immunity with repeated exposure. Because antibody titers may persist in some individuals for years after the original exposure, only demonstration of recent changes in titers between paired specimens can be considered reliable confirmation of an acute scrub typhus infection.

Rapid diagnostic test (RDTs)

RDTs targeting anti-Orientia IgM and IgG are available for scrub typhus diagnosis. Rapid tests to detect IgM antibodies to scrub typhus have sensitivity ranging from 34.7% to 96.7% and specificity between 93.3% and 99.7%.

Weil-Felix test (Heterophile antibody test)

Weil-Felix OX-K agglutination test based on the cross-reactivity of anti-Orientia antibodies to *Proteus mirabilis* was discovered in 1916. Although the test is found to be positive in 50% of cases in second week of illness (lack of high sensitivity and specificity), this test is not routinely recommended.

Comparison of different diagnostics methods for scrub typhus diagnosis

TABLE 3.1: COMPARISON OF DIFFERENT DIAGNOSTICS METHODS FOR SCRUB TYPHUS DIAGNOSIS

S. N	Method	Assay	Sensitivity	Specificity	Cost	Time	Facility
1	Molecular	RT- PCR	++++	+++++	+++++	4-5 hours	Reference laboratory / Tertiary level
2	Serology	ELISA	++++	+++	+++	3-4 hours	Reference laboratory/ Tertiary level/secondary level
3	Serology	RDT	+++	+++	++	< 30 mins	All level
4	Serology	IFA/IPA	+++	++++ When paired sera used	++++	2 hours	Reference laboratory/ Tertiary level/secondary level
5	Serology	Weil Felix	+	++	++	6-18 hours	Reference laboratory/ Tertiary level/secondary level

Disease dynamics of scrub typhus clinical manifestation, bacteremia and anti-Orientia tsutsugamushi antibodies.

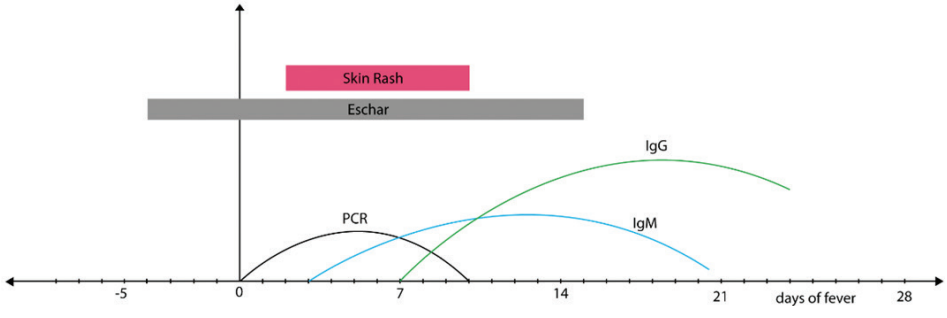


FIGURE 3.1: DISEASE DYNAMICS OF SCRUB TYPHUS CLINICAL MANIFESTATION, BACTEREMIA AND ANTI- ORIENTIA TSUTSUGAMUSHI ANTIBODIES.

Eschar: After the mite bite, an eschar (Fig. 2.1 and 2.2) may appear 2-3 days before fever onset and remains until approximately 14 days later.

Skin rash: Skin rash may appear after 2-3 days of fever but is not always present.

Bacteremia: Bacteremia phase persists for about 10 days after onset of fever, during this time PCR test will be positive.

IgM: IgM antibodies appears 3-5 days after fever onset and can persist up to 3 weeks.

IgG: IgG antibodies appears after 1st week of fever onset and may persist for years.

OTHER SUPPORTIVE INVESTIGATIONS

a. Hematology

- Leucocytes count may be normal during the early course of the disease but may become elevated in the later course of the disease.
- Thrombocytopenia is common.

b. Biochemistry

- Elevated C-reactive protein (CRP) may be seen in more than two-third of scrub typhus patients.
- Elevated transaminases may be seen in 75-95% patients. Hyperbilirubinemia, and hypoalbuminemia occur in 50% patients.
- Renal function tests: raised urea, creatinine and abnormal urinary sediments may be seen.

c. Radiology

- Chest X-ray: chest radiographic abnormalities in patients with scrub typhus is common (59% to 72%) Bilateral diffuse areas of reticulonodular opacity, hilar lymph node enlargement, septal lines and pleural effusion are the most common findings. Airspace consolidation is less common and usually in the lower zone of both lungs.
- CT chest: common findings in pneumonia in scrub typhus include interlobular septal thickening, axial interstitial thickening, ground-glass opacity, and centrilobular nodules. Consolidation and large nodules are less common. The distribution is bilateral and lower zones are predominantly involved.
- USG abdomen may reveal splenomegaly, ascites and thickened gall bladder wall.

d. ECG

- ECG may show ST-T changes and conduction abnormalities.

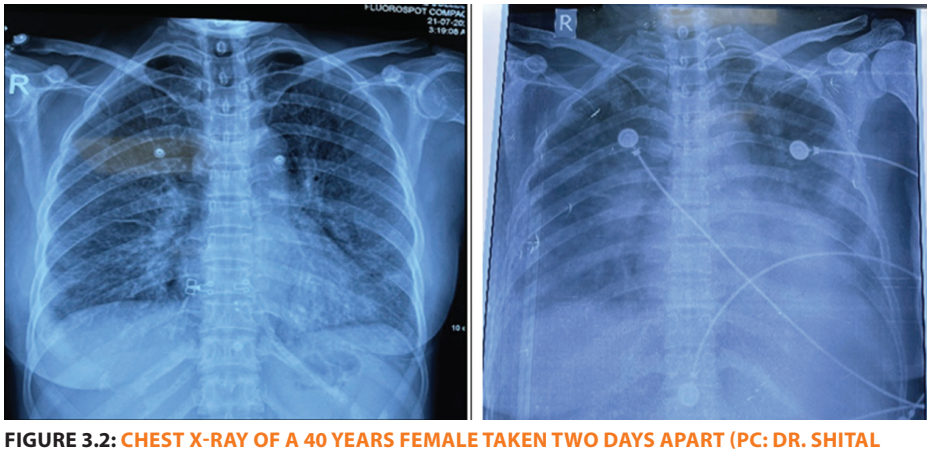


FIGURE 3.2: CHEST X-RAY OF A 40 YEARS FEMALE TAKEN TWO DAYS APART (PC: DR. SHITAL ADHIKARI, CMC, CHITWAN, NEPAL)

Specimen for diagnosis

For diagnosis of scrub typhus, various specimens are used viz. serum, whole blood, buffy coat, CSF, biopsy tissue, a swab from eschar or rash, etc.

Eschar: Molecular detection of Orientia from eschar specimen has now become an acceptable method of diagnosis globally. With the help of a sterile swab, an eschar sample can be easily collected by simple swabbing. The scabs or crusts of the eschar should be removed prior to collection. The Orientia DNA can be isolated from eschar swab. Details on collection of an eschar swab is provided in Annex 1.

Serum: The serum samples should be collected as a paired sera (an acute sample taken during the first week of illness and a convalescent sample taken 2-4 weeks later) for diagnosis of scrub typhus. Collecting single serum may mislead in interpreting as antibodies may not have developed.

Blood: Targeting cellular constituents (i.e., detached endothelial cells and WBCs) of whole blood for detection of rickettsia can be done as these microbes have an affinity for endothelial cells rather than RBC. The preferred order of detection by PCR in the blood specimen is buffy coat > whole blood > serum sample.

Cerebrospinal fluid (CSF): The neurological symptom is a key feature in some rickettsial infection as in scrub typhus. So along with other samples, CSF can be used for laboratory diagnosis.

3.2 RECOMMENDED DIAGNOSTICS AT THE HEATH SERVICE DELIVERY LEVEL

TABLE 3.2: RECOMMENDED DIAGNOSTICS AT THE HEALTH SERVICE DELIVERY LEVEL

Diagnosis	Basic Health Service Center/ Basic Hospital	General Hospital (25-50 beds)	General Hospital (≥100 beds)
Clinical diagnosis	√	√	√
Laboratory diagnosis			
▪ Molecular assay	-	-	√
▪ IFA/IPA	-	-	√
▪ ELISA	-	-	√
▪ RDTs	√	√	√
▪ Weil-Felix test	-	-	√

CHAPTER - 4

CASE MANAGEMENT

4.1 GENERAL APPROACH

Patients with scrub typhus may present with mild illness but can progress to severe infection with multiple organ dysfunction. Rapid assessment of organ function is important. Treatment should be initiated early on clinical suspicion as morbidity and mortality increases rapidly with delay in the treatment. Patient with mild illness without organ dysfunction can be managed with antipyretics (e.g. paracetamol) and antibiotic. Doxycycline is the drug of choice. The response to doxycycline is dramatic and if fever persists beyond 48 hours of initiation of doxycycline, possibility of alternate diagnosis or co-infection should be considered. A few cases taking longer than 48 hours for resolution of fever have been reported. Clinically stable patients without red flag signs can be managed with oral therapy but need close observation because rapid worsening of the condition may occur.

Supportive

Multiple organ dysfunction is common in scrub typhus. Hence, depending upon degree of organ dysfunction, patient may need respiratory support: oxygen and or mechanical ventilation. Circulatory collapse requires intravenous fluids and vasopressor support. Acute kidney injury may need renal support in the form of hemodialysis. Close monitoring of the patient with clinical parameters and laboratory investigations are the cornerstone of successful management. Details of management strategies are described in the section of management of complications below.

4.2 SPECIFIC TREATMENT

Antibiotic therapy for scrub typhus may be administered even before the laboratory tests confirmation if scrub typhus is suspected based on clinical suspicion.

Antibiotics currently recommended for the treatment of scrub typhus are as follows:

- Doxycycline
- Azithromycin
- Chloramphenicol
- Tetracycline
- Rifampicin

ADULTS		
Doxycycline (Drug of choice)	100 mg twice daily for individuals above 45 kg for 7 days	The capsule should be swallowed with a glass of water in sitting or standing position preferably 2 hours after food.
Azithromycin	500 mg once daily orally for 5 days	
CHILDREN		
Doxycycline (Drug of choice)	4.5 mg/kg body weight/ day in two divided doses for children below 45 kg.	Doxycycline is also the drug of choice even in children of any age. Concern of teeth staining, or enamel hypoplasia was not found with this dose.
Azithromycin	10 mg/kg in single dose for 5 days	

When patient cannot swallow or is critically ill such as has circulatory collapse, intravenous therapy of doxycycline or azithromycin is preferred until condition improves followed by oral doxycycline or azithromycin. The total duration of intravenous and oral therapy of doxycycline is 10-15 days in critically ill patients. Injectable antibiotics should be administered as infusion as described below.

- Intravenous doxycycline 100 mg infusion in 100 mL normal saline over 30 minutes twice daily OR
- Intravenous azithromycin 500 mg once daily infusion in 100 ml of normal saline over 1 hour OR
- Intravenous chloramphenicol 50-100 mg/kg/day in 4 divided doses as infusion over 1 hour.

Antibiotics such as rifampicin is found to be effective, but its use should be avoided as far as possible because of the endemicity of tuberculosis in the country. In one in vitro study, *O tsutsugamushi* were found to be intrinsically resistant to fluroquinolones, hence it is not included in the treatment list.

Doxycycline resistance

Doxycycline has been the drug of choice for management of scrub typhus. However, there are reports of poor response or delayed response to doxycycline and progression to involve central nervous system, especially from South-East Asia (mainly Thailand). The slow response could be due to

- Infection with more virulent strains of O. tsutsugamushi
- Potential infection with resistant strains
- A combination of the two

Strains having poor susceptibility to doxycycline have been identified. These patients quickly responded to azithromycin.

4.3 MANAGEMENT IN PREGNANCY

A systematic review on estimating the burden of scrub typhus reported miscarriages in 17% and poor neonatal outcomes (defined as stillbirths, preterm birth and low birth weight) in 42% of women with scrub typhus during pregnancy, which is more than the consequences of malaria in pregnancy.

Doxycycline can be used to treat scrub typhus even in pregnant women. The therapeutic doses and duration of doxycycline (not tetracycline) to treat scrub typhus during pregnancy are unlikely to produce substantial teratogenic risk. But few authorities recommend azithromycin for better safety profile.

4.4 MANAGEMENT OF COMPLICATIONS

Meningitis and encephalitis

Acute meningitis and encephalitis are life threatening manifestations of scrub typhus that require prompt evaluation and management. Encephalopathy, seizure, optic neuritis, myelitis are other manifestations of neural involvement in scrub typhus. Up to one-fifth of affected patients can have central nervous system (CNS) involvement. Invasion into CNS by the organism could be either in monocytes or through the endothelium and presence of bacteria has been confirmed by PCR of cerebrospinal fluid (CSF). High degree of clinical suspicion is required as clinical features differentiating meningitis due to scrub typhus from other acute bacterial and viral meningitis are not helpful, except presence of eschar which is found in less than 50% of cases. Laboratory methods specific for scrub typhus such as serum IgM antibody is not readily available. Moreover, delay in the diagnosis is associated with high mortality.

Neurological manifestations of scrub typhus are fever, headache, altered sensorium, seizure etc. with features of meninism. Other systemic features like jaundice, difficulty breathing, shock, renal impairment may co-exist.

Common findings in CSF includes mild pleocytosis with lymphocyte dominance, low to normal glucose and mild-to-moderate elevation in protein. Differential diagnosis include tubercular and viral meningitis.

Management

- Supportive treatment
- Antibiotics
  - Doxycycline 100 mg twice daily IV infusion over 1 hour or 4.5mg/kg followed by oral therapy to complete 10-14 days of therapy OR
  - Azithromycin 500 mg IV infusion over 1 hour OD or 10 mg/kg in children followed by oral therapy to complete for 5-7 days of therapy OR
  - Chloramphenicol 50–100 mg/kg/day, 6 hourly doses, followed by oral therapy to complete 7–15 days of therapy

Recovery is good and rapid with appropriate therapy. Mortality is 15-30% if associated with multiorgan dysfunction syndrome.

Acute Respiratory Distress Syndrome (ARDS)

Pulmonary involvement is common in scrub typhus. In mild and or promptly treated cases mild interstitial pneumonitis is found but in severe cases, pulmonary hemorrhage, edema, vascular damage and cellular infiltration leading to ARDS may develop.

ARDS is a serious manifestation of scrub typhus requiring intensive care unit (ICU) admission. In a study from South India, ARDS was diagnosed in 43.5% patients with scrub typhus.

Diagnosis

- **Onset:** within 1 week of pneumonia, or new worsening respiratory symptoms
- **Chest imaging:** Bilateral opacities, (not fully explained by effusions, lobar/ lung collapse, nodules)
- **Edema origins:** Respiratory failure not fully explained by cardiac failure or fluid overload; echocardiography may be required to exclude hydrostatic edema if no risk factor of cardiac failure
- **Adult:** Oxygenation impairment
  - Mild ARDS: 200 mmHg <PaO2/ FiO2 ≤ 300 mmHg {with positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5cmH2O}
  - Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O)
  - Severe ARDS: PaO2/FiO2 ≤100 mmHg (with PEEP ≥ 5 cmH2O)
- **Children:** Oxygenation impairment

  Use oxygen index (OI) when available. If PaO2 not available, wean FiO2 to maintain SpO2 ≤ 97% to calculate OSI or SpO2/FiO2 ratio: Bilevel (NIV or CPAP) ≥ 5cmH2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 264.
  - Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI <7.5
  - Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI <12.3
  - Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥12.3

Management

Mild-Moderate ARDS: Trial of high flow nasal cannula, non-invasive ventilation with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) for one hour (provided hemodynamic instability; no multi-organ failure or abnormal mental status).

If failure to respond to increasing oxygenation - proceed to intubation

Severe ARDS: Proceed to intubation and invasive mechanical ventilation (IMV):

- Young Children, pregnant women; obese patients may desaturate quickly: Pre oxygenate with 100% FiO2 for 5 minutes, using face mask with reservoir before intubation.
- IMV: Use low tidal volumes (TV) and Lower plateau pressures; PEEP and FiO2 as per ARDS Guideline (Annex 4)
  - Adult: Initial target TV is 6ml/kg predicted body weight (PBW); Lower plateau pressures <30cm H2O; Prone positioning for 12-16 hours
  - Child: Adapt TV to disease severity; 3-6mL/kg PBW (in poor respiratory compliance) and 5-8mL/kg PBW (in better predicted compliance); Lower plateau pressures (<28cmH2O) is targeted, lower target of pH is permitted (7.15-7.30)
- Positioning: Adults: prone ventilation for 12-16 hours (expertise needed). Pregnant women (3rd Trimester) may benefit from lateral decubitus positioning
- Avoid disconnecting the patient from ventilator, which results in loss of PEEP, atelectasis and increased risk of airborne transmission to HCWs
- Sedate patients, use neuromuscular blockades intermittently
- Vasopressor to maintain mean arterial pressure (MAP)
- Use conservative fluid to prevent fluid overload
- Monitor and Document: vital signs according to ICU protocol; neurological status; arterial blood gas; laboratory results, fluid balance, venous/arterial thromboembolisms
- Nursing care, physiotherapy and nutritional support

Acute kidney injury (AKI)

Scrub typhus can be the cause of AKI in a patient presenting with acute undifferentiated febrile illness. AKI is usually mild and non-oliguric. In a prospective study done in Nepal, urinary abnormalities and AKI were seen in 42.3% and 35.8% patients respectively. The majority were having Stage 1 AKI (66%) followed by Stage 2 (33%). In majority of the cases, AKI occurred in 5th and 6th day of fever by KDIGO criteria. Hemodialysis was required for 3.94% of patients. Similarly, a retrospective study in South Korea (n=510) found the incidence of AKI was 35.9% in patients with scrub typhus.

Appropriate fluid and electrolyte management, avoidance of nephrotoxic medications are important measures to prevent acute kidney injury. A few patients may need dialysis. AKI requiring hemodialysis is associated with poor outcome.

Sepsis and septic shock

Sepsis is defined as acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs and symptoms of organ dysfunction include:

- Alerted mental status
- Difficult or fast breathing
- Low oxygen saturation
- Reduced urine output
- Fast heart rate
- Weak pulse
- Cold extremities or low blood pressure
- Skin mottling
- Laboratory evidence of coagulopathy
- Thrombocytopenia
- Acidosis
- High lactate
- Hyperbilirubinemia

Septic Shock Definition

Adults

Persistent hypotension despite volume resuscitation, requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65mmHg and serum lactate level > 2mmol/L, in the absence of hypovolemia

Child

Severe infection leading to cardiovascular dysfunction (including hypotension, need for treatment with a vasoactive medication, or impaired perfusion) and "sepsis associated organ dysfunction" in children as severe infection leading to cardiovascular and/or non-cardiovascular organ dysfunction.

Fluid resuscitation with or without appropriate use of vasopressors are the main therapies.

Recommended resuscitation strategies for adult and pediatric patients with septic shock

- The resuscitation for septic shock is to rapidly administer a minimum of 30 mL/kg crystalloid solution intravenously (Normal saline or Ringer lactate) within the first three hours. Further fluid management is based on hemodynamic assessment to determine if fluid is likely to be beneficial. Overzealous fluid resuscitation may lead to volume overload, including respiratory failure, particularly with ARDS.

- If there is no response to fluid loading or signs of volume overload appear (e.g. jugular venous distension, crackles on lung auscultation, pulmonary edema on imaging, or hepatomegaly), then reduce or discontinue fluid administration.
- Determine the need for additional fluid boluses (250–500 mL in adults; 10–20 mL/kg in children) based on clinical response and improvement of perfusion targets and reassess for signs of fluid overload after each bolus.
- Perfusion targets include MAP (> 65 mmHg or age-appropriate targets in children), urine output (> 0.5 mL/kg/hr. in adults; 1 mL/kg/hr. in children), and improvement of skin mottling and extremity perfusion, capillary refill time, heart rate, level of consciousness, and lactate <2mmol/L.
- Consider dynamic indices of volume responsiveness: passive leg raises, fluid challenges with serial stroke volume measurements, or variations in systolic pressure, pulse pressure etc. to guide volume administration beyond initial resuscitation based on local resources and experience.

Use of vasopressors

In adults, administer vasopressors when shock persists during or after fluid resuscitation. Noradrenaline is the drug of choice. The initial blood pressure target is MAP ≥ 65 mmHg in adults and the goal is improvement of markers of perfusion.

In children, administer vasopressors (adrenaline is the drug of choice) if signs of fluid overload are apparent or the following persist after two fluid boluses:

- Signs of shock such as altered mental state
- Bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children)
- Prolonged capillary refill (> 2 seconds) or feeble pulses
- Tachypnoea; mottled or cool skin or petechial or purpuric rash; increased lactate; oliguria persists after two repeat boluses or
- Age-appropriate blood pressure targets are not achieved

4.5 CASE FATALITY RATE

There is a wide variation in the case fatality rates (0-33%, median 1.4%) with lower rate in countries with well-established health system. In untreated cases, estimated mortality is 6% (0-70%). In studies from Nepal, the reported mortality was 1.7-7.92%. Mortality in complicated scrub typhus varies depending upon severity and number of organ involvement, with highest mortality rate in patients with multi-organ dysfunction (24.1%)

4.6 PREDICTORS OF POOR OUTCOME

In various studies, older age, higher APACHE II score, AKI requiring dialysis, ARDS, septic shock, meningoencephalitis, gastrointestinal bleeding, pneumonia, arrhythmias, and myocarditis are found to be predictors of poor outcome.

4.7 RECOMMENDED MANAGEMENT OF SCRUB TYPHUS AT THE HEALTH SERVICE DELIVERY LEVEL

Assessment and therapy	Basic Health Service Center/ Basic Hospital	General Hospital (25-50 beds)	General Hospital (≥100 beds)
Recognition of severity of disease by clinical parameters and/or SOFA score	√	√	√
Oral therapy	√	√	√
Intravenous therapy	-	√	√
Complications management	Refer to higher level	Refer to higher level	√

Referral criteria

Scrub typhus patients may present with severe illness or deteriorate requiring close monitoring and intensive care support. Referral to secondary or tertiary care hospital is indicated if

- Patient not getting better with initial treatment (no improvement in signs and symptoms)
- Complications
  - Meningoencephalitis
  - Jaundice or deranged liver function
  - Sepsis, septic shock
  - Acute kidney injury
  - Difficulty in breathing, tachypnea or features of respiratory failure
  - Heart failure

CHAPTER - 5

SURVEILLANCE

Disease surveillance is an ongoing systematic collection, recording, analysis, interpretation and dissemination of data for initiating suitable public health interventions for prevention and control of the disease. It is a critical component of any disease prevention and control programme as it provides the information necessary for risk assessment, epidemic response and programme evaluation.

5.1 OBJECTIVES OF SCRUB TYPHUS SURVEILLANCE

The objectives of scrub typhus surveillance are:

- To identify high risk areas for outbreak prevention
- To detect localized transmission (clusters) of disease for prompt interventions
- To detect scrub typhus epidemics early for preparedness and timely intervention
- To estimate the burden of scrub typhus and provide data for the assessment of the social and economic impact of the disease on the affected community
- To monitor trends in the distribution and spread of scrub typhus over time
- To facilitate planning and resource allocation based on the lessons learnt from programme evaluation

5.2 CASE DEFINITIONS

TYPE	CASE DEFINITION
Suspected case	Acute undifferentiated febrile illness (AUFI) of five days or more with or without eschar should also be suspected as a case of scrub typhus. If eschar is present, fever of less than 5 days duration should be considered as suspected scrub typhus. Other presenting features may be headache, rash (rash more often seen in fair person), lymphadenopathy, multi-organ involvement like lung, liver and kidney involvement. The differential diagnosis of dengue, malaria, pneumonia, leptospirosis and typhoid should be kept in mind.
Probable case	A suspected clinical case plus ▪ IgM positive by RDTs ▪ Showing titers of 1: ≥ 80 in OX2, OX19 and OXK antigens by Weil Felix test
Confirmed case	One or more of the following: ▪ An optimal density > 0.5 for IgM by ELISA for scrub typhus ▪ Detection of nucleic acid of the organisms in the blood, eschar or tissue sample by PCR ▪ A ≥ 4 fold increase in IFA or IPA titer (IgG) in paired sera* ▪ ≥ 1:400 IFA in acute serum (IgG and/or IgM)

*Paired sera: acute and convalescent sera. Acute sera taken during the first week of illness and convalescent sera taken 2-4 weeks later.

5.3 SURVEILLANCE METHODS

Passive surveillance

Passive surveillance is the routine reporting of diseases, where the health care provider provides notification of the disease. In Nepal, scrub typhus cases can be reported by health facilities through the early warning and reporting system (EWARS). Although scrub typhus is currently not reported through the health management information system (HMIS), it will be included in the list of diseases to be reported in HMIS following the endorsement of this national guideline.

Active case surveillance

Active case surveillance involves outreach by the public authorities, such as regular telephone calls or visits to laboratories, hospitals and providers to stimulate reporting of specific diseases. However, it requires intensive resources. An active surveillance system will allow health authorities to monitor scrub typhus transmission in a community and tell, at any point in time, where transmission is occurring and what kind of illness is associated with the scrub typhus infection. However, to accomplish this, the system must be active and have good diagnostic laboratory support.

CHAPTER - 6

PREVENTION AND CONTROL MEASURES

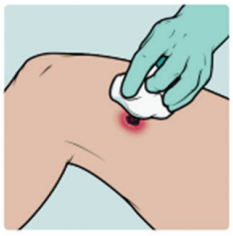
Scrub typhus, a re-emerging and globally expanding disease along with increasingly resistance to doxycycline demand us for implementing effective preventive and control measures. The most important preventive measure for reducing the risk of getting scrub typhus is by avoiding contact with infected chiggers. When traveling to areas where scrub typhus is common, areas with lots of vegetation and brush where chiggers may be found should be avoided. Till date, there is no vaccine available for prevention of scrub typhus. Advocacy, awareness and educational activities should be targeted at high risk groups such as children, women and farming communities in endemic areas.

Type	Method	Remarks
Prevention of chigger bite	Insect repellents	▪ Use of insect repellents containing N,N-diethyl-meta-toluamide (DEET) or other active ingredients registered for use against chiggers, on exposed skin and clothing. ▪ When using insect repellants product instructions should be followed. ▪ Insect repellant should be reapplied as directed in the product instructions. ▪ Skin repellant need not to be applied on the skin under clothing.
	Protective clothing	▪ Protective clothing such as long sleeve covering exposed parts such as arms and legs should be used. ▪ Trousers can be tucked inside socks during outdoors.
	Insecticide treated clothing	▪ For frequent exposures, clothing and gears treated with insecticide permethrin (0.5%) can be used during outdoor activities. ▪ Permethrin SHOULD NOT be used directly on skin. It is intended only for treating clothing.
Chigger control	Removal of vegetation	▪ The control of mites by killing them in their habitats is very difficult because of the patchy distribution of their populations. If it is possible to identify the patches of vegetation that harbor large numbers of larval mites (mite islands), it may be advantageous to remove them by burning or cutting and then to scrape or plough the top-soil. Mowing grass or weeds in these areas also helps. Such measures are recommended in the vicinity of camp sites and buildings. ▪ The chiggers can be controlled by spraying of residual insecticides in woodland or bush areas. However, this is expensive.
	Residual spraying of vegetation	▪ Where the removal of vegetation is not possible, mite islands can be sprayed with residual insecticide. The spraying of vegetation up to a height of 20 cm around houses, hospitals and camp sites was effective against grass mites in Europe. The insecticides can be applied as fogs with ultra-low-volume spray equipment. Some suitable compounds are diazinon, fenthion, malathion, propoxur and permethrin.

ANNEXES

ANNEX 1: ESCHAR SWAB COLLECTION FOR MOLECULAR ANALYSIS

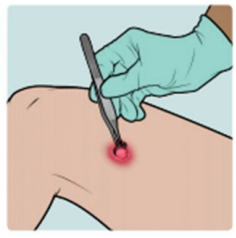
1



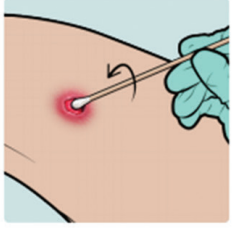
Cleanse the eschar with a standard disinfectant solution. Use sterile saline to remove remaining disinfectant.

2

Use sterile tweezers to lift the scab partially or completely. It is not necessary to remove the scab entirely if it is firmly attached. If removed, place the scab into an empty, sterile specimen container.



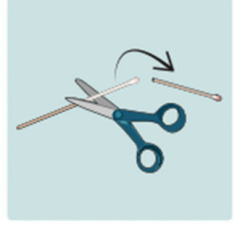
3



Use a dry, sterile cotton swab to sample the ulcerated area. Rotate the swab vigorously on ulcerated area while applying steady, gentle pressure.

4

Place the swab in a sterile specimen container. Swab can be placed in the same sterile specimen container as the scab.



5

Ship specimen immediately overnight on cold packs or freeze and ship on dry ice.

Source: CDC

ANNEX 2: ESTABLISHING CLINICAL DIAGNOSIS USING DIFFERENTIAL DIAGNOSIS TABLES

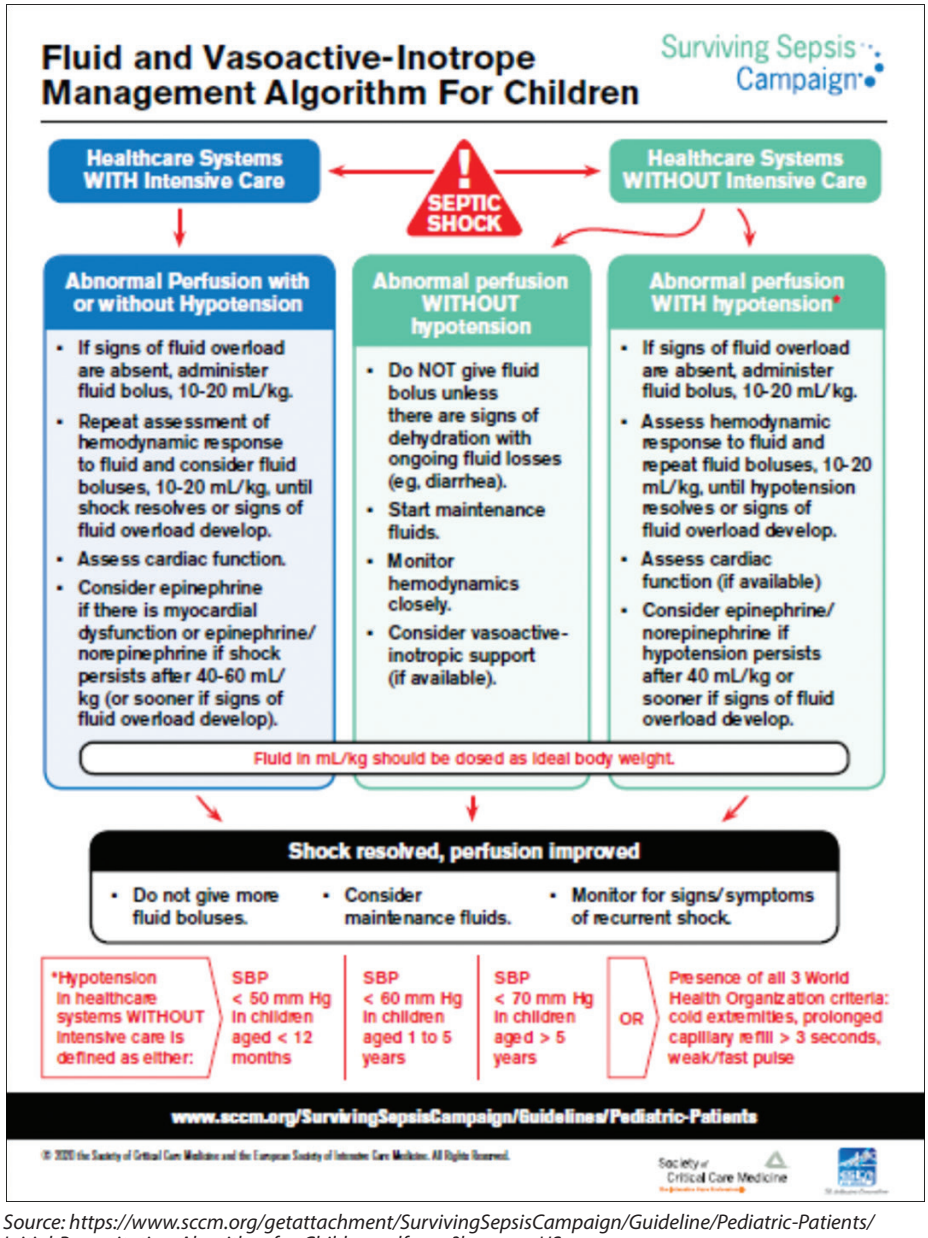
Clinical decision-making is centered on a differential diagnosis

Use appropriate infection prevention and control measures

1. Make a list of all the possible diagnoses causing the signs/symptoms presented in the case.
2. Now go over the list:
   - 2.1. What are the most likely/common conditions ?(consider geography, season, epidemiology, age)?
   - 2.2. Which conditions are life-threatening?
3. Go over the list again
   - 3.1. What are least likely?
   - 3.2. Are there conditions in the list that do not fit because key signs and symptoms are missing?
4. Do further clinical examination and appropriate lab tests: consider what lab tests are appropriate and available
5. Decide on the several top priorities (most likely & life-threatening) conditions
6. Identify patients who need hospitalization and institute any indicated infectious disease precautions.
7. Determine whether clinical findings or diagnostic test results support a condition from the initial differential diagnosis list.
   - 7.1. If yes, treat accordingly.
     - 7.1.1. If treatment was successful, follow the patient as indicated.
     - 7.1.2. If treatment was unsuccessful, re-evaluate the patient, modify the differential diagnosis, and return to step 1
   - 7.2. If no, re-evaluate the patient, modify the differential diagnosis, and return to step 1.
8. If the diagnosis is uncertain:
   - 8.1. Consider initiating empirical therapy for serious or life-threatening conditions including
     - 8.1.1. fluid resuscitation,
     - 8.1.2. oxygen
     - 8.1.3. specific antimicrobials
     - 8.1.4. other supportive care and symptom management
   - 8.2. Consider initiating empirical therapy for non-severe conditions when a diagnosis is likely and treatment is accessible and likely to be effective.

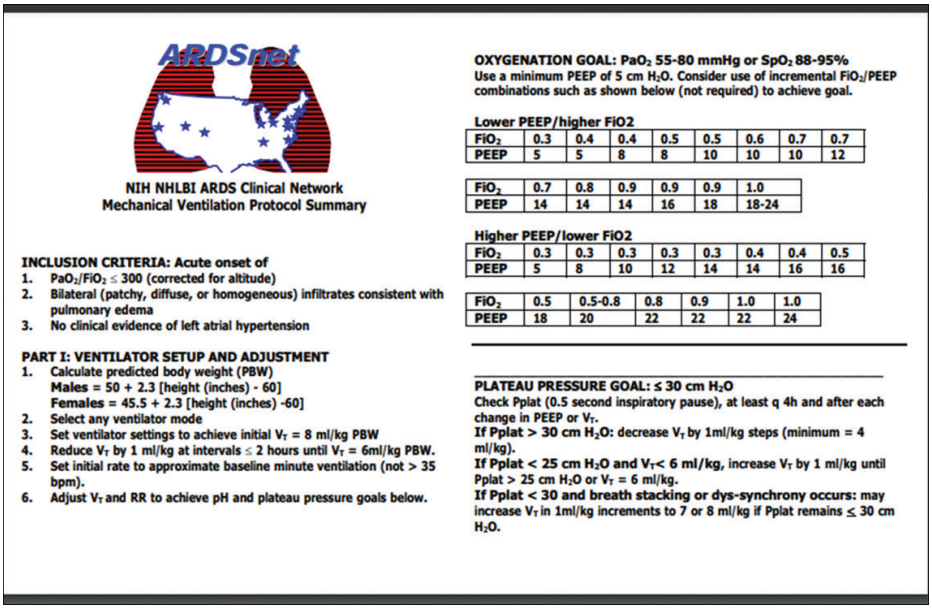
Reference: Clinician's role in Disease Surveillance and response, SEARO- January 2021

ANNEX 3: FLUID AND VASOACTIVE -INOTROPE MANAGEMENT ALGORITHM FOR CHILDREN



Source: https://www.sccm.org/getattachment/SurvivingSepsisCampaign/Guideline/Pediatric-Patients/Initial-Resuscitation-Algorithm-for-Children.pdf.aspx?lang=en-US

ANNEX 4: ARDS CLINICAL NETWORK MECHANICAL VENTILATION PROTOCOL SUMMARY



NIH NHLBI ARDS Clinical Network
Mechanical Ventilation Protocol Summary

INCLUSION CRITERIA: Acute onset of

1. $PaO_2/FiO_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT

1. Calculate predicted body weight (PBW)
   Males = 50 + 2.3 [height (inches) - 60]
   Females = 45.5 + 2.3 [height (inches) -60]
2. Select any ventilator mode
3. Set ventilator settings to achieve initial V_T = 8 ml/kg PBW
4. Reduce V_T by 1 ml/kg at intervals $\leq$ 2 hours until V_T = 6ml/kg PBW.
5. Set initial rate to approximate baseline minute ventilation (not > 35 bpm).
6. Adjust V_T and RR to achieve pH and plateau pressure goals below.

OXYGENATION GOAL: PaO_2 55-80 mmHg or SpO_2 88-95%
Use a minimum PEEP of 5 cm H_2O. Consider use of incremental FiO_2/PEEP combinations such as shown below (not required) to achieve goal.

Lower PEEP/higher FiO2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

PLATEAU PRESSURE GOAL: ≤ 30 cm H_2O
Check Pplat (0.5 second inspiratory pause), at least q 4h and after each change in PEEP or V_T.
If Pplat > 30 cm H_2O: decrease V_T by 1ml/kg steps (minimum = 4 ml/kg).
If Pplat < 25 cm H_2O and V_T< 6 ml/kg, increase V_T by 1 ml/kg until Pplat > 25 cm H_2O or V_T = 6 ml/kg.
If Pplat < 30 and breath stacking or dys-synchrony occurs: may increase V_T in 1ml/kg increments to 7 or 8 ml/kg if Pplat remains $\leq$ 30 cm H_2O.

Source: http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf

ANNEX 5: APPROACH TO ACUTE UNDIFFERENTIATED FEBRILE ILLNESS (AUFI)

Approach to acute undifferentiated febrile illness (AUFI)

Epidemiological information

Local prevalence of disease: rural (scrub typhus, leptospirosis); urban (dengue)
Season: Dengue, scrub, leptospirosis, etc. usually peak in rainy seasons; typhoid usually after rainfall
Potential exposure: Insect bites (scrub, dengue, malaria); contact with body fluids or contaminated water and soil through skin abrasions or conjunctiva (leptospirosis)

Clinical presentation

Onset: abrupt onset of fever (scrub, malaria, dengue, leptospirosis); insidious onset (typhoid fever).
Incubation period: Dengue (4-10 days), scrub typhus (10-12 days), influenza (3-5 days), COVID-19 (2-7 days)
Pattern of illness: Organ dysfunction after apparent recovery (dengue, leptospirosis); intermittent (malaria), rising (typhoid)

Laboratory tests

CBC, urea, creatinine, sugar, LFTs, CRP, CXR, ECG, RDTs and microscopy for malaria, NS1antigen for dengue

Syndromic approach

AUFI with rash/thrombocytopenia: Dengue, meningococcal infection, malaria (usually falciparum), leptospirosis, measles, rubella and other viral exanthem
AUFI with ARDS: COVID-19, influenza, scrub typhus, severe pneumonia, leptospirosis
AUFI with hepatic dysfunction: Leptospirosis, scrub typhus, dengue, COVID-19, bacterial sepsis, hepatitis A and E
AUFI with AKI: COVID-19 pneumonia, influenza including H1N1, leptospirosis, Falciparum malaria, hantavirus infection, melioidosis, severe community acquired pneumonia, alveolar hemorrhage
Febrile encephalopathy: Encephalitis (Herpes simplex virus encephalitis, Japanese B and other viral encephalitis), meningitis (S. pneumoniae, Neisseria meningitidis, Hemophilus influenzae, enteroviruses), cerebral malaria, typhoid encephalopathy
AUFI with multiorgan dysfunction: Bacterial sepsis, falciparum malaria, leptospirosis, dengue, hepatitis A or E with fulminant hepatic failure and hepato-renal syndrome, Hanta virus infection

Confirmatory tests

Dengue, Scrub typhus: IgM ELISA after 6th days of illness; Malaria: RDTs and microscopy; Influenza/COVID-19: RT-PCR; Leptospirosis: IgM ELISA; Typhoid: Blood culture

Empirical treatment

Ceftriaxone and doxycycline (or azithromycin) will cover typhoid, leptospirosis, scrub typhus and other rickettsial diseases

Monitoring

Clinical monitoring of patients, therapeutic response, co-infection or secondary infection

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