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FEVER OF UNKNOWN ORIGIN



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FEVER OF UNKNOWN ORIGIN: BRIEF DESCRIPTION

Fever is a known manifestation of several disorders including infections, and is one of the common reasons for patients visit to a physician's office. Several causes of fever are known. Fever of unknown origin (FUO) is a clinical entity traditionally defined as temperature of $\geq 38.3^{\circ}\text{C}$ (or $\geq 101^{\circ}\text{F}$) on several occasions for duration ≥ 3 weeks without an established cause, even after 1 week of investigations in the hospital. The term was first described by Dr. Petersdorf and Dr. Beeson in the early 1960s. Since then, this entity has remained an enigma for physicians across the world; posing several difficulties and diagnostic challenges when dealing with these patients.¹

In 1991, certain changes were proposed to the original definition of FUO. Four distinct subtypes of FUO were introduced:

- Classic FUO (FUO based original definition)
- Nosocomial FUO
- Neutropenic FUO
- HIV-related FUO

Another major change suggested was reducing duration of investigations prior to diagnosing this condition from 1 week in the original definition to a minimum of 3 outpatient visits or 3 days of in-hospital investigations.² Many experts in the following years emphasized that while temperature $\geq 38.3^{\circ}\text{C}$ on multiple occasions for duration more than 3 weeks were indeed

important criteria for diagnosing FUO and differentiating it from other febrile illnesses, it was prudent to exclude immunocompromised patients or those recently immunocompromised from FUO diagnosis as the spectrum of underlying diseases for these patients may be different from the rest. Also, immunocompromised patients, due to their compromised immune status, may require a more aggressive approach and early initiation of empirical antibiotics as opposed to the more prolonged diagnostic wait and watch approach recommended in other patients with FUO.³

POTENTIAL CAUSES OF FUO

There is a wide range of differential causes for FUO (Table 1). They can be divided into broad categories including infectious causes, malignancy, non-infectious inflammatory diseases (such as autoimmune and rheumatic diseases), vasculitis syndromes, and other miscellaneous causes. Many-a-times the diagnosis remains unknown. Predominant known causes of FUO, however, may differ based on the geographical location. While infections seem to be the most likely etiological cause of FUO in developing countries, non-infectious inflammatory disorders are the more likely underlying causes in the developed nations.¹

Notwithstanding rapid strides made in the field of medical technology and advancements in diagnostic imaging in the last few years, the subset of FUO where underlying cause remains "undiagnosed" seems to be growing. In a prospective study of 73 patients with

Table 1: Some important causes of FUO¹

Infections
<ul style="list-style-type: none">• Tuberculosis• Enteric fever• Brucellosis• Complicated UTI• Rickettsial infections• Coxiella burnetti (Q fever)• Culture negative endocarditis• Epstein–Barr virus• Cytomegalovirus• HIV• Toxoplasmosis• Malaria• Histoplasmosis• Cat scratch disease• Tickborne infections
Malignancy
<ul style="list-style-type: none">• Multiple myeloma• Malignant histiocytosis• Renal cell carcinoma• Leukemia• Non-Hodgkin lymphoma• Hepatocellular carcinoma• Metastatic lesions
Inflammatory
<ul style="list-style-type: none">• Systemic lupus erythematosus• Giant cell arteritis• Polyarteritis nodosa• Granulomatosis with polyangiitis• Rheumatoid arthritis• Antiphospholipid syndrome
Miscellaneous
<ul style="list-style-type: none">• Drug fever• Hyperthyroidism• Cirrhosis• Factitious fever• Inflammatory bowel disease• Cyclic neutropenia

FUO performed from December 2003 to July 2005, with patients included from one university hospital and five community hospitals in the Netherlands, infections were cited as the cause of FUO in 16%, neoplasm in 7%, non-infectious inflammatory diseases in 22%, and miscellaneous causes in 4% patients; though in 51% cases the cause of fever remained undiagnosed (Figure 1).⁴

APPROACH TO A PATIENT WITH FUO

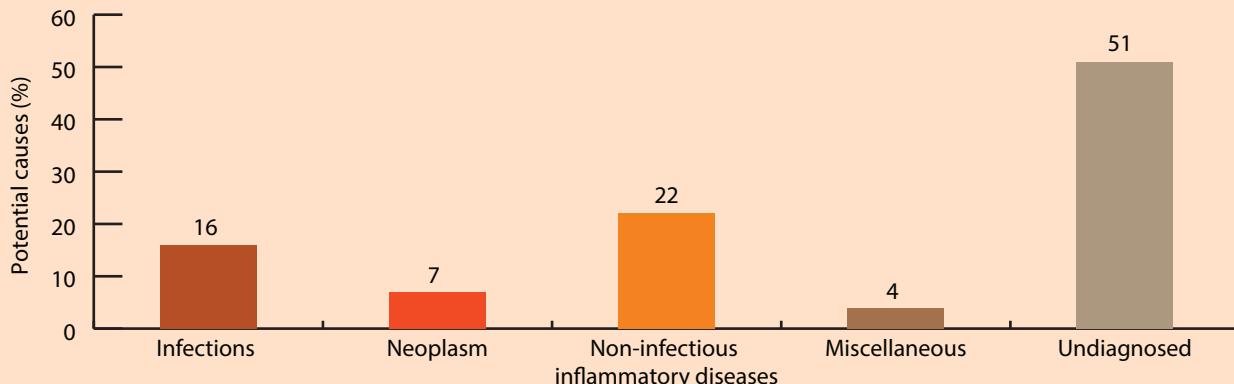
Given the wide array of underlying causes of FUO and need for an extensive work-up, its diagnosis can be challenging. In a patient with FUO, clues to diagnosis of the underlying cause can be difficult to find, and attempt should be made to identify it from a detailed history, examination, and investigation findings. History should include knowledge about the pattern of fever, patient's health condition in between febrile episodes, past medical/surgical history including history of hospitalizations, and treatment history, if any. Factitious fever needs to be excluded and all medications which the patient is on should be discontinued. Temperature charting may also be helpful as it can provide valuable information on the pattern of fever, which can provide vital diagnostic clues to potential underlying cause.^{2,5} Examination should be meticulous focusing both on general physical examination and systemic examination. Investigations should be segregated into initial baseline tests, and subsequent second-line tests if diagnosis remains uncertain after first-line testing.⁴

Although there is no consensus on which baseline investigations should be initially performed, broadly they should include complete blood counts, ESR, C-reactive protein (CRP), kidney and liver function tests, serum electrolytes, creatinine kinase, rheumatoid factor, antinuclear antibodies, serum protein electrophoresis, and two to three blood cultures.^{5,6} Chest X ray and ultrasound may also be included in the initial testing, if deemed necessary.⁵ Testing for HIV may be included either in the initial testing or as a part of second-line tests. Microbiological tests, advanced imaging, lactate dehydrogenase, ferritin, thyroid function test, and biopsies, if needed, constitute possible second-line tests which can be chosen for these patients if they remain undiagnosed after baseline testing.^{5,6} Other less commonly used invasive tests such as bone marrow biopsy or transoesophageal echocardiography or biopsy may occasionally be needed in select cases.⁶

MANAGEMENT APPROACH

Overall, management of FUO primarily involves adoption of a wait and watch approach for results of the investigations. After the diagnosis is established specific therapy needs to be instituted.⁶ Fever control involves use of antipyretics. Several antipyretics are available, though paracetamol has remained the antipyretic of first choice due to its safety. In fact, safety of paracetamol is the primary basis for its recommendation as the standard and first-line treatment for fever and even acute pain. Many experts cite its "outstanding" safety record at therapeutic doses compared to several non-

Figure 1: Potential causes of FUO in a study⁴



steroidal anti-inflammatory drugs (NSAIDs).⁷ However, reports also suggest that paracetamol can even be used safely in higher doses but for short duration.⁸ Empirical antibiotics are not routinely indicated in patients with FUO, unless the patient is neutropenic. Similarly policy of using empirical corticosteroids are strongly discouraged, except when suspicion of rheumatological disorders is high. Nevertheless in patients with clinical deterioration, empirical antimicrobials or corticosteroids may be considered. Specific treatment may be started after the cause of FUO is known.¹ Overall prognosis depends on the etiology, though mortality rates are usually less than 10%. A large majority of deaths are due to malignancy. Patient counseling may be beneficial wherein they may be explained about the investigations and reassured of overall favorable prognosis in most "undiagnosed" FUO, particularly in those without "danger signs".⁶

CONCLUSION

Fever of unknown origin (FUO), first described by Dr. Petersdorf and Dr. Beeson in 1960s, is a clinical enigma described as fever $\geq 38.3^{\circ}\text{C}$ or $\geq 101^{\circ}\text{F}$ for a duration of more than 3 weeks after at least 1 week of in-patient investigation, the latter duration subsequently reduced to minimum of 3 outpatient visits or 3 days of in-hospital testing. There are several underlying causes of FUO; while in developing countries infections appear to be the predominant cause, in developed world non-infectious inflammatory disorders are more likely etiology for FUO. A detailed history, meticulous examination, and

a set of initial baseline testing with second-line tests if necessary can suggest the possible underlying cause. There is no set management protocol for FUO. In most patients a wait and watch approach has to be adopted till the investigation results suggest possible diagnosis. For fever management paracetamol is among the safest antipyretics and can be recommended as per the physician's advice. Patients should be counselled; overall prognosis appears to be favorable in most cases of "undiagnosed" FUO, particularly those without "danger signs".

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APPROACH TO FEVER AND PAIN IN THE ELDERLY WITH PARACETAMOL



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FEVER IN ELDERLY

Introduction

There exists a direct relationship between advancing age and development of chronic illnesses and comorbid conditions, polypharmacy and immunosuppressive medications, and changes in the immune system. Furthermore, there is an increased likelihood of infection with aging; such that both morbidity and mortality is several-fold higher in the elderly individuals as compared to their younger ones.¹

With the advancing age and increase in elderly population, there is considerable increase in need for medical and healthcare resources, especially emergency medical care. According to available data, older people account for 12–24% of all emergency department (ED) visits, out of which 10% have a fever. Amongst those having fever, 70–90% are admitted and 7–10% die within a month; making fever a worrisome in the geriatric population.²

Fever is the cardinal manifestation of infection in elderly population and is a useful indicator for diagnosing non-infectious diseases such as rheumatic disease and malignancy. Available data states that infectious diseases are the cause of acute fever requiring hospitalization in 75% of geriatric patients. However, 20–30% of the elderly with an infection present to the ED with a blunted fever response.¹⁻⁴

There are two ways in which a reduced fever response holds a clinical significance. First, a reduced response is associated with diagnosis delay and thereafter initiation of appropriate management. This delay is associated with poor clinical outcomes with respect to increased disease severity as well as the incidence of complications from infection. Secondly, fever has important prognostic implications and may be an important host defense.³

Definition of fever in older adults

In elderly people, fever should be considered to be present under the following conditions:^{3,5}

- Single oral temperature $>100^{\circ}\text{F}$ ($>37.8^{\circ}\text{C}$)
- Repeated oral temperatures $>99^{\circ}\text{F}$ ($>37.2^{\circ}\text{C}$) or rectal temperatures $>99.5^{\circ}\text{F}$ ($>37.5^{\circ}\text{C}$)
- An increase in temperature of $>2^{\circ}\text{F}$ (1.1°C) over the baseline temperature, regardless of technique used for temperature measurement.

Significance of blunted or absent fever response

Approximately 20-30% of elderly people show blunted or absent fever response, which could be accounted to be due to disturbance in thermal homeostasis, quantitative and qualitative abnormalities in both the production of and response to endogenous pyrogens, such as IL1, IL-6, and tumor necrosis factor, reduced

sensitivity of the hypothalamus to endogenous pyrogens, failure to produce and conserve body heat, comorbidities and drugs.^{2,4} Furthermore, aging is also associated with reduced ability of the hypothalamic circumventricular organs, thereby limiting the passage of endogenous pyrogens from the blood stream to exert their effect on the CNS.^{3,4}

Evaluation of fever

It is often burdensome and challenging to evaluate geriatric patients with fever as it is associated with an atypical disease, drug effects, or multiple comorbidities. Based on mortality predictors, various studies have proposed decision rules to aid clinicians in managing geriatric patients with fever. Leukocytosis (WBC >12,000 cells/mm³), Severe coma (GCS ≤ 8), and Thrombocytopenia (platelets <150 × 10³/mm³) (LST) are the three independent mortality predictors, based on which a Geriatric Fever Score, a simple and rapid rule was established that stratifies patients into two mortality-risk and disposition groups, low and high.

These factors were easy to both memorise and apply in clinical practice. Moreover, this score is helpful for physicians in emergency care, critical care, and geriatric care to manage geriatric patients with fever based on the urgency of their clinical condition.²

Management of fever in elderly: Paracetamol in focus

Paracetamol, a non-opioid analgesic has been recommended for the first-line management of pyrexia. It is widely preferred in older patients, in whom the use of NSAIDs does not produce significant results or is inappropriate as it is less of an irritant to the gastrointestinal tract than aspirin.⁶ Paracetamol has been considered as a safe and effective first-line agent in almost all patients, irrespective of liver disease etiology. Though dose reduction seems unnecessary in the healthy population, it should be taken into consideration in patients with severe or decompensated hepatic disease states, malnourished patients or patients having dry weight less than 50 kg. Furthermore, liver damage from standard dosage of paracetamol is rare, though the risk of liver problems associated with paracetamol overdose is well established. It is, therefore, advisable to consider lowering the dose in frail patients with low body weight and other risk factors for hepatotoxicity.^{6,7}

Dosage of paracetamol

- **Recommended oral formulation:** 0.5 to 1 g every 4–6 hours up to a maximum of 4 g in 24 hours with no dose reduction advised for older people⁶

- **In individuals <50 kg:** Maximum dose of 60 mg/kg/day or 3000 mg/day
- **In individuals with cirrhosis/consuming alcohol regularly:** Maximum dose of 2–3 g/day
- **For individuals with severe renal impairment (creatinine clearance <30 mL/min):** Dosing interval of at least 6 h is recommended.⁸

KEY HIGHLIGHTS

- Age itself is not a risk factor; healthy older individuals weighing >50 kg do not require a dose reduction⁶
- Since aging is associated with frailty, low weight and renal or hepatic impairment, a lower starting dose and/or reduced frequency of dosing should be considered.⁶

CHRONIC PAIN MANAGEMENT IN ELDERLY

Introduction

Chronic geriatric pain has been defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage in individuals aged >65 years, who have had pain for greater than 3 months. It is one the most common health conditions seen in older people, significantly affecting their activities of daily living (ADLs) and associated with depression, sleep impairment, disability and poor quality-of-life. It exerts a considerable burden on the health care economy.⁹⁻¹²

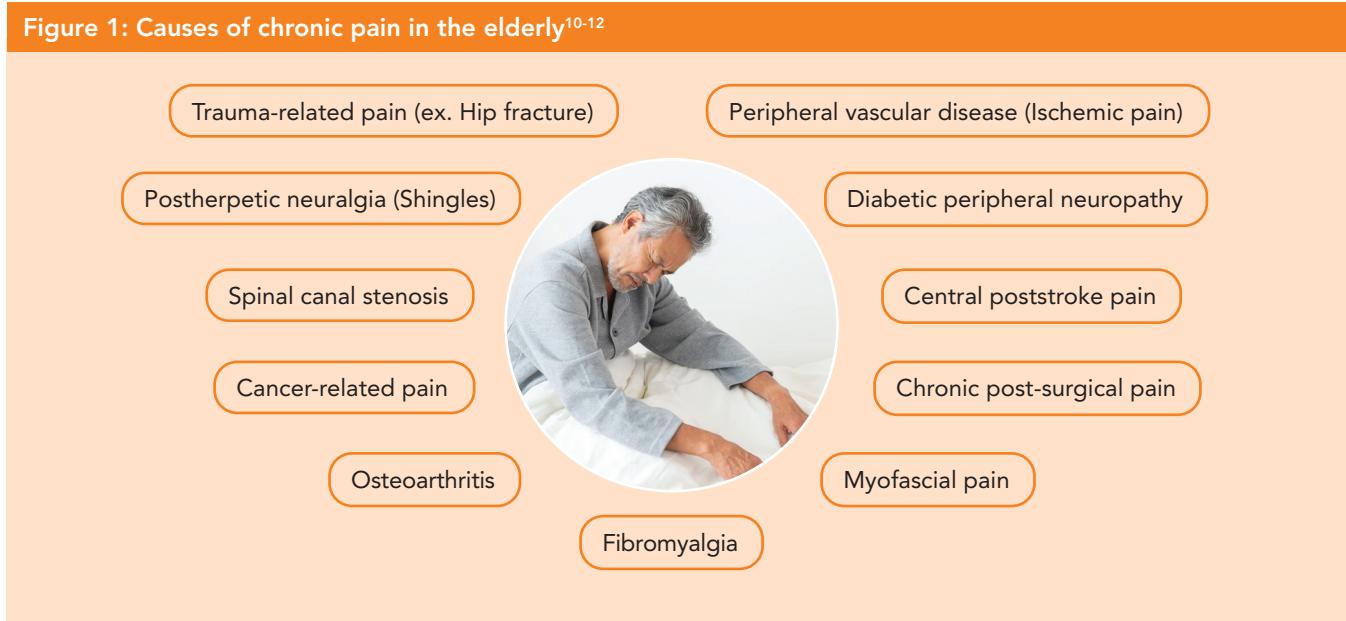
Based on the available data, prevalence of chronic pain increases with age; it is as high as 25–50% in community dwelling elders and 80% in institutionalized individuals.¹³ Approximately 70% of these older individuals complain of pain in multiple sites.¹⁰ In older individuals, chronic unspecified joint pain, chronic back pain and chronic neck pain are the common chronic pain conditions that affect 40, 5–45, and 20% of individuals, respectively.¹⁴

Causes and risk factors

Musculoskeletal disorders are the most common cause of chronic pain in the elderly, followed by neuropathic pain, ischemic pain, and pain due to cancer as well as its treatment. Furthermore, there is an increased prevalence of vertebral compression fractures associated with pain and discomfort in elderly women. Figure 1 highlights the common causes of chronic pain in elderly.¹⁰⁻¹²

Aging, females, lower socioeconomic status and educational level, obesity, tobacco use, history of injury,

Figure 1: Causes of chronic pain in the elderly¹⁰⁻¹²



history of a physically strenuous job, childhood trauma, and depression or anxiety are the risk factors associated with chronic pain development in older adults.¹²

Mechanism of chronic pain

Increased pain and pain sensitivity in the older adults could be accounted to be due to physiological changes in the elderly that includes reduced neurotransmitters such as gamma-aminobutyric acid (GABA), serotonin, noradrenaline, and acetylcholine, reduced number of peripheral nociceptive neurons, increased pain thresholds, and reduced endogenous analgesic responses. These changes are then associated with increase in the pain.¹¹

Pain assessment in older adults

Visual analogy scale (VAS), verbal descriptor scale, and numerical rating scale are the tools available to assess pain intensity. Below mentioned tools hold an important place when assessing pain intensity in elderly individuals with cognitive impairment:

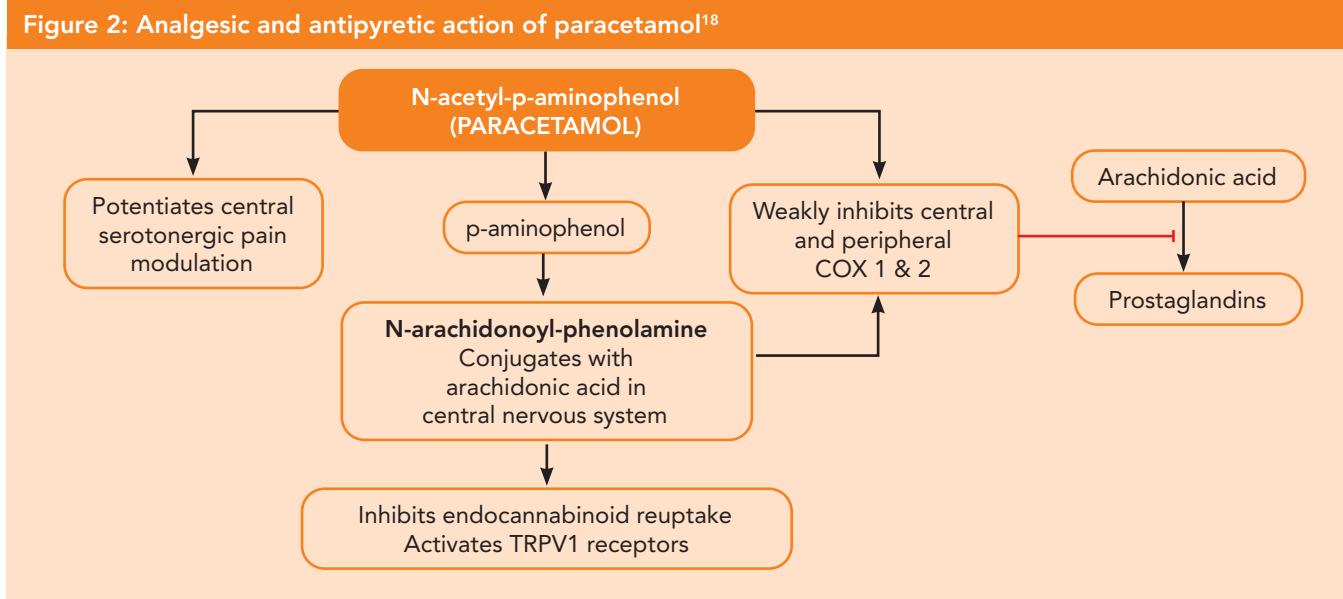
- **Wong-Baker FACES scale:** For elderly with limited cognitive ability
- **Behavioral observation tools like Pain Assessment in Advanced Dementia (PAINAD) and Checklist on Nonverbal Pain Indicators (CNPI):** In elderly persons with advanced dementia.¹¹

Therapeutic management of chronic pain in elderly: Paracetamol in focus

Paracetamol has been recommended by the American Geriatric Society as the first-line agent for mild to moderate chronic pain in the elderly due to its evident effectiveness and favorable safety profile. Maximum daily recommended dosage is 4 g per 24 hours with required dose adjustments of 50-70% in patients with hepatic dysfunction.^{9,11,15} Evidence had shown that in elderly patients with chronic pain, paracetamol plays a vital role as an non-steroidal anti-inflammatory drug (NSAID) sparer, owing to the benefits in terms of reduced adverse effects and cost savings.¹⁶

Guideline recommendations for paracetamol use in elderly patients with chronic pain ¹⁷	
American Geriatric Society	<ul style="list-style-type: none"> • Recommend as initial pharmacological therapy in the treatment of persistent pain, particularly musculo-skeletal pain (MSP), because of its efficacy and safety profile • It recommends a 50–75% dose reduction in patients with liver failure • High quality of evidence; strong recommendation
British Geriatric Society and British Pain Society	First-line treatment in older patients, particularly for MSP
European League against Rheumatism (EULAR)	Recommends as the first and preferred long-term oral analgesic

Figure 2: Analgesic and antipyretic action of paracetamol¹⁸



Paracetamol exerts both antipyretic and analgesic effects, with complex mechanisms that distinguish it from NSAIDs and opioids (Figure 2).¹⁸ Paracetamol has opioid sparing activity, with its efficacy being enhanced in fast-dissolving formulations that is associated with reduced adverse events and risks from high doses of opioids.¹⁷

Older adults with associated comorbidity and frail patients are more prone to opioid adverse effects and exert negative impact on cognitive function. Paracetamol, with opioid sparing activity exerts positive effects on cognition with respect to improved tasks of information sampling, spatial planning, and working memory; signifying its clinical efficacy on CNS.¹⁷

CONCLUSION

Fever is the cardinal manifestation of infection in elderly population and is a useful indicator for diagnosing non-infectious diseases. Chronic pain is one the most common health conditions seen in older people significantly affecting their activities of daily living, with incidence increasing with age. Paracetamol exerts both antipyretic and analgesic effects, with complex mechanisms that distinguish it from NSAIDs and opioids. Paracetamol has been recommended by the American Geriatric Society as the first-line agent for mild to moderate chronic pain in the elderly due to its evident effectiveness and favorable safety profile. Maximum daily recommended dosage is 4 g per 24 hours with required dose adjustments of 50-70% in patients with hepatic dysfunction.

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FEVER WITH DIFFERENT INFECTIOUS DISEASE: FOCUS ON ENT INFECTIONS



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FEVER: AN OVERVIEW

Regulation of body temperature above the normal range occurring as a result of IL-1-mediated elevation of the hypothalamic set point is defined as fever or pyrexia.¹ The causes of fever can be either infectious or non-infectious (Table 1).²

Table 1: Causes of fever²

Infectious	Non-infectious
<ul style="list-style-type: none"> • Viruses • Bacteria • Fungi • Parasites 	<ul style="list-style-type: none"> • Allergic reactions, CNS injury, Inflammatory conditions • Medications, Neoplasm • Hyperthyroidism • Thromboembolic disease

CNS: central nervous system.

DIFFERENT INFECTIOUS DISEASES

Infectious diseases	Infectious cause	Symptoms	Salient features of fever	Treatment
1. Sinusitis	Viruses, fungi, and bacteria ³	Facial pain/pressure, facial congestion/fullness, nasal obstruction, nasal or postnasal purulence, hyposmia, and fever ³	<ul style="list-style-type: none"> • Fever is a major symptom for acute sinusitis • It is a minor symptom for subacute and chronic sinusitis • Bacterial sinusitis is associated with high fever (over 39°C or 102°F); last for 3 to 4 consecutive days at the initial stage⁴ 	<ul style="list-style-type: none"> • Humidification • Nasal wash • Decongestants • Steroids • Antibiotics • Paracetamol for symptomatic management of pain^{3,5}
2. Tonsillopharyngitis	Virus and bacteria (Group A streptococcus (GAS) is most common) ⁶	Sore throat, odynophagia, fever, headache, abdominal pain, nausea, and vomiting ⁶	Fever lasts for one to two weeks ⁷	<ul style="list-style-type: none"> • Amoxicillin or penicillin • Paracetamol or NSAIDs for symptomatic management of fever and pain⁶

Infectious diseases	Infectious cause	Symptoms	Salient features of fever	Treatment
3. Otitis media	Viruses, bacteria, genetic factors ⁸	Fever, otalgia, pulling or tugging at the ears, irritability, headache, disturbed or restless sleep, poor feeding, anorexia, vomiting, or diarrhea ⁹	Low grade fever ⁸	Symptomatic treatment using paracetamol for fever and pain and antibiotics ^{8,9}
4. Croup (Laryngotracheobronchitis)	Parainfluenza virus ¹⁰	Inspiratory stridor, fever, cough, hoarse voice and a variable degree of respiratory distress ¹⁰	Ranging between 38 and 39°C, in those with bacterial infection presenting with stridor, higher degrees of fever seen in children ¹⁰	Paracetamol 10–15 mg/kg for symptomatic treatment of fever, O ₂ in case of hypoxia, dexamethasone to reduce respiratory distress ¹⁰
5. Infectious mononucleosis	Epstein-Barr virus ¹⁰	Fever, pharyngitis and posterior cervical lymphadenopathy ¹⁰	<ul style="list-style-type: none"> Last 4 days to 2 or 3 weeks, peaking on the fifth day of illness Intermittent fever, with a usual range between 38.5 and 39.5°C¹⁰ 	Symptomatic treatment, paracetamol to reduce fever and pain ¹⁰

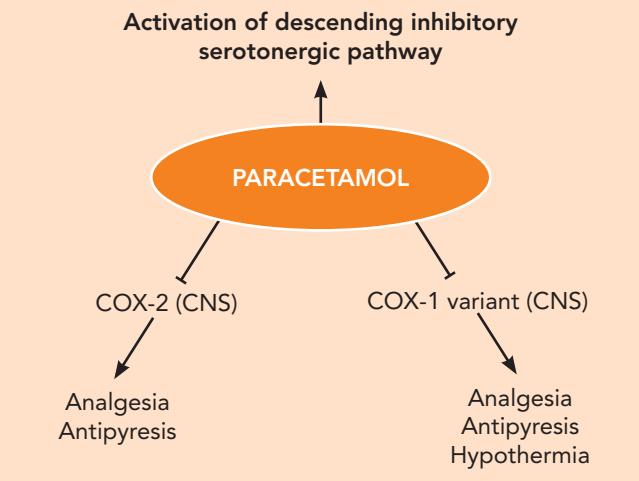
PARACETAMOL: A PROMISING SYMPTOMATIC TREATMENT FOR FEVER ASSOCIATED WITH INFECTIOUS DISEASES

Paracetamol is a standard and first-line treatment for fever and pain. It is a centrally acting temperature lowering drug as it exhibits the ability to temporally reduce brain PGE2 synthesis. The mechanism of pharmacological action is well-elaborated in Figure 1.¹¹ Box 1 showcases advantages of paracetamol over other NSAIDs.¹² Pierce and his colleagues conducted a meta-analysis¹³ to assess the efficacy and tolerability of ibuprofen and paracetamol and it was concluded that paracetamol is also well-tolerated for the management of fever among children or adults with fever.

WHY IS PARACETAMOL A PREFERABLE DRUG OF CHOICE FOR PAIN AND FEVER MANAGEMENT ASSOCIATED WITH ENT INFECTIONS?

Paracetamol has been considered as first choice antipyretic, despite the availability of various other antipyretics. This could be due to its better safety profile, which makes its recommendation as standard and first-line treatment for fever and acute pain. As compared to other non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol has an outstanding safety record when given at therapeutic doses.¹¹ Moreover, when given

Figure 1: Pharmacological action of paracetamol in fever management¹¹



Box 1: Advantages of paracetamol¹²

- Wide therapeutic application
- Well-tolerated
- Good bioavailability after oral administration ($t_{1/2}$ 2h)
- Fast elimination
- A small number of interactions with other drugs
- Low toxicity at low doses (≤ 2 g/d) to the digestive tract and kidneys
- Low toxicity in children
- Rare side-effects (main allergic skin reactions)

in higher doses but for short duration, paracetamol has been considered safe.¹⁴ Additionally, it has opioid sparing activity, with its efficacy being enhanced in fast dissolving formulations that is associated with reduced adverse events and risks from high doses of opioids.¹⁵

CONCLUSION

Fever is an elevation of an individual's core body temperature above a 'set-point' which is regulated by the body's thermoregulatory center in the hypothalamus. It can be caused due to various causes including the infectious causes. There are numerous methods through which fever can be alleviated among which paracetamol holds an important position as it exhibits the ability to temporally reduce brain PGE2 synthesis. It is widely used for fever in infectious diseases as it illuminates various advantages like good tolerability and bioavailability. Hence, it can be considered a safe option for treatment of fever in infectious diseases. It not only is used for its anti-pyretic and analgesic properties, but also has an anti-inflammatory effect due to which it hastens the cure when used judiciously with other appropriate medications.

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DENGUE FEVER AND ITS MANAGEMENT



Reviewed by

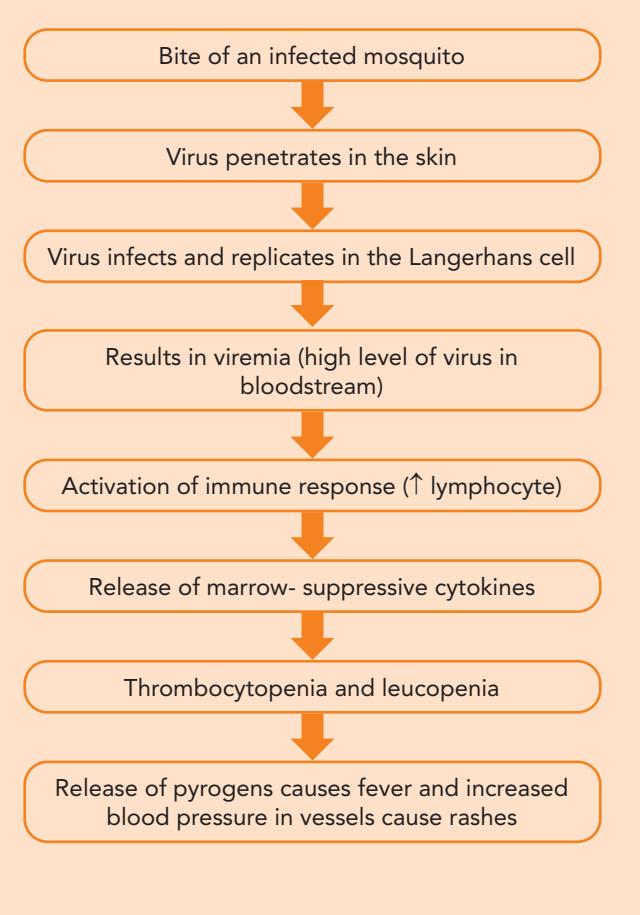
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INTRODUCTION

Dengue fever is rapidly emerging acute febrile disease and is estimated to cause nearly 390 million infections per year, of which approximately 96 million result in overt illness. It is estimated that around 20,000 people die from dengue fever. Unplanned urbanization, changes in environmental conditions, host-pathogen interactions, and immunological characteristics of the population are all associated with the spread of dengue fever. Furthermore, inadequate vector control techniques contribute to the spread of dengue virus and its mosquito vectors. The primary vectors of the disease are female mosquitoes of the *Aedes aegypti* and *Aedes albopictus* species.¹⁻⁴

Dengue fever is caused by the dengue virus (DENV) which belongs to the genus Flavivirus and consists of four antigenically related, but distinct virus DENV serotypes (DENV-1, DENV-2, DENV-3 and DENV-4). Due to these four different serotypes, it is likely that a person will be exposed to the virus multiple times throughout their life. Dengue transmission generally follows two patterns: epidemic dengue and hyperendemic dengue. When a single strain of DENV is responsible for introduction and transmission, it is called epidemic dengue fever. Hyperendemic is the simultaneous spread of different DENV serotypes in a community.^{1,3,5} Immunopathogenesis of dengue fever is shown in Figure 1.^{1,3,6}

Figure 1: Immunopathogenesis of dengue fever^{1,3,6}



CLINICAL COURSE OF DENGUE FEVER

In its early stages, dengue fever presents flu-like symptoms, which include fever, nausea, myalgia, retroorbital pain and headache. Dengue fever is typically a self-limiting illness, but some patients experience severe symptoms that include shock, bleeding, and plasma leakage. According to WHO guidelines, dengue fever is categorized into dengue fever, dengue fever with warning signs and severe dengue fever (Figure 2). Warning signs include hepatomegaly, abdominal pain, mucosal bleeding, and a rising hematocrit accompanied by a rapidly decreasing platelet count.¹

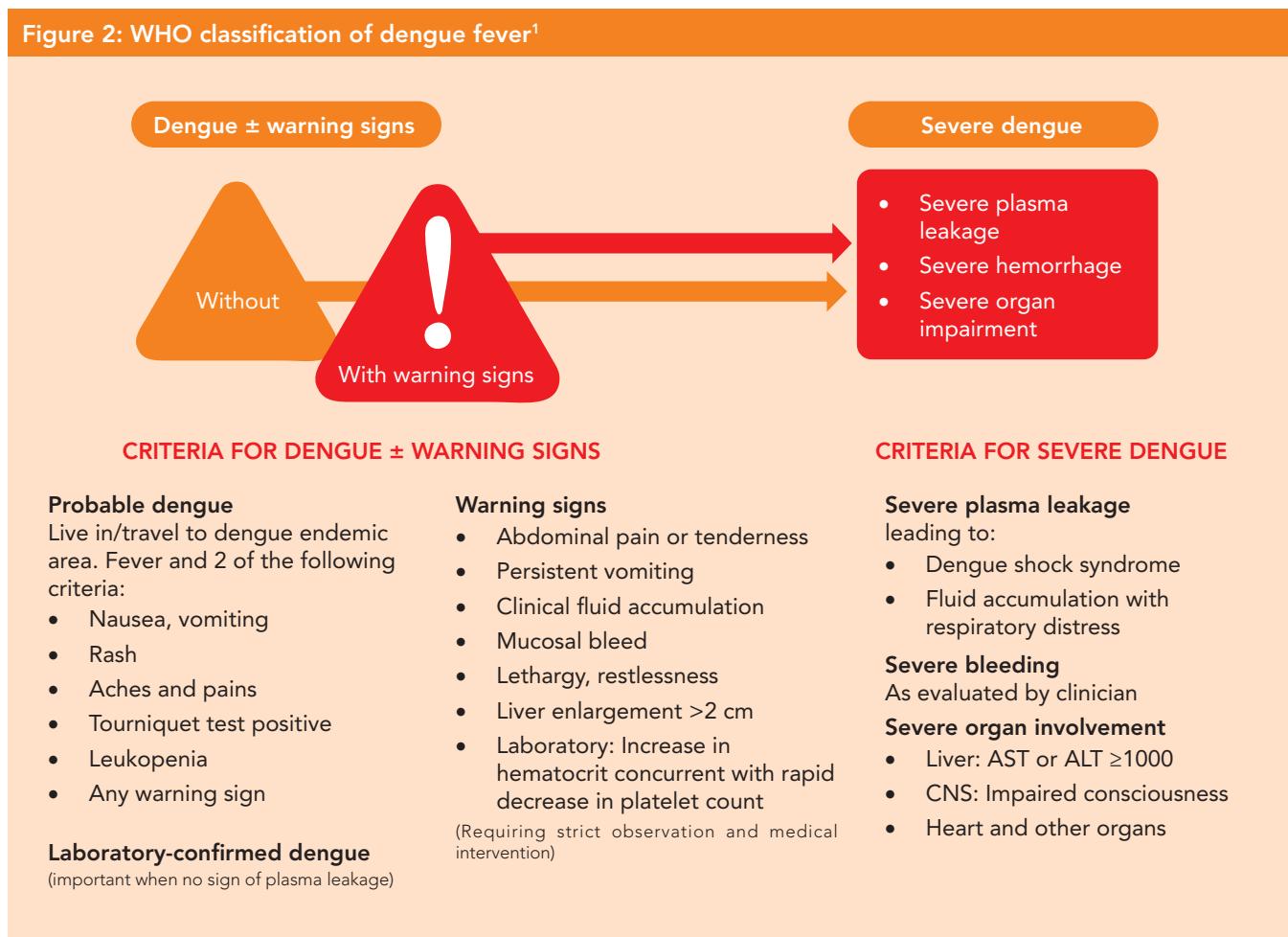
Dengue fever begins abruptly after a typical incubation period of 5 -7 days and progresses in three phases: Febrile phase, critical phase and recovery phase.

- The febrile phase is due to an increased viral load and is characterized by high-grade fever around 40°C/104°F, which usually lasts two to seven days, headache, arthralgia, myalgia, backache and anorexia. Dengue fever is also known as break-bone fever due to the severity of muscle spasms and joint pain. Fever can occur in saddleback or

biphasic pattern. From the second day of fever, the complete blood count shows leukopenia, thrombocytopenia and rising hematocrit. An increase in liver transaminases such as alanine transaminase (ALT) and aspartate transaminase (AST) is often observed. In later part of febrile phase cutaneous bleeding manifestations such as petechiae, purpura or ecchymoses can be observed

- The critical phase is accompanied by increased capillary permeability. As a result, the patient may experience thrombocytopenia and/or plasma leakage, which in severe cases manifests as hemoconcentration and fluid accumulation in the tissues. These complications eventually lead to dengue hemorrhagic fever (DHF). If DHF is left untreated, it can cause multi-organ failure and shock, known as dengue shock syndrome (DSS). An increase in hematocrit of more than 20% of baseline and hypoalbuminemia are indicators of the critical phase. The vascular leak can last 24-48 hours and is dynamic in nature, usually peaking 24 hours after onset

Figure 2: WHO classification of dengue fever¹



- During the recovery period, gradual reabsorption of the extravasated fluid begins. This phase is recognized clinically by the fact that the patient's well-being improves significantly and in some cases an itchy rash appears. Additionally, patients develop bradycardia, which is called recovery bradycardia. Hemodilution results in a decrease in hematocrit and a rapid increase in the number of white blood cells, followed by an increase in platelets.^{1,3,7}

DIAGNOSIS OF DENGUE FEVER

Efficient and accurate diagnosis of dengue is of primary importance for clinical care (i.e. early detection of severe cases, case confirmation and differential diagnosis with other infectious diseases).

Dengue fever can be diagnosed clinically using predefined lists of signs and symptoms and confirmed by a variety of methods, including anti-DENV antibodies, nonstructural protein 1 (NS1) antigen, or DENV-specific nucleic acid detection.^{3,8}

MANAGEMENT OF DENGUE FEVER

There are no definitive curative medications for dengue. Management is symptomatic and supportive. Dengue fever is a systemic and dynamic disease. Therefore, treatment modalities vary depending on the three phases of the clinical course. It is important to recognize plasma leakage, shock, and early or severe organ damage. This can be achieved through frequent clinical and laboratory monitoring.^{6,7,9}

Based on the clinical manifestation at the initial stage of the disease, patients are divided into three treatment groups: group A - can be managed at home, group B - needs in-hospital management, group C - needs emergency management. Treatment of dengue fever in different groups is shown in Table 1.⁶

Platelet transfusions are usually given to patients who develop severe hemorrhagic manifestations or have a very low platelet count. Studies have shown that urgent platelet transfusion is required when platelet counts fall to <20,000 cells/microliter.^{3,9}

PARACETAMOL AND ITS ROLE IN DENGUE FEVER

Paracetamol (N-acetyl-p-aminophenol) is one of the most commonly used over-the-counter analgesic and antipyretic. Due to its remarkable safety profile at therapeutic concentrations compared to nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol is currently standard and first-line treatment for fever and pain.¹⁰

Antipyretic and analgesic effect of paracetamol

The cause of fever and pain is mostly mediated by prostaglandins, which are lipid mediators derived from arachidonic acid. Paracetamol induces antipyretic and analgesic effect by blocking prostaglandin synthesis from arachidonic acid in brain by inhibiting the enzymes, COX-1 and -2.¹¹

Table 1. Treatment of dengue fever in different groups⁶

		Treatment
Group A		<ul style="list-style-type: none"> Take paracetamol as an antipyretic (avoid NSAIDs) Maintain adequate oral intake of fluid Seek medical advice if they experience warning symptoms
Group B	Without warning* signs	<ul style="list-style-type: none"> Oral fluids; if not tolerated, intravenous fluids for 24–48 h (0.9% saline or Ringer lactate) at maintenance rate Clinical and laboratory parameter monitoring
	With warning signs	<ul style="list-style-type: none"> Baseline hematocrit Isotonic fluids: 5–7 mL/kg/h for 1–2 h; 3–5 mL/kg/h for 2–4 h; 2–3 mL/kg/h till patient is able to take orally adequately Increase or decrease fluid rate based on hematocrit Clinical and laboratory parameter monitoring
Group C		<ul style="list-style-type: none"> Meticulous fluid resuscitation Treatment of bleeding manifestations Glycemic control Discontinue intravenous fluids once hemodynamics stabilize

* Hepatomegaly, abdominal pain, mucosal bleeding, and a rising hematocrit accompanied by a rapidly decreasing platelet count

Another possible underlying mechanism of paracetamol as an antipyretic and analgesic is its metabolism to N-acetylphenolamine (AM404), which acts on transient receptor potential vanilloid 1 (TRPV1) and cannabinoid 1 receptors in the brain and terminals of C-fibers in the spinal dorsal horn.¹¹

Studies have also shown that systemic administration of paracetamol may activate descending serotonergic pathways and spinal 5-HT (7) receptors to produce central antinociceptive effects.¹²

As previously mentioned, treatment for dengue fever is symptomatic and supportive. Adequate bed rest, fluid intake, and analgesic-antipyretic therapy are often helpful in relieving the fever, lethargy, and malaise associated with the disease. Therefore, WHO recommends paracetamol to treat pain and fever in dengue, which ultimately shortens the duration of the disease and prevents risk of progression to severe dengue. Paracetamol is preferred over aspirin and other NSAIDs because it does not inhibit platelet function in antipyretic doses.^{13,14}

WHO recommendation for paracetamol in dengue fever^{13,15}

- Administration of paracetamol for high fever
- Dosage: Recommended dose of 10 mg/kg/dose.
 - Maximum dose for adults is 4 g/day
 - Interval of paracetamol dosing should not be less than six hours
- Transaminase levels should be monitored.

WHO guidelines contraindicate aspirin and other NSAIDs in dengue fever due to their antiplatelet effects and bleeding risk.

CONCLUSION

Dengue fever is rapidly emerging acute febrile disease and is associated with sudden onset of high fever and a variety of nonspecific signs and symptoms,

including headache, retro-orbital pain, body pain. Treatment of dengue fever is symptomatic and supportive, depending on the phases of the clinical course. To treat high fever and associated pain, WHO recommends paracetamol in therapeutic doses with regular monitoring of transaminase levels. Aspirin and NSAIDs are contraindicated in dengue fever due to their antiplatelet effects and risk of bleeding.

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MANAGING TYPHOID FEVER: TREATMENT STRATEGIES AND SUPPORTIVE CARE



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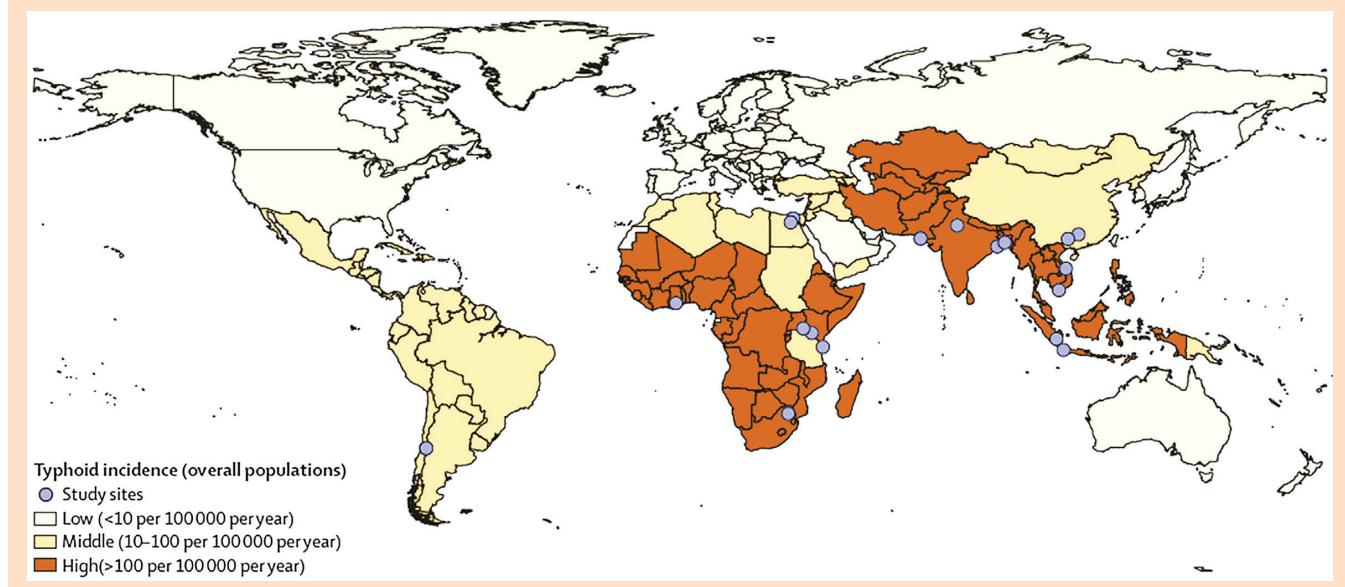
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OVERVIEW

Typhoid fever, also known as enteric fever, is a systemic illness characterized by "step-ladder" pattern of fever followed by headache and abdominal pain. Typhoid fever has historically been a significant public health concern, particularly in the developing world. The disease course ranges from early gastrointestinal symptoms to more severe complications, including sepsis, gastrointestinal bleeding, intestinal perforation,

and even death. The disease, primarily caused by *Salmonella typhi*, is transmitted through various means, often referred to as the 'four Fs': flies, fingers, feces, and fomites. Children under the age of 15 years are more vulnerable to the disease because adults tend to develop immunity from recurrent infections and subclinical cases. Effective public health interventions and comprehensive research is required to reduce its burden.¹⁻³

Figure 1: Typhoid incidence in low-income and middle-income countries⁴



BURDEN OF TYPHOID: GLOBAL AND INDIAN PERSPECTIVE

Typhoid fever is a global health issue with an estimated annual incidence of 11–21 million cases, leading to 120,000–160,000 deaths.² This disease is more common in temperate and tropical climates and is closely linked to the state of sanitation, sewage, and water treatment systems. Economically developing nations, especially low-income countries in Asia and sub-Saharan Africa, face significant challenges in combating typhoid fever due to limited access to safe water and inadequate sanitation infrastructure.^{1,3} High-risk regions with an incidence exceeding 100 cases per 100,000 population per year include south-central Asia, southeast Asia, and possibly southern Africa. Medium-risk areas (10–100 cases per 100,000) encompass the rest of Asia, Africa, Latin America, and Oceania, excluding Australia and New Zealand. In other parts of the world, the incidence of typhoid fever is relatively low (Figure 1).⁴

A significant portion of the worldwide burden of typhoid fever is concentrated in South Asia, particularly in India, where there is a high incidence of the disease.² In 2017, an estimated 14.3 million cases of enteric fever caused by *S. typhi* and *S. paratyphi* occurred globally. Out of these, *S. typhi* was responsible for 11 million cases of typhoid fever and 120,000 deaths. Intriguingly, more than half of these global cases (around 8.3 million cases and 72,000 deaths) occurred in India.⁵

Data from global burden of disease studies further underscore the prevalence of typhoid fever cases in the Indian subcontinent, with India having the highest prevalence among five Asian countries studied by the International Vaccine Institute in Korea (Figure 2).⁶ Recent data shows notable geographic variation in typhoid incidence across India, with higher rates in the southwestern states and urban regions in the north. Despite improvements in water hygiene and sanitation,

typhoid remains highly prevalent in urban India, especially among the poorest households.^{2,5}

ETIOLOGY

The main causative agents of typhoid fever are *S. typhi* and *S. Paratyphi* (A, B, and C), all the three belonging to the Gram-negative bacteria of Enterobacteriaceae family. Infection sources include the stool and urine of infected individuals, and transmission occurs through the fecal-oral route, usually via contaminated water, undercooked foods, and contact with fomites from infected individuals. This disease is more prevalent in areas with overcrowding and poor sanitation. Salmonella can only be transmitted from one infected person to another, as humans are its only reservoir. The onset and severity of the disease are primarily determined by the virulence of the bacteria and the infective dose.^{1,3}

DIAGNOSTIC APPROACH IN TYPHOID FEVER

Clinical manifestations

After a person gets infected with *S. typhi*, an asymptomatic period (incubation period) follows that usually lasts about 7–14 days. The onset of bacteremia is characterized by fever and malaise. The fever pattern typically exhibits progressive rises and falls in a stepwise manner. Patients usually present to the clinic towards the end of the first week after symptom onset (Table 1).^{7–10} The characteristic features of typhoid fever include step ladder pattern of fever, coated tongue, relative bradycardia, diffuse abdominal pain, constipation/diarrhoea, muttering delirium, and rose spots.⁹

Step-ladder pattern of fever

Typhoid fever exhibits a distinct fever pattern described as a 'step ladder.' The fever gradually rises in the late

Figure 2: Surveillance data for typhoid incidence from sites in five Asian countries⁶

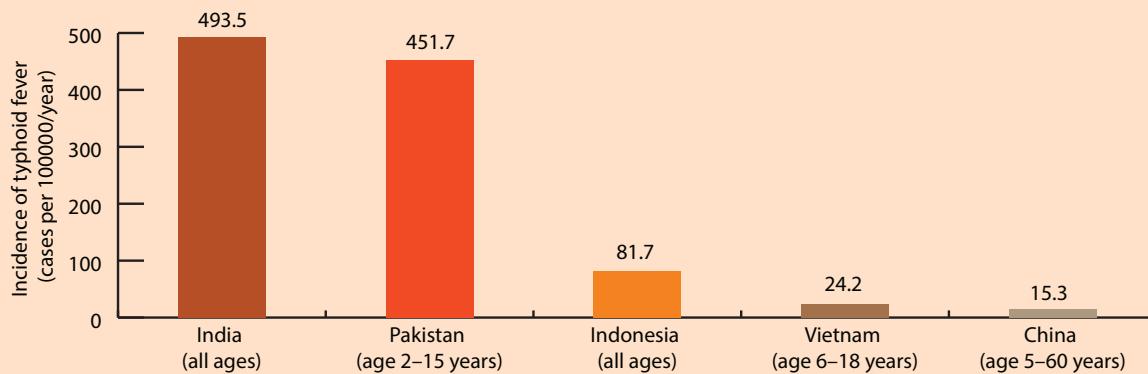


Table 1: Typical presentation of typhoid fever⁷⁻¹⁰

First week	<ul style="list-style-type: none"> Fever: Step-ladder pattern Gastrointestinal features <ul style="list-style-type: none"> Diffuse abdominal pain and tenderness Constipation Coated tongue Other symptoms <ul style="list-style-type: none"> Dry cough, dull frontal headache, delirium, stupor, malaise
Second week	<ul style="list-style-type: none"> Progression of above signs and symptoms Fever plateaus at 39-40°C Rose spots, 1-4 cm in width, < 5 in number, resolve within 2-5 days Abdominal distension Soft splenomegaly Relative bradycardia Dicrotic pulse: Double beat, the second beat weaker than the first
Third week	<ul style="list-style-type: none"> Fever persists Increase in toxemia Anorexia, weight loss, conjunctivitis Thready pulse, tachypnea Crackles over lung bases Severe abdominal distension Sometimes, foul, green-yellow, liquid diarrhea (pea-soup diarrhea) Typhoid state, characterized by apathy, confusion, psychosis

afternoon, reaching its peak late at night, and then decreases during the day. In the second week of the disease, the fever tends to become higher, often reaching 39-40°C, and persists. Following effective treatment, fever defervescence occurs gradually, characterized by lysis (Figure 3).^{11,12}

Laboratory evaluation

- Hemogram¹³
 - Hb normal/low
 - TLC normal/low
 - Relative lymphocytosis and eosinopenia
 - Thrombocytopenia may also be present
 - Mild elevation of transaminases may be observed
- Culture and sensitivity¹³
 - Gold standard and the most important diagnostic investigation
 - Automated blood culture systems like BACTEC have improved recovery rates and long-term cost-effectiveness
 - Blood culture can yield positive results in approximately 90% of cases during the first week and up to 40% in the fourth week of disease
 - Urine and stool cultures peak the positivity from 2nd week of disease
 - As the disease duration increases the sensitivity of blood culture decreases and that of stool culture increases
- Serology¹³
 - Serological tests are not diagnostic on their own but may provide supportive information
 - Widal test detects the presence of antibodies against the H (flagellar antigen) and O (somatic antigen) antigens of *S. typhi* and paratyphi A and B
 - A positive test is indicated by an antibody titer of both O and H in the range of 1:160 dilution or higher
 - Conventional method involves a four-fold rise in titer in paired samples taken 1 week apart

Figure 3: Step-ladder pattern of fever^{11,12}

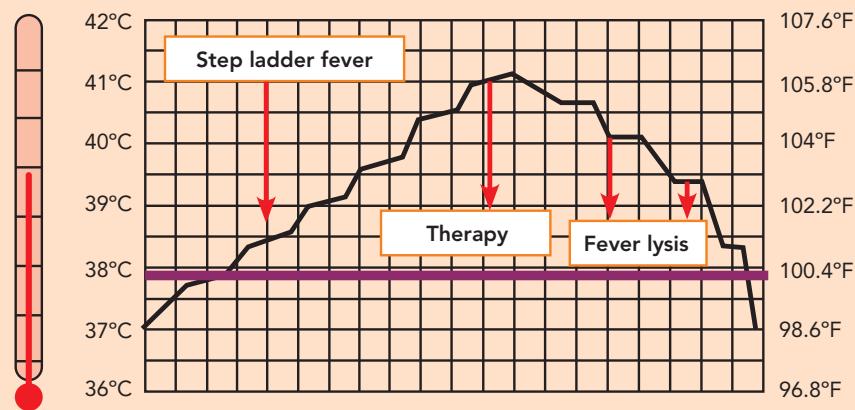


Table 2: Treatment of uncomplicated enteric fever¹⁰

Susceptibility	Patient group	Antibiotic	Daily dose	Duration
Quinolone sensitivity	Adult	Responders		
		Fluoroquinolones: Ciprofloxacin or ofloxacin	15 mg/kg	10 days
		3 rd generation cephalosporin like cefixime	15-20 mg/kg	10 days
		Nonresponders		
	Child	Chloramphenicol	50-75 mg/kg	14 days
		Amoxicillin	75-100 mg/kg	14 days
		Responders		
		3 rd generation cephalosporin like cefixime	15-20 mg/kg	10 days
Quinolone resistance	Adult	Nonresponders		
		Chloramphenicol	50-75 mg/kg	14-21 days
	Child	Amoxicillin	75-100 mg/kg	14 days
		Responders: Cefixime	20 mg/kg	14 days
		Nonresponders: Azithromycin	10-20 mg/kg	7 days
	Child	Responders: Azithromycin	10-20 mg/kg	7 days
		Nonresponders: Cefixime	15-20 mg/kg	14 days

- Rising titre of paired sera is more diagnostic than a singular measurement; earliest rise may be seen by the end of first week
- Newer diagnostic test (Typhidot, Tubex) allow the direct detection of IgM antibodies against the specific *S. typhi* antigens. The tube method is preferred over the slide method. (Early initiation of anti-typhoid antibiotics will blunt HTR serological response)
- Being an antibody response, once it is positive, it may remain positive from few weeks to months
- Imaging
 - USG abdomen is unremarkable except some subcentric LN and features of ileocecalis with mild splenomegaly.

CURRENT APPROACHES IN THE TREATMENT OF TYPHOID FEVER

Early diagnosis and prompt initiation of appropriate antibiotics and antipyretics are crucial for the optimal management of typhoid fever. When treatment is started within the first few days of the full-blown disease, the disease begins to improve within about 2 days, and condition of the patient markedly improves within 4-5 days. Any delay in treatment increases the risk of complications and prolongs the recovery time.^{8,14}

Antibiotic therapy

Prompt administration of the appropriate antibiotic therapy prevents severe complications in typhoid

fever. The choice of initial drug therapy depends on the susceptibility of the bacterial strains causing the infection. In many regions, fluoroquinolones are the most effective first-line treatment. In severe cases requiring immediate intervention, fluoroquinolones can be administered empirically based on clinical suspicion before diagnostic culture test results are available. Fluoroquinolones have a high cure rate of about 98% and result in fecal carriage rates of less than 2%.¹ The selection of antibiotics for different patient populations depends on factors such as the severity of their condition, response to treatment, and the potential for antibiotic resistance. It is important to adjust the antibiotic dose for each case based on the patient's age and body weight (Table 2).¹⁰ Duration of antibiotic treatment is 10-14 days. A shorter course may result in early relapse of enteric fever.

Vaccination

In the 1980s, two newer-generation vaccines with good tolerance were introduced that promised protection without significant side effects: the live, attenuated oral vaccine Ty21a, and the Vi-polysaccharide (Vi-PS) vaccine. Both parenteral Vi-PS vaccine and the oral Ty21a vaccine have demonstrated safety and efficacy in preventing clinical typhoid disease. Vi-PS, prequalified by WHO in 2011, is licensed as a single-dose vaccine for individuals as young as 2 years of age.^{3,15}

Supportive care

Besides antibiotics, symptomatic and supportive care such as bed rest, tepid sponging, antipyretics like

Box 1: General principles for the management of typhoid^{9,14}

- Rapid diagnosis and initiation with appropriate antibiotic therapy
- Maintain adequate rest and hydration and correct fluid-electrolyte imbalance
- **Administer antipyretic therapy as needed, such as paracetamol 120-750 mg PO every 4-6 hours**
- Ensure adequate nutrition with a soft, easily digestible diet, unless abdominal distension or ileus is present
- Emphasize on hand hygiene and limit close contact with susceptible individuals during the acute phase of infection
- Ensure regular follow-up and monitoring for complications and clinical relapse, including stool clearance confirmation in non-endemic areas or high-risk groups like food handlers

paracetamol, proper oral hydration, and appropriate nutrition are essential components of supportive treatment for all cases of typhoid fever (Box 1).^{9,14}

PARACETAMOL IN TYPHOID FEVER

Typhoid fever often presents with prolonged, debilitating fever and systemic symptoms. Even when successfully treated with 2- to 3-day courses of fluoroquinolones, a considerable proportion of patients may not experience fever relief until after completion of antibiotic treatment, despite negative blood cultures and no recurrence of infection. This prolonged fever not only delays functional recovery but also raises concerns about treatment adequacy and increases hospitalization costs. Regular antipyretic treatment can help to alleviate this issue. In this context, paracetamol is considered one of the most appropriate drugs for this role. This approach provides relief from fever-related discomfort and debility, offering a practical solution to the persistence of fever and its associated challenges in typhoid fever management.¹⁶

Paracetamol has evolved into the most widely used non-narcotic, over-the-counter analgesic for managing mild to moderate pain and fever. It is the most frequently prescribed drug for both pediatric and adult patients with fever.^{17,18}

In a double blind randomized study involving 80 children with uncomplicated typhoid fever, it was shown that reduction in fever clearance time was not statistically significantly different with paracetamol or ibuprofen ($p=0.055$). Moreover, among children with nalidixic acid-susceptible typhoid fever, fever clearance time was similar with paracetamol or ibuprofen (68 h). Abdominal discomfort and diarrhoea were less frequent

in children treated with paracetamol as compared to those treated with ibuprofen.^{16,19}

CONCLUSION

Typhoid fever, also known as enteric fever, is a systemic illness characterized by a "step-ladder" fever pattern, headache, and abdominal pain. It has historically been a major public health concern in the developing world, particularly South Asia, including India. Early diagnosis and prompt antibiotic therapy for a duration of 10-14 days with good compliance lead to symptom improvement within days and total cure of the disease with least chance of recurrence. Supportive care with paracetamol, an effective antipyretic, is vital to manage prolonged fever and its associated challenges. Paracetamol is widely used for fever management in typhoid cases. It can effectively reduce fever clearance time and improve patient comfort.

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