A Handbook for Paediatric Care

FEVER

From Evidence to Action

Compilation of articles from

FeFCon-2018

Fever Foundation Conference 2018, Bengaluru

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FOREWORD

Fever in children

Children are uniquely predisposed to fever. This is because of their ever changing physiology and seeking to find a homeostasis with the myriad microorganisms that surround them. Fever most of the time is benign in nature and self-limiting. However it is a major cause of anxiety in parents and caregivers who have myths around fever.

Some infants and toddlers may convulse when the fever rises. Parents facing this for the first time may have misconceptions and apprehensions forcing them to overreact and over treat. Infections are not the only cause of fever. Many immune mediated diseases and childhood cancers can also present with fevers.

Irrational beliefs make parents want to go down the path of ever increasing investigations and potent medications. Such beliefs are common amongst medical practitioners too. It is left to the astute health care worker to ascertain the cause of fever and counsel parents to manage appropriately.

The Fever foundation envisages to just doing this. To sensitise not only to recognise, investigate and treat fever but also to act as a sounding board for parents to rely on. This would be done by disseminating evidence based information to all the stake holders. This book is an example of that endeavour.

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PROLOGUE

Fever Foundation is an Independent, non commercial foundation supporting the educational/ academic activities to address the unmet needs in fever management. The foundation is committed to conceive, build, and sustain programs and make scientific initiatives aimed at providing evidence based updates to the health care professionals.

The First Annual National conference of Fever Foundation, FeFCon 2018 was held on 17th and 18th November, 2018 at Le Meridien, Bengaluru. Interesting presentations by highly esteemed and renowned speakers from across India was delivered in the two days academic feast.

This book is the salient capture of the sessions on fever management which can be of substantial help in day to day practice.

Happy Reading!

Dr Manjula S
Organizing Secretary,
FeFCon 2018

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Myths around fever

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Introduction

Myth is a traditional story, especially those which explains the early history, a cultural belief, practice of a group of people or a natural event.[1] Existence of myths can be traced from time immemorial. Humoral theory, put forwarded by Hippocrates, is one of the fever-related myths and it continued for many centuries. According to this theory, illness is caused by an imbalance of the four humours: blood, phlegm, black bile and yellow bile.[2] Philippus Aureolus Paracelsus is the first person who debunked the humoral theory and identified that illness has external causes (rather than an imbalance of humours). He replaced traditional remedies with chemical remedies.[3]

Based on the book *History of Science, Technology and Medicine in India* by O P Jaggi; during the Raj times, Dr. Twinning and Dr Morehead are the two famous personalities who studied more about fever. They have identified the following three types of fever in India:

- Intermittent and continuous fever of summer
- Remittent fever of rains
- Insidious congestive fever of winter

In the last century, there were several myths surrounding the causes and treatment of fever. Some of the myths related to fever in India have ascribed idiopathic fever to vicissitudes of temperature, increased heat, violent exercise, excitement of mind, excessive eating, intemperate habits, and imperfect excretion. Some of the common myths confronted by clinicians during clinical practice and their facts are discussed in the following sections.

MYTH-1. The forehead of my child is very hot and legs are cold; hope it is not the beginning of brain fever.[4]

The fact is that a child's forehead can feel warm due to many reasons like increased blood supply to the surface area, playing hard, crying, soon after getting out of a warm bed and due to hot weather. The parents should be instructed to measure the temperature at the following different sites and identify the fever.

- Rectal (bottom), ear or forehead temperature: 100.4°F (38.0°C) or higher
- Oral (mouth) temperature: 100°F (37.8°C) or higher
- Under the arm (Armpit) temperature: 99°F (37.2°C) or higher

MYTH-2. All fevers are bad for children.[5]

The fact is that the fever is a symptom of an underlying infection. It activates the body's immune system and helps to fight against infection. Fevers between 100° and 104°F (37.8°- 40°C) are good and it helps in clearing the cause of infection.

MYTH-3. Fevers above 104°F (40°C) are dangerous. They can cause brain damage.[4]

Fever due to infections does not cause brain damage, unless it is due to meningitis or encephalitis. Only temperatures >108°F (42°C) with infection can cause brain damage. Such temperatures are rare and seen only in hyperpyrexia secondary to heat stroke or drug reaction.

MYTH-4. My neighbour's child developed fits after fever. Should I also aggressively treat my child's fever to prevent fever-related fits?[5]

Only 4% of the children can have a seizure accompanied by fever. Controlling the fever is going to prevent fits and aggressive treatment is not likely to prevent convulsion.

MYTH-5. If my child gets a fever-related seizure, he may get epilepsy in future.[4]

Fever in a child does not increase the risk for speech delays, learning problems or epilepsy.

MYTH-6. All fevers need to be treated with fever medicine.[6]

Fevers need to be treated only if they cause discomfort. The child does not need any antipyretics if active with 99°F temperature. Most fevers do not cause any discomfort, until they progress beyond 102° or 103°F (39° or 39.5°C).

MYTH-7. Without treatment, fevers will become higher.[4]

Thermostat in the brain regulates the temperature. Most fevers due to infection do not progress >103° or 104°F (39.5°- 40°C).

MYTH-8. With treatment, fevers should come down to normal.[7]

Treatment assists in reducing the fever by 2° or 3°F (1° or 1.5°C). Administration of antipyretics helps in marginal reduction of fever and decreasing the discomfort. The higher the fever, the larger the decrease in temperature with medication.

MYTH-9. Once the fever reduces with medicines, it should stay down.[5]

In most cases, fever due to viral infections persist for 2 or 3 days and it may return with reduction in response to the effect of medication. Once the immune system is able to overpower the infection, the fever will gradually reduce, mostly in 3 to 4 days.

MYTH-10. If the fever is high, the cause is serious.[7]

If the fever is high, the cause may or may not be serious. If the child is looking very sick, there is increased probability of underlying cause to be serious. If the child is playful after the reduction of fever with antipyretics, the cause of the fever may not be serious. The activity and the behavior of the child are more important than the fever by itself.

MYTH-11. The exact number of the temperature is very important. It is necessary to monitor the fever accurately.[4]

How the child appears and behaves is more important that the exact number of the temperature.

Myth-12 -Strict diet control is necessary in a child with fever. Some foods like rice will aggravate fever. "Feed a cold, starve a fever."[5]

No diet control is necessary in most cases of fever. Increasing fluid intake is very important (12% for every degree persistent rise). It will prevent dehydration and the child will pass adequate urine.

Myth-13. Sponging with ice cold water reduces temperature faster than warm water.

Ice water increases vasoconstriction and prevents heat exchange.[8] It is recommended to use tap water. It will slightly increase the vasodilatation and improve the heat exchange.

Myth-14. It is important to give antipyretics round the clock.

Antipyretics are used for making the child comfortable and not for keeping the temperature down.[7]

Myth 15. My family does not respond to oral medicines; please give injection.

The action of antipyretics is the same, irrespective of the route of administration (oral, rectal or parenteral). Parenteral route is not necessary for common fever.

Myth 16. I have already given 4 bottles of paracetamol, my child's liver will be damaged.

Therapeutic doses of paracetamol do not cause liver damage, unless the liver is already damaged. The toxic dose is close to 200 mg/kg/day; and in general practice, it rarely crosses 60 mg/kg/day.[9] It is important to communicate the right dose to the parents. Chewable tablets and concentrated drops are more likely to cause damage.

Conclusion

Many parents have most of the aforementioned false beliefs regarding their child's fever. They lose their peace and sleep, thinking that fever will harm their child. Clarifying the parental misconceptions by pediatricians helps them to better understand the fevers and the right ways to manage them.

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Fever pathophysiology

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Introduction

Fever, an adaptive mechanism noted in vertebrates in response to an infection, is caused by substances known as pyrogens.[1] These pyogenes may act directly or indirectly on the hypothalamic thermoregulatory center. The present paper summarizes control mechanisms of body temperature, the circadian rhythm of body temperature, pathogenic and physiologic factors associated with the temperature elevation, normal and abnormal body temperature, etiologic classification of fever and treatment of the fever (in high-risk patients).

Control mechanisms of body temperature

Fever is defined as any elevation of body temperature mediated by an increase in the hypothalamic heat regulatory set-point.[2] The body maintains its core temperature at around 37° C by physiological adjustments mediated by the brain, more specifically hypothalamus. The preoptic area of hypothalamus serves as temperature-regulating centers (the anterior portion). This area receives signals from the peripheral cold and warm neuronal receptors present in the skin and mucous membranes (peripheral thermoreceptors) as well as from central thermoreceptors (from internal structure. The sensory signals from the preoptic area and periphery are combined in the posterior hypothalamus to regulate the heat generating and conserving reactions of the body. Other hypothalamic, autonomic and higher nervous thermoregulatory centers also play a crucial role in keeping the temperature constant.[3]

The hypothalamus sends signals to the skin, glands, muscles, and organs for regulating the temperature (Fig. 1). For example, when the body senses hot external environment or high levels of exercise activity, the temperature of the body rises, causing the hypothalamus to send signals to the skin cells for producing sweat and for inhibition of the adrenergic activity of the sympathetic nervous system. This in turn causes cutaneous vasodilation and basal metabolic rate (BMR) reduction. In contrast, in response to a cold environment, the body sends signals for shivering reflex and activation of arrector pili muscles in the skin. These processes in turn assist in bringing warmth and heat to the body.[4] The gradual decrease in environmental temperature contributes to the release of thyroid stimulating hormone (TSH), which in turn induces thyroid gland to increase metabolic rate to increase the production of body heat. As the body gets warmer, the hypothalamic sensors reduce the heat production and the stimulus activating heat loss prevention responses.[3] The factors determining the rate of heat production in the body include: BMR, muscle activity, and effects of thyroid hormones, epinephrine and norepinephrine.

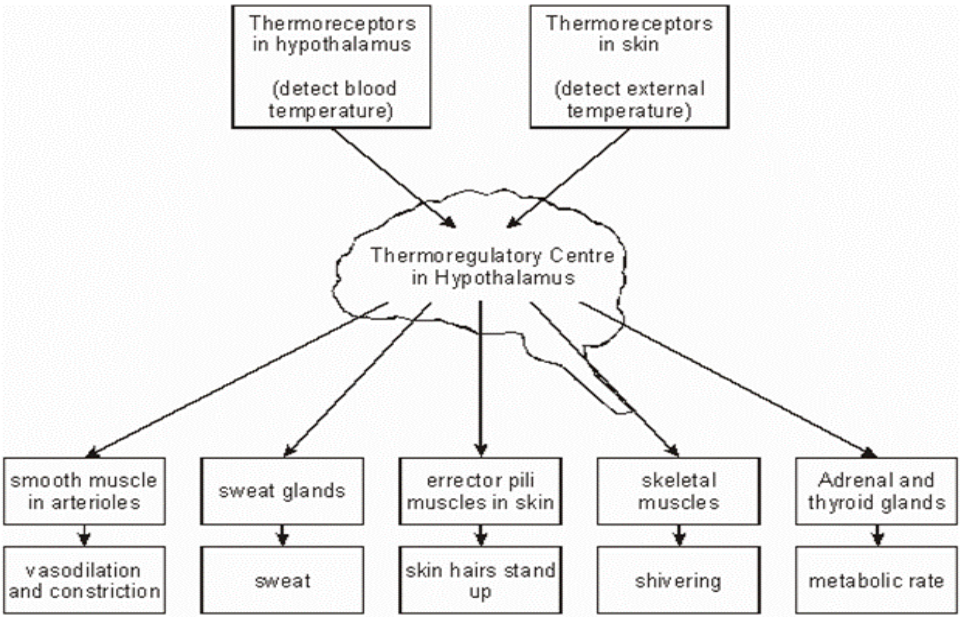

Fig. 1: Action of thermoregulatory center in hypothalamus[5]

The mechanisms through which the body regulates the temperature are listed below:[6]

Heat loss

- Radiation: Loss of heat from body in the form of infrared rays.
- Conduction: Heat is conducted from body to objects in contact, e.g. chair, bed, etc.
- Convection: Heat is lost from body through air currents.
- Evaporation: Evaporation of water from body surface in the form of sweat
- Vasodilation

Heat production

- Increased cell metabolism
- Muscle activity
- Involuntary shivering
- Heat conservation
- Vasoconstriction

Stages of fever

The fever generally develops through 4 stages. However, not all patients pass through all the 4 stages. The stages noted are describe below:[7]

- Prodromal stage

The patient may show non-specific symptoms including fatigue, mild headache, general malaise and body pain

- Second stage

In this stage, the patient's skin may appear pale with generalized shaking, chills and feeling of being cold. Vasoconstriction and piloerection are commonly noted.

- Third stage or flush

The patient feels too hot, as the cutaneous vasodilation makes the skin warmer and flushed.

- Defervescence

The patient's body temperature becomes normal and the stage is marked by sweating.

Pathogenesis of fever

Bacterial products and other external fever-causing substances constitute exogenous pyrogens.[8] For example, lipopolysaccharide (endotoxin) of gram-negative bacteria and enterotoxins of *Staphylococcus aureus*. Whereas endogenous pyrogens are host-derived, fever producing molecule (example: cytokines). Pyrogenic cytokines include IL-1, IL-4, IL-6, TNF, ciliary neurotropic factor (CNTF), IFN-alpha.[8] The endogenous pyrogenic cytokines mediate the resetting of temperature regulatory set point through prostaglandin E2. The fever response to endogenous pyrogens happens within 10-15 minutes, the response to exogenous pyrogens may take 60- 90 min, as it requires the production and release of pyrogenic cytokines.

Physical factors influencing body temperature

Gierse in 1842 studied the circadian rhythm of core body temperature based on his own oral temperature. The researcher demonstrated that minimum temperature occurs early morning and the maximum in the early evening between 4-6 PM.[9] The physical factors that may influence the body temperature include physical activity (maximum 1.1° C), digestion, changes in environmental temperature, after ovulation in women, first 3 months of gestation and excitement.[10]

The comparison table given below provides the approximated range of fever for each type of fever

Table 1: Temperature scales based on the fever grade

Fever grade	Celsius (°C)	Fahrenheit (F)
Hypothermia	<35	<95
Subnormal	35-36.7	95-97
Normal	36.7-37-2	98-99
Mild fever	37.2-37.8	99-100
Moderate fever	37.8-39.4	100-103
High fever	39.4-40.5	103-105
Hyperpyrexia	>40.5	>105

Patterns of fever

Though the clinical usefulness of fever patterns is still unclear, generally 5 patterns are noted. The 5 patterns are intermittent, remittent, continuous or sustained, hectic, and relapsing. The characteristics and examples of each pattern is listed in table 2.[11]

Table 2: Characteristics and examples of each fever pattern

Fever patterns	Characteristics	Examples
Continuous fever	Temperature >37°C throughout the day, does not fluctuate > 1° C in 24 hrs	Lobar pneumonia, urinary tract infection, infective endocarditis, brucellosis
Remittent fever	Temperature may persist above normal throughout the day, fluctuate > 1° C in 24 hrs	Typhoid, viral upper respiratory tract, legionella, mycoplasma infections
Intermittent fever	Elevated temperature persists for some hours in a day and remits to normal	Pyogenic infection, lymphoma, miliary TB
Relapsing fever	Fever spikes are noted with intermittent normal temperature for days or weeks • Daily spike- quotidian • Every alternate day- Tertian • Every third day –Quartan	Malaria, kala-azar, cholangitis, infections with *Borrelia recurrentis,* Hodgkin's disease (Pel-Ebstein fever), and other neoplasms

Diseases with distinct fever patterns

Some diseases are associated with characteristic fever pattern. Aseptic fever is noted in: acute myocardial infarction, sarcoidosis, chronic renal failure, collagen vascular diseases, drug fever, radiation sickness, and post-surgical patients. Some of the diseases with distinct patterns are discussed below:[11]

Drug fever

It is characterized by prolonged fever, relative bradycardia and hypotension. It persists 2-3 days even after drug is withdrawn. Eg. fever related to penicillin, procainamide, propylthiouracil, sulphonamides, and anticonvulsant.

Fever with relative bradycardia

This characteristic fever pattern is noted in typhoid fever, meningitis, viral fever (influenza), brucellosis, leptospirosis and drug-induced fever.

Fever with rigors

This pattern is generally found in malaria, kala azar, UTI, septicemia, infective endocarditis, Collection of pus in body, lobar pneumonia, cholangitis and pyelonephritis.

Fever with rash

In chicken pox, the rashes appear on the 1st day of fever. Whereas, in measles and typhoid, the rashes commonly appear on the 4th and 7th day respectively.

Fever with delirium

It is commonly seen in encephalitis, typhoid, meningitis and hepatic encephalopathy.

Hyperpyrexia

The extremely elevated temperature beyond 105°F is termed as hyperpyrexia. The causes include: pontine hemorrhage, rheumatic fever, meningococcal meningitis, cerebral malaria, septicemia and encephalitis.

Pyrexia of unknown origin (PUO)

The key features of PUO are persistence of temperature >102.2°F, fever >3weeks duration and failure to conclude the diagnosis even after 1 week of evaluation. The causes of PUO include: abscesses – subphrenic / liver / retroperitoneal, UTI, endocarditis, hepatobiliary infections, osteomyelitis, HIV, parasitic infections, malignancy, collagen vascular disease, factitious fever, hyperthyroidism and sarcoidosis.[12] The following are the malignancies associated with PUO: Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, hepatoma, renal cell carcinoma and colon cancer.

Neuroleptic malignant syndrome

It is a rare, life-threatening, idiosyncratic reaction to neuroleptic medications. The disease is characterized by lead pipe muscle rigidity, extrapyramidal side effects, autonomic dysregulation and hyperthermia. The disease is generally indistinguishable from malignant hyperthermia. The drugs that can cause the syndrome include succinylcholine, phenothiazine, haloperidol fluoxetine, loxapine etc.[13]

Malignant hyperthermia

It is a rare autosomal dominant disorder that manifests as a hypermetabolic reaction to volatile anesthetic agents (e.g., desflurane, enflurane, halothane, sevoflurane) or the depolarizing muscle relaxant, succinylcholine. Absence of the hypothalamic regulated circadian rhythm is seen in affected subjects. It is also noted in patients with various myopathic disorders.[14]

Limitations of current treatment

The use of antipyretic therapy is controversial in normal children, as it does not alter the course of common infectious diseases.[15] It is recommended in high-risk patients with chronic cardiopulmonary diseases, metabolic disorders, neurologic diseases and febrile seizures. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the commonly used antipyretic agents with proven antifever effect.[16]

The widely used NSAIDs include aspirin, ibuprofen and acetaminophen. Studies report that administration of aspirin may increase the risk of Reye's syndrome.[17] High dose acetaminophen is associated with renal injury and hepatic failure. The continuous use of Ibuprofen may increase the risk of dyspepsia, gastrointestinal bleeding, reduced renal blood flow, aseptic meningitis, hepatic toxicity, and aplastic anemia.

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Immunology of fever and interpretation of immune markers

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Introduction

Inflammation is body's natural response against any external or internal stimuli that perturb the normal homeostasis.[1] Although inflammation was initially noted as a part of simple clinical symptoms; over the years, it has evolved to define a more complex phenomenon. Despite the recent advances in understanding immunology, the exact definition of inflammation is still uncertain.

Over 600 million years of evolution, fever has evolved as a cardinal response to infection that has been conserved in vertebrates.[2] Integrated physiological and neuronal circuitry is essential for executing fever response during infection and it offers a survival benefit.[2] Generally, elevated body temperature helps the person to resolve an infection and the recent research has identified that fever enhances the functioning of certain immune cells.[3] However, in certain scenarios, the increase in temperature may be too high, which can be serious leading to several complications.[4]

Even the temperature elevation is seen in highly localized inflammation like cellulitis. This response, termed as calor, is one of the cardinal signs of inflammation. In general terms, it is considered as fever. The fever response, which has been identified as a hallmark of infections and inflammatory diseases, assists in limiting the multiplication of infectious agents and enhancing the host immunological response against infections.[5] Febrile temperature is closely associated with inflammatory response, subsequently contributing to survival and resolution of infections.[2]

Elevated temperature enhances the innate immunity

Fever-range temperatures play a paramount role in triggering several important aspects of innate immunity. They induce the production of neutrophils from the bone marrow in a granulocyte–colony-stimulating factor (G-CSF)-driven manner. They are responsible for neutrophil recruitment to the lungs and other local infection sites in a CXC-chemokine ligand 8 (CXCL8)-dependent fashion. The thermal stress at the site of infection further accentuates the respiratory burst, which in turn contributes to the bacteriolytic activity of neutrophils. Thermal treatment enhances the cytolytic activity of natural killer (NK) cell in 2 ways: 1) induction of MHC class I polypeptide-related sequence A (MICA) expression on target cells (for example, tumor cells) 2) promoting the clustering of the MICA counter-receptor NKG2D on the surface of NK cells.

The febrile-range temperatures enhance the potential of antigen-presenting cells in eliciting adaptive immune response. The phagocytic potential of the macrophages and dendritic cells (DCs) is enhanced by the heat and it also improves their responsiveness to invading pathogens by increasing the expression of both Toll-like receptor 2 (TLR2) and TLR4. Elevated temperature also enhances the production of various immunomodulatory molecules such as cytokines (for example, TNF), nitric oxide (NO) and heat shock protein 70 (HSP70). It also enhances the expression of MHC class I and II molecules as well as co-stimulatory molecules (CD80 and CD86) by mature DCs and their CC-chemokine receptor 7 (CCR7)-dependent migration via the afferent lymphatics. The exposure of DCs to febrile temperatures improves their efficiency in cross-presenting antigens and inducing T helper 1 (Th1) cell polarization.[2]

Elevated temperature and adaptive immune response

In lymph nodes, fever-range temperature augments adaptive immunity by targeting two distinct aspects of T cell activation. In peripheral lymph nodes, the effects of heat on each step of the adhesion cascade enhance the rate of lymphocyte trafficking across high endothelial venules (HEVs). The heat exposure of lymphocytes increases the frequency of L-selectin-dependent tethering and rolling interactions. The independent action of febrile-range temperatures on HEVs improves the transition of lymphocytes from transient rolling to stable arrest by enhancing the intravascular density of CC-chemokine ligand 21 (CCL21) and intracellular adhesion molecule 1 (ICAM1). Lymphocyte crawling to inter-endothelial cell junctions and transendothelial migration are also supported by ICAM1. Within the lymphoid organs, elevated temperature has a direct effect on the T cells by pre-clustering components of the immunological synapse (TCRβ and CD8) into lipid rafts. This assists in persisting the contacts with APCs and promoting $CD8^+$ T cell differentiation towards an effector phenotype marked by enhanced cytotoxic function, L-selectin downregulation, and production of interferon-γ (IFNγ) (Fig. 1).[2]

Increased temperature helps in achieving optimal immune response, but at the cost of elevated metabolic and neuro-endocrinal functions.

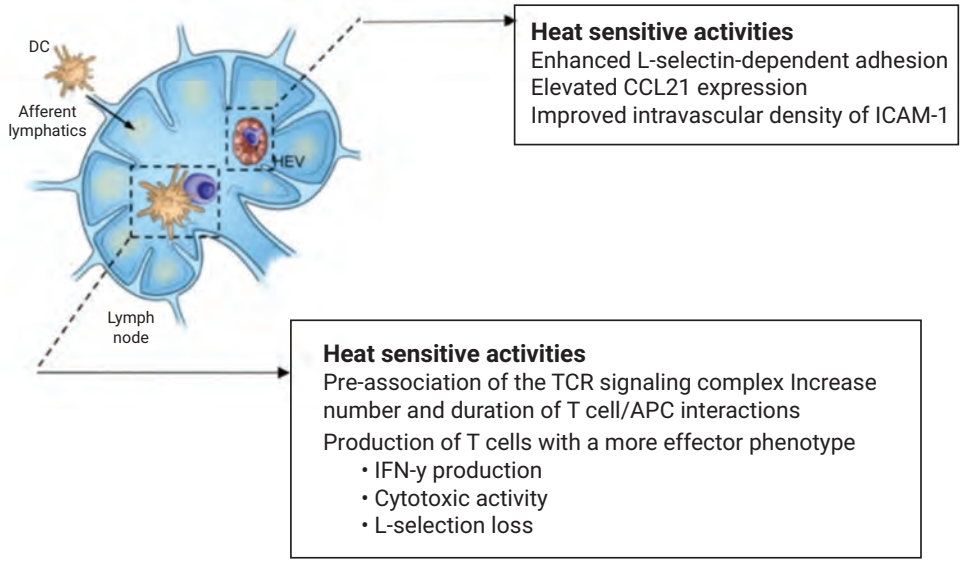

Fig. 1: Role of elevated temperature in eliciting adaptive response[2]

Markers of inflammation

The inflammation may be intense and may sometimes spill over to the surrounding milieu. This may be reflected in multiple organs at various levels. Hence, a measure of inflammation should consider all the associated factors to quantify the effect. The markers of inflammation may depict different perspective of this spill. For example, acute phase response from the liver for the localized inflammation (septic arthritis) suggests a systemic spill. This effect depicts the quantum of spill rather than the intensity of inflammation (Fig. 2).[6]

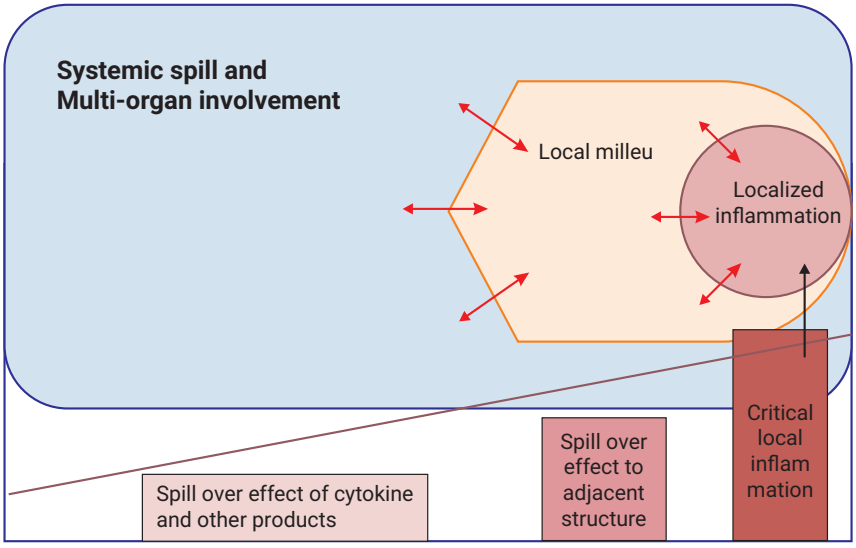

Fig. 2: Effects of inflammation at various levels and sites

The observable variables, indicating inflammation, can be broadly classified as clinical variables and biological markers. The clinical variables assist in qualifying and quantifying the cause of inflammation. Whereas, the biological markers employed represent different stages of inflammation. Several possible ways to measure an inflammation are depicted in figure 3. Acute phase responses occur as a consequence of inflammation. They assist physician in decision making on management strategies.

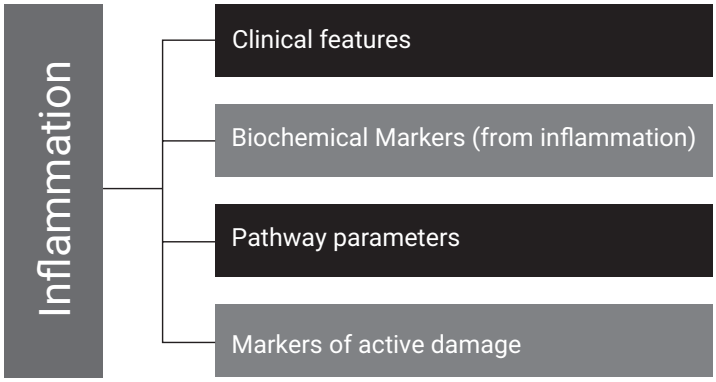

Fig. 3: potential biomarkers of inflammation

The role of inflammatory parameters, especially in acute phase response, is already well established in clinical conditions like fever and infections, autoimmune diseases including rheumatological disease, and in risk profiling of cardiovascular diseases.[7] The probable role of inflammatory parameters is yet to be established in cancer treatment, diabetes and other metabolic syndrome, ischemic heart disease and stroke, psychiatric disorder and neurological disorders of degenerative nature. Increase in the levels of serum proteins, which are referred as acute phase reactants (APR), occur as a consequence of set of systemic and metabolic changes associated with inflammation. Increase in APR levels is noted in tissue injury, infection, trauma, rheumatoid and systemic inflammatory disease, advanced malignancy, child birth, and sometimes in extraneous exercise.[8] APRs are highly non-specific and need to be investigated along with other clinical features. Assessment of clinical features, along with APR, assists in regionalizing the site of inflammation/infection as well as in identifying the reason for altered lab investigations. CRP, ESR, procalcitonin and ferritin are already established parameters used to measure inflammation. The role of other parameters like NLR, PLR, IL6 and other hematological parameters is yet to be established.

Some of the markers like pro-calcitonin may indicate the cause for the inflammation. Their levels assist in concluding the presence of infection. NLR ratio can suggest the possibility of sepsis and increased mortality. Non-specificity is the major limitation of these inflammatory markers. Their ratios and proportions may vary, based on the etiological factors responsible for the trigger, and they are yet to be elucidated.

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Investigating a fever outbreak -An overview

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Introduction

According to World Health Organization, *"a disease outbreak is the occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season".* The extent of outbreakmay vary from a limited area to several vast countries.[1] The present review discusses how the investigations need to be carried out for a fever outbreak, which helps in preventing similar outbreaks happening in the future.

Fever investigation: Basics and objectives

Investigating a fever outbreak is necessary to identify the source of illness and to formulate guidelines on public health intervention. An outbreak can be recognized through surveillance activities (e.g. Integrated Disease Surveillance Program[IDSP])and by analyzing the reports of clinicians, laboratories, press and media.[2]

The key objectives of outbreak investigations are:[3]

- To control ongoing outbreaks and prevent future outbreaks
- To provide statutorily mandated services
- To strengthen surveillance at local level
- To advance knowledge about a disease
- To provide training opportunities

Steps involved in outbreak investigations

The following are the steps to be followed for investigating an outbreak (Fig. 1).[4]

1. Verify the diagnosis and confirm the outbreak
2. Define a case and conduct case finding
3. Tabulate and orient data: time, place, person
4. Take immediate control measures
5. Formulate and test hypothesis
6. Plan and execute additional studies
7. Implement and evaluate control measures
8. Communicate findings

In practice, it may be inevitable to do several steps simultaneously or to follow a different order, depending on the circumstance of the outbreak.[5]

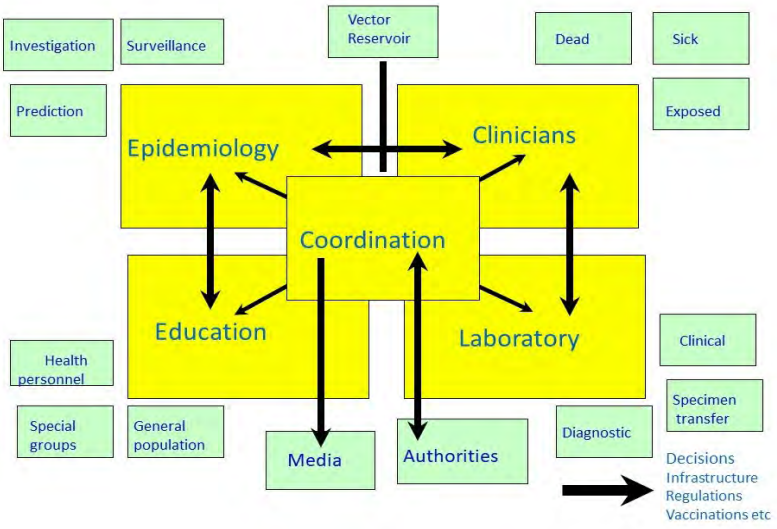

Fig. 1: Flow chart depicting the coordinated team work involved in outbreak investigation

1:Verify the diagnosis and confirm the outbreak

The primary step is to confirm the diagnosis through laboratory tests after ruling out misdiagnoses and laboratory errors. The occurrence of outbreak, i.e. the exact number of cases in excess of normal expectancy, needs to be established. It is important to compare current data with previous incidence happened in the area during the same timeof the year to establish whether the observed number of cases exceeds the expected.[6]

2. Define a case and conduct case finding

This step involves developing a case definition based on symptoms or lab results, time period and location. This is followed by conducting surveillance for identifying and counting cases. The two types of surveillance carried out are passive surveillance (e.g. cases coming to health centres/hospitals) and active surveillance (e.g. community searches, review medical records, etc.);interviewing and

examination of patients are performed to establish the cases.[6]

3. Tabulate and orient data

Investigators should organize the data obtained from medical records and patient interviews in a line listing (Fig. 2).[7]

		Signs/Symptoms			Labs	Demographics	
Case #	Date of Symptom Onset	Diarrhea	Vomiting	Fever >37°C	Positive stool culture	Age	Gender
1	22/10/05	Y	Y	Not done	Y	19	M
2	25/10/05	N	Y	N	N	17	M
3	22/10/05	N	Y	N	Y	23	F
4	27/10/05	Y	?	?	Pending	18	?
5	23/10/05	N	Y	N	Y	21	M
6	21/10/05	Y	Y	Y	Not submitted	18	F

Fig. 2: Example of a line listing

Creating a line listing assists in easy tabulation of the data, and organizing and reviewing the information about place, time and person. The person details to be entered include: who was affected and what do the cases have in common.[8] Each row indicates a different case and each column an important variable (e.g. identifier, age, gender, Fig. 3).

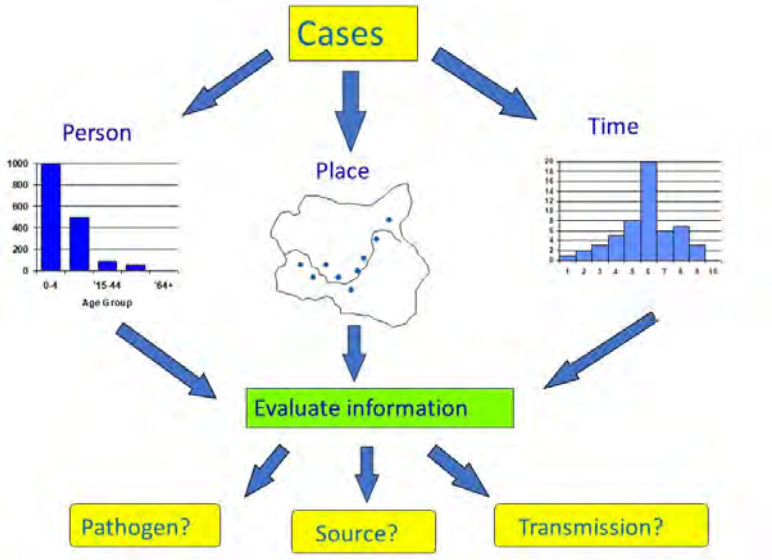

Fig 3: Flow chart depicting the tabulation of data

The location details to be collected include estimating the attack rates of cases at different locations such as at the place of employment, residence and at the site of exposure. Location with increased attack rates signifies the source of infection. Drawing a spot map with locations is helpful to identify the source of infection (Fig. 4). Moreover, it can provide clues to potential exposure patterns.

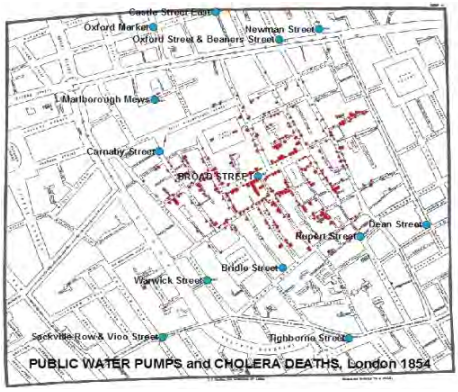

Fig. 4: Spot map of outbreak of cholera in London, 1854

It is recommended to draw an epidemic curve to depict the frequency of new cases over time, based on the date of disease onset. Examples of epidemic curves are point source, continuing common source and multiple waves-person to person or further outbreak. These forms of distribution assist in proposing the nature of the disease and mode of transmission (Fig. 5).[9]

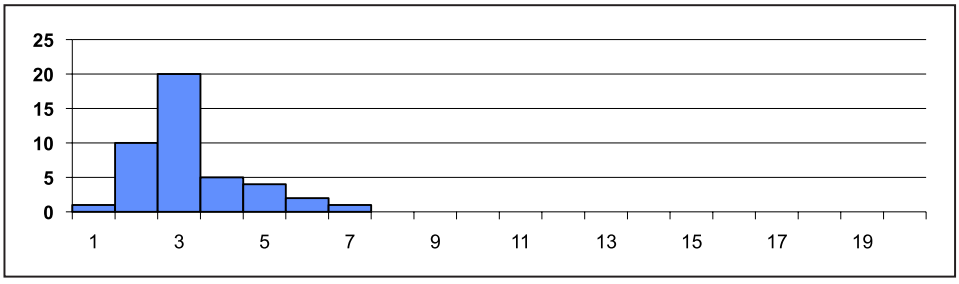

Fig. 5: Point source epidemic curve

4. Take immediate control measures

The outbreak investigation team comprises of epidemiologist, clinician, public health personnel, microbiologist/lab personnel and others. Conducting public heath announcement and implementing plant closure or product recalls are examples for control measures.[7]It is necessary to take immediate control measures, if an obvious source of contamination is identified. The use of barrier and isolation precautions are important infection control measures.[10]

5. Formulate and test hypothesis

Formulating a hypothesis helps in understanding the source of outbreak, the most probable cause and the case distribution. Developing a hypothesis requires reviewing of literature of previous outbreaks, conducting patient interviews, and evaluating the microbiology and epidemiology of the pathogen. In order to test the hypothesis, it is necessary to conduct analytic studies such as case control and retrospective cohort studies.[7]

6.Plan and execute additional studies

It is advocated to parallelly perform environmental sampling. If analytic study results are conclusive, it is necessary to implement preventive measures before obtaining positive samples of infection.

7. Implement and evaluate control measures

In the final stages of outbreak investigation, the team needs to closely work with health educators, directorate, and public health personnel to implement infection control measures. These measures are aimed at preventing further exposure and future outbreaks by eliminating or treating the source. The team should formulate mechanisms to assess the short- and long-term success of infection control.

8. Communicate findings

At the end, the team should summarize investigation, make recommendations, and disseminate report to authorities, all participants and stake holders. Communication within the team and with public is crucial for the success of outbreak investigation. One individual from the team should serve as the point of contact (usually epidemiologist) to interact with media and communicate the progress and findings.[7]

Conclusion

This paper provides a brief summary ofoutbreak investigation to be carried out to plan and implement necessary measures to control outbreak and to prevent further infections. Investigations help in identifying risk factors associated with outbreaks,andproviding newer researchinsights on the emerging pathogen. Only by participating ininvestigations repeatedly, public health professional scan learn the 8-step process of outbreak investigations.

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Serological markers in fever

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Introduction

Fever can be referred to a Pandora's box, as it is surrounded by so many mysteries. The proper investigation of fever is important, as it provides important diagnostic clues. This review discusses the microbiological experiences with fever from the perception of a physician, which could assist in fever investigation.

Epidemiology and causes

Fever is highly variable. In western countries, inflammatory causes are more common and infection plays a major role in causing fever in low- and middle-income countries. The most commonly reported infections are enteric fever, brucellosis, tuberculosis, endocarditis and intra-abdominal abscesses.[1]

The infectious etiologies of fever include enteric fever, tuberculosis, dengue/viral fever, malaria, leptospirosis, brucellosis, typhus fever, focal abscesses, infectious mononucleosis, and infective endocarditis. The non-infectious etiologies include connective tissue disorders, autoimmune disorders and malignancies.[1]

History collection

The methodology to investigate a fever starts from the history. A careful history should be comprised of previous infectious illnesses, family history of infection, exposure to similar infections, residence and country of origin, recent travel, zoonotic exposure and leisure activities. Physical examination

requires special attention to the eyes, heart, spinal tenderness point, liver/spleen, lymphadenopathy, skin lesions and oropharynx.[1]

Approach to undifferentiated fever

Thangarasu et al. (2011) have formulated a protocol to manage acute undifferentiated febrile illness in adult Indian patients. The interesting article, published in the *International Journal of Emergency Medicine*, suggested how to carry out the investigation of an undifferentiated fever in the OPD. According to the protocol, if the patient presented with fever to the outpatient department is a case of sepsis, the sepsis protocol should be followed. The authors recommended to carry out investigation of localizing signs, if present, or to go by the day of fever. Only symptomatic treatment is required on the day 1 or 2 of the fever and antimicrobials should be deferred. On day 3 or 4, it is advocated to perform WBC count, malaria parasite detection by quantitative buffy coat and urine routine examination. On day 5 or 7, blood cultures, liver function test, dengue serology and Weil-Felix test can be carried out based on the requirement. The study has reported non-specific infection (n=107) in majority of the subjects, followed by dengue (n=21), malaria (n=21), UTI (n=16), enteric (n=14) and other specific diagnosis (n=20).[2] D'Acremont et al. (2014) has reported higher incidence of malaria (23%) among Tanzanian children. The common cause of febrile illness noted in children included non-bacterial infection such as the upper respiratory tract infection (15%), non-radiologically (16%) and radiologically (6%) confirmed pneumonia, UTI (4%), nasopharyngeal infection (4%) and meningitis (1.2%).[3]

Basic laboratory and radiology to start with

The basic laboratory investigations include CBC, peripheral blood smear, erythrocyte sedimentation rate, CRP, liver function tests, and blood and urine culture. Radiological investigations such as the chest radiograph, CT and MRI scans of the abdomen and pelvis are performed, if required.[1]

CBC is the most important non-definite investigation performed in cases with fever. The observations from CBC are suggestive of the following diseases:

- Leukopenia: enteric fever, TB, HIV, SLE
- Leukocytosis: pyogenic infection, vasculitis
- Reactive lymphocytosis: EBV, CMV
- Eosinophilia: drug reactions, parasitic infections
- Eosinopenia: enteric fever
- Thrombocytosis: pyogenic infection, inflammation
- Thrombocytopenia: malaria, SLE, HIV
- Pancytopenia: bone marrow infiltration, SLE

Liver function test also play a vital role in the investigation. Elevated ALT/AST indicates viral hepatitis or infectious mononucleosis. Elevated alkaline phosphatase and gamma glutamyl transpeptidase indicate granulomatous hepatitis, sepsis or cholangitis.[4]

Segal et al. (2014) have reported CRP as the most useful marker in children to differentiate bacterial and viral infections. CRP increases during the first 36 h of fever and declines more rapidly with viral infections. Ina patient with fever duration >24 hours, If CRP is >11 mg/dL, the probability of having a

bacterial infection is 75%; whereas if CRP is ≤5 mg/dL, the chance of a bacterial infection is unlikely (>95% accuracy).[5]

Procalcitonin is more specifically elevated in bacterial infections and the levels can correlate with the severity of sepsis. It can be used as a trend to monitor a sepsis patient, rather than a single diagnostic marker.[6]

Enteric fever

Timing of tests is very important in the investigation of enteric fever.

Week 1: Isolation of Salmonella from blood/bone marrow. Automated culture systems do better. The success of a culture lies in the blood volume and proper timing of the collection of the sample. Sample collection before the initiation of antibiotic therapy is preferred.

Week 2: Widal by tube method is preferred. Slide method can also be used, but there are chances of false positive results.

Week 3: Stool culture

Week 4: Urine culture

As per the WHO, there is no definitive role for rapid typhoid antibody tests like tubex, typhidot, typhidot rapid and IgM dipstick, and there are no other molecular tests in the market for routine diagnosis. Culturing remains the gold standard.[7]

Brucellosis

IgM raises first and peaks at around 3 months (Fig. 1). IgM ELISA is usually preferred, followed by Brucella agglutination test. However, blood culture remains the gold standard, but prolonged incubation may be required.[8]

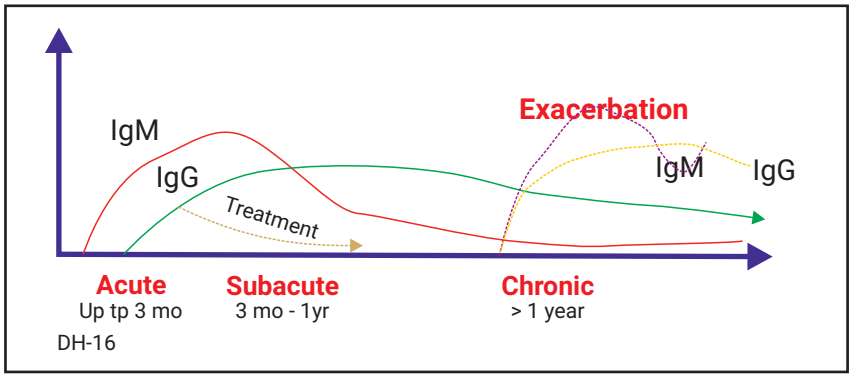

Fig. 1: Immune response during brucellosis

Dengue

NS1 antigen level elevates during the first 5 days of fever, followed by IgM and IgG in a primary infection. Secondary infection witnesses an accelerated IgG response. The serological markers include ELISA for NS1, IgM and IgG.[9] Real time PCR is helpful during an acute viremic phase. Rapid test does not have any role.

Chikungunya

Markers include IgM, IgG and circulating viruses. According to the testing algorithm by CDC, if the disease onset is <6 days, PCR should be performed and if it is >6 days, IgM ELISA should be carried out.[10]

Leptospirosis

Around 90% of the infection is presented as undifferentiated febrile illness. Itis often misdiagnosed at onset as aseptic meningitis, influenza, hepatic disease or fever (pyrexia) of unknown origin. The tests available for the diagnosis of leptospirosis include dark field microscopy, IgM ELISA, microscopic agglutination test and PCR. Dark field microscopy requires 104 leptospires/ml to be visible under the microscope. However, it lacks sensitivity and specificity. IgM ELISA has chances of false positivity. The gold standard is the microscopic agglutination test, followed by PCR.[11]

Infectious mononucleosis

The immune response of infectious mononucleosis involves several antigens and antibodies, and they include early antigens, followed by heterophile antibodies and later viral capsid antigens (VCA IgM, VCA IgG and Epstein Barr nuclear antigen (EBNA)-1 IgG). A positive VCA IgM and negative VCA IgG and EBNA-1 IgG, and a positive VCA IgM and IgG and negative EBNA-1 IgG indicate acute infection. A positive EBNA-1 IgG and VCA IgG indicate past infection. A late primary infection is indicated when all three markers are positive.[12]

Malaria

The target antigens are *P. falciparum*-specific proteins like histidine-rich protein II or lactate dehydrogenase and pan-specific antigens (aldolase or pan-malaria pLDH). PCR, generally used to confirm malaria infection, detects only 1-5 parasites/µl of blood. However, peripheral smear and rapid tests can detect 50-100 parasites/µl of blood.[13] Recently the Ministry of Health and Family Welfare prohibited the use of antibody detecting rapid diagnostic tests for the diagnosis of malaria.[14]

Typhus fever

Scrub typhus and Indian tick typhus predominate in India. Weil-Felix test can be used only after 1 week and has low sensitivity and specificity due to cross-reactivity of *Proteus* antigens used. However, ELISA has good sensitivity and specificity. IgM ELISA and *R. conorii* ELISA IgG/IgM kit are used correspondingly for the detection of scrub typhus and Indian tick typhus.[15] Scrub typhus IgM should be interpreted with caution, as IgM levels persist for a longer duration and there are possibilities for false positive results when single serum samples are interpreted.[16] Therefore, further research should focus on antigen detection assays.[17]

Tuberculosis

The Ministry of Health and Family Welfare, Government of India has banned the use of inaccurate serological blood tests for the diagnosis of TB.[18] Quantiferon TB gold test (QFT) measures the release of interferon gamma produced in whole blood in response to stimulation by purified protein derivative. The Centers for Disease Control and Prevention (CDC) recommends initial and serial testing of persons with an increased risk for latent TB (recent immigrants, injection drug users, residents and employees of prisons and jails) and also for individuals who are, by history, at low risk for latent TB

but whose future activity might place them at increased risk for exposure (health-care workers and military personnel).[19] However, Quantiferon gold is contraindicated in the evaluation of suspected active tuberculosis; assessment of contacts of persons with infectious tuberculosis; screening of children aged <17 years, pregnant women, or for persons with clinical conditions that increase the risk for progression of latent to active TB; detection of latent TB after suspected exposure; confirmation of tuberculin skin test results; and diagnosis of *M. avium* complex disease.[20]

Invasive fungal infections

Biologic markers include galactomannan Aspergillus antigen and the fungal wall component (1–3)-β-D-glucan. However, it is associated with high negative predictive value. The 2016 Infectious Diseases Society of America (IDSA) guidelines for Aspergillosis recommends that galactomannan and 1,3-β-D-glucan assays are useful in high risk patients and is not recommended for routine blood screening in patients receiving antifungal therapy or prophylaxis, but can be applied to bronchoscopy specimens from these patients.[21] Invasive fungal infection should be tested in conjunction with other methods for the diagnosis of invasive fungal infections and should precede antifungal therapy. Positive test results should be confirmed with a second new specimen or repeated from the initial specimen.[22]

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Normal temperatures and measurement of fever

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Introduction

Before labelling a child as having fever of unknown origin (FUO), it is necessary to rule out two other causes of fever. The first one is pseudo FUO.[1] For example, the child may be having a recurrent fever with normal intervals of 5-10 days, however the parent may report the same as prolonged fever for nearly 20-30 days. An example of this is back to back viral infections in young children often seen in in winter months. The second cause is pseudo fever, which will be discussed in detail subsequently.

A case of pseudo fever

An 8-year-old, single child of overprotective parents, had high grade fever for 3 days (39°- 40°C). On day 1 of the fever, the parents did CBC, dengue NS1, IgG, IgM and malarial antigen. On day 2, they did CBC, urine routine and culture, Widal test, blood culture, and SGPT tests. The fever decreased on the 3rd day. From day 4 to 12, the temperature recorded by the parents ranged from 37.4°C to 37.6°C. The child was forced to stay in bed. The child ate well and had gained weight of around 1.5 kgs in 9 days. All the investigations were repeated, and the findings were all normal. Upon consulting the physician, the parents were asked on how the temperature was measured. They replied that they were measuring the oral temperature, which is always higher when compared to axillary temperature. The physician advised the parents to measure axillary temperature for the next 3 days. The 3 days of axillary temperature ranged between 36.5°C- 37°C. This is an example of pseudo fever, because the normal upper limit of oral temperature is 100.4°F (37.5°C),while for axillary temperature the normal cutoff is 37 degrees celcius.

This case brings forth certain important questions with regard to the measurement of body temperature and they are discussed below:

1. What is the normal body temperature?

Normal body temperature, which is labelled as core temperature, is the temperature of the hypothalamus. The hypothalamus regulates the temperature in our body with the help of neurons known as preoptic nuclei.[2] Since it is impossible to measure the temperature of the hypothalamus, the core temperature monitoring sites have been identified and they are pulmonary artery, esophagus and urinary bladder. Obviously these sites are only for research purposes and not for day-to-day settings.[3]

The peripheral sites, such as axilla, oral cavity, ear canal and the rectum, provide a rough approximation of the body temperature but none is equal to the core temperature.[4] Another question frequently asked is whether there is a correction formula to equilibrate with core temperature. The answer is no as the conversion formulae are too imprecise to be useful in all clinical situations.[5] Rather, it is preferable to relate the temperature recorded with the normal range for that particular site. The normal core body temperature is 36.5^{o}C- 37.5^{o}C. The thumb rule to be followed is rectal temperature overestimates the core temperature i.e, if the upper limit of core temperature is 37.5^{o}C then the corresponding rectal temperature is 38^{o}C. The oral, aural, and axillary temperatures underestimate the core body temperature.[5]

Normal body temperature varies at different body sites (Table 1).[6] Also it is to be borne in mind that there is no definite number to depict as absolute normal core temperature, and it is a range with a diurnal variation peaking between 5 and 7 in the evening while the nadir is between 2 AM and 7 AM with a diurnal variation up to 1.5^{o}C.

Table 1: the ranges and means of the temperatures according to the body site

Body Site	Type of thermometer	Range (Normal Mean) (^{o}C)	Fever ^{o}C
Axilla	Hg in- glass, electronic	34.7-37.3(36.4)	37.4
Sublingual	Hg in- glass, electronic	35.5-37.5(36.6)	37.6
Rectal	Hg in- glass, electronic	36.6-37.9(37.0)	38.0
Ear	Infrared emission	35.7-37.5(36.6)	37.6

2. Which is the best site for measuring body temperature?

The National Institute for Health and Care Excellence (NICE) guidelines and the guidelines from the Canadian Pediatric Society (CPS) are the two standard guidelines for measuring temperature. According to these guidelines, no single site is superior than the other. It should be noted that these two guidelines concur in avoiding the use of oral thermometry in children of <5 years of age. The comparison of the guidelines with reference to the age of the child is given in table 2 and 3.[4, 7]

Table 2: NICE recommendations

< 5yrs	Do not use oral/ rectal
< 4 weeks	Axilla
4 week - 5 yrs	Axilla Tympanic
> 5 yrs	Oral/Rectal/ Tympanic
< 5yrs	Do not use oral/ rectal

Table 3: CPS Statement: CP 2000-01

Birth - 2 yrs	Rectal [definitive] Axillary [screening]
2 - 5 yrs	Rectal Tympanic Axillary
> 5yrs	Oral Tympanic Axillary

Axillary thermometry

It is the simplest and easiest method of measuring temperature. However, it has certain limitations such as chances of displacement if not supervised, inaccuracy, and time intensive when compared to other methods. It takes about 3-5 minutes for equilibration, especially if a mercury thermometer is used. In addition, there are increased chances for inaccuracy, as it is susceptible to ambient temperature. Another big disadvantage is that when there is a sudden rise of temperature, the intense peripheral vasoconstriction due to the elevated hypothalamic thermostat set point, the axillary temperature may indicate that the body temperature is normal, while the core temperature will be very high.[6]

As per the literature evidence, axillary thermometry is not a reliable method. However, it can be used for monitoring the course, once fever has been confirmed at another site. It is useful in neonatal ICU, as the ambient temperature is maintained constantly, and also as a screening device in OPD.

Oral thermometry

It is easily accessible and correlates better with core temperature. The major disadvantages are that the child should be co-operative while measuring, and it cannot be used in children <5 years of age and comatose patients. Moreover, it may give false reading if the patient has had a hot or cold drink or a mouth breather.[6]

Rectal thermometry

The technique reflects the temperature of rectal arteries and it is considered as gold standard, especially for diagnosing hypothermia. The major disadvantage of rectal thermometry is that most of the children and adults may not like this mode of measurement, as it can cause pain, mucosal abrasion and psychological discomfort. It is contraindicated in neutropenic patients.[7] There is a risk of rectal perforation, albeit very rare (around 1 in 1 million patients). Since the blood flow to the rectum is poor, there may be a significant lag period for rectal temperature to equilibrate with the core temperature.[8]

Tympanic thermometry

The technique reflects the thermal radiation emitted from ear canal and tympanic membrane. Hence it is also called infra-red radiation emission detector (IREDS). The probe of the thermometer measures the heat lost from the membrane as radiation. The closest approximation to the core body temperature is possible in this technique, as both tympanic membrane and hypothalamus share carotid artery for blood supply.[9] The probe should be properly placed and should be directed at the tympanic membrane and it is not useful in children of <2 years of age. It can become the gold standard for measuring temperature in future with the availability of smaller probes for use in children <2 years of age and sensor to confirm the correct placement of the thermometer.

Skin thermometry

There are 2 methods for measuring skin temperature. The first method is using thermophototropic liquid crystals. These crystals change color on exposure to heat or various temperatures. The parent has to keep the probe on the forehead and based on the change in color, the temperature can be measured. The other method is measuring the infrared radiation from the skin. Skin thermometry is a non-touch technique and reasonably reliable and quick. But it can give falsely low reading if there is intense peripheral vasoconstriction at the onset of fever or if there is cold ambient temperature.

3. What is the commonest mode of assessment?

Among the lay public, the tactile method is the commonest method of assessment. Studies have shown that mother's hand (80%) is more sensitive than hands of medical personnel (40%) in detecting fever.[10] If there is peripheral vasoconstriction in the early stages of fever, the tactile method may give a false impression that the patient does not have fever. It has a very low positive predictive value (PPV), but a very high negative predictive value (NPV). The thumb rule to be followed is that if the patient feels hot on touch, it is mandatoty to measure the temperature.

4. Is it always necessary to document temperature?

It is not always necessary to document temperature repeatedly in a child with fever. Fever per se, even if very high, never does any harm. However, documentation of temperature is necessary in certain clinical situations. Important clinical conditions requiring accurate temperature documentation are listed below:[11]

- Fever in neutropenic children with cancer
- Drowning and near drowning
- Febrile seizures vs. epilepsy
- Hypothermia, especially in neonates
- Therapeutic hypothermia
- Fever without source in <3 months of age
- Maternal intrapartum fever
- During anesthesia
- Hyperthermia diagnosis
- Shock - to measure the difference between core and peripheral temperature

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Approach to fever

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Introduction

According to William Osler, *"the humanity has three enemies, fever, famine and war, but fever is by far the greatest."* In a more optimistic way, this quote can be interpreted as, three major benefits happened to mankind in relation to fever and they are introduction of cinchona as a treatment for malaria, discovery of vaccinations and concept of asepsis.

Fever is a very common condition for a doctor in his routine working life. Fever is the result of an immune response by the body to a foreign invader such as viruses, bacteria, fungi, drugs, or other toxins. To discuss the approach to fever in detail, it can be broadly classified under the following 3 different headings:

- Approach to fever- educators
- Approach to fever- Define/classify
- Approach to fever- clinical decision making

Approach to fever- Educators

As an educator, it is important to enlighten the students about the complexity of pediatric presentation and they need to be to be trained to innovate, extrapolate, economize. With regard to decision making process, they should be exposed to various cases of fever both at the UG and PG levels. It is important to note that acute respiratory infection is the predominate presentation in outpatient visits due to fever and higher proportion of fever etiologies are due to viral pathogens. Global approach to fever

has noted that identification of multiple pathogens after molecular laboratory investigations may cause difficulty in concluding a specific diagnosis. Due to the use of various approaches, there has been an overestimated diagnosis of malaria compared to RDT or microscopy-confirmed diagnosis.

As educators, it is recommended to develop both fast and slow thinking skills, as a part of fever approach. This is important, as there are certain guidelines or criteria based on instinctive (type 1 thinking) and reflective or analytical cognition (type 2). Integrated Management of Childhood Illness (IMCI) is an example for guidelines based on type 1 thinking, whereas Yale observation scale, Rochester, Boston and Philadelphia criteria are examples for reflective or analytical thinking. These two models assist clinicians in day-to-day practice to achieve a balance between efficiency and effectiveness.

A 'fever ladder' demonstrating effect of fever on children helps to explain and counsel the parents in OPD regarding the effect of fever in a child's body. The ladder explains from the bottom how the body sets the thermal point and the other changes till the body gets hotter at the top of the ladder. It also explains child's appearance and behavior while having the fever.[1]

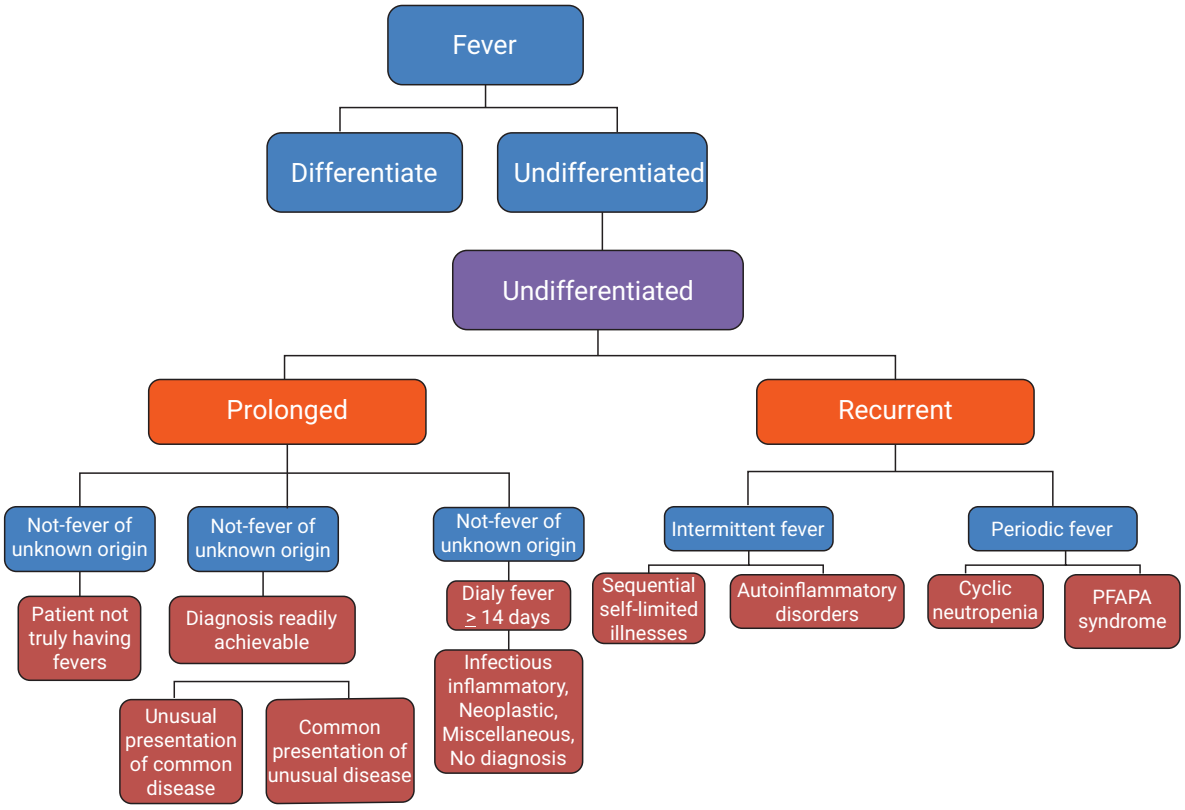
Approach to fever- define/classify

Classification of fever are of different types. Among them, the following is a very simple classification:[2]

- Fever of short duration with localizing signs and diagnosis by clinical history and physical examination
- Fever of short duration without localizing signs for which the history and examination do not suggest a diagnosis but laboratory tests may establish diagnosis (occult bacteremia)
- Fever of unknown(many) origin (PUO)
- Recurrent fever

Around 95% of all the fevers can be defined using the aforementioned classification. A more structured classification of fever is given in table 1.

Table 1: A structured flow chart on classification of fever



This classification needs to be carried out only in 15% of the children with fever, as 85-90% would have some kind of differentiated fever.

Approach to fever- Clinical decision making

It is preferred to design the approach to fever based on the principle of '**As Low As Reasonably Achievable** (**ALARA)'.** This is a very common principle followed by radiologists in order to use very minimal radiation to pick-up certain signs.[3]

Current challenges in the approach to fever

The overall low probability of significant pathology could be attributed to the 85-90% presentation of viral fevers. Based on the case, the clinician needs to decide on either the path of reassurance and avoidance of overtreatment/over investigation, or the path of investigation or possibly empirical treatment. Clinicians with the necessary experience in assessing children do not tend to rely on guidelines or tests to make decisions. Senior decision-makers generally follow their gut feeling/ Gestalt philosophy. Most of the time, path of reassurance and avoidance will be selected.

Individual components of approach to fever

Bacteremia

In the absence of treatment, bacteremia either resolve spontaneously, persist or may progress with symptomatic complications. A positive blood culture will not differentiate a bacteremia from a serious active bacterial infection. The most serious complications due to occult bacteremia often appear before the results of the blood culture are known. There are no highly reliable indicators known at the present time. This is not a reliable method to assess the fever due to serious bacterial infection.

Age

Bacteremia appears at all ages. However, infants between the ages of 3 and 36 months are more prone to develop bacterial infections, secondary to bacteremia. As a rule, bacterial infections are more serious and insidious in infants <3 months of age.

Temperature

The degree of temperature is an important criterion, but many a times a misleading indicator. The risk of bacterial infection tends to increase with the degree of temperature. Response to antipyretics may not really indicate whether the child is having a bacterial infection.

General appearance of the febrile child

General appearance of the child during the febrile / inter-febrile period can be a positive sign of bacterial infection, but it may not be always true in children <3 month of age. It is not a reliable method in one-month-old children.

Leukocytosis

Bacterial infections are more likely to have a leukocytosis count of ≥15,000/mm^3 than viral infections. Leukocyte count results can be misleading if there is an obvious discrepancy between the number of leukocytes and the child's general condition. Other markers of infection include C-reactive protein, interleukin- 8, and procalcitonin.

General principles and guidelines on approach to fever

During the first 4 weeks of life of an infant, any fever warrants a 'full sepsis evaluation'. Most guidelines advocate comprehensive evaluation of the very young febrile infant (28 days and younger) and a less conservative approach for older infants. In 10% of the febrile children, especially < 3 months, occult bacteremia may lead to septicemia and various invasive infections.[4]

Criteria for clinical decision making

- The commonly used criteria for clinical decision making are: Boston criteria, Milwaukee criteria, Philadelphia protocol, Rochester criteria, Young Infant Observation Scale (YIOS) and Yale criteria.[5]
- Traffic light system for identifying risk of serious illness, put forth by National institute for health and clinical excellence, is an approach commonly used in UK and European countries. It uses color code for risk stratification.[6]
- 'Step-By-Step' Approach has been developed by European group of pediatric emergency physicians.[7] The primary objective of the approach is to identify low-risk group of Infants who could be safely managed as outpatients. According to a recent research, it has been identified as

the best validated approach for identifying a child with serious bacterial infection. In addition, it has higher sensitivity and more accuracy than other criteria.

However, these guidelines are not completely applicable in India due to varying epidemiology of pathogens and the clinicians are not confident about the test characteristics of various screening tools. In addition, newer screening tools such as procalcitonin have not been studied or integrated into clinical decision making in a robust manner.

Indian scenario and guidelines

Epidemiology of the febrile child in India is different from that of the Western Countries. Hence, published guidelines need to be modified to apply in Indian clinical scenarios. Moreover, there is no wide-spread, comprehensive data available to systematically report the epidemiology of febrile illnesses that present to the emergency departments across the country.

The commonly used criteria for clinical decision making, which is faceable in Indian scenario, are WHO guidelines and F-IMNCI approach. In 2017, Paediatric Emergency Medicine (PEM) Section of Academic College of Emergency Experts in India (ACEE-INDIA) has come up with consensus guidelines on evaluation and management of the febrile child presenting to the emergency department in India.[8]

INDIA/WHO guidelines

India/ WHO guidelines follow the below given step-by-step approach:[9]

- First, healthcare professionals should identify any immediately life-threatening features, including compromise of the airway, breathing or circulation, and decreased level of consciousness.
- Second, children with feverish illness should be assessed for the presence or absence of symptoms and signs that can be used to predict the risk of serious illness using the traffic light system.
- Third, healthcare professionals should look for a source of fever and check for the presence of symptoms and signs that are associated with specific serious diseases.

Based on these principles, children should be classified into the following categories:

- children younger than 3 months of age with a temperature of 38oC or higher
- children aged 3–6 months with a temperature of 390C or higher.

F-IMNCI approach or ALMANACH - ALgorithm for the MANAgement of CHildhood illness[10]

Children presenting with fever have been classified into the following 4 major categories:

- Fever due to infection without localized signs (no rash)
- Fever due to infection with localized signs (no rash)
- Fever with rash
- Fever lasting longer than 7 days

Approach to fever-phobia

Antipyretics should not be prescribed as a preventive during a vaccination visit. There is no role of antipyretics in the prevention of febrile seizures. Alternation of antipyretics has no clinically significant benefit and increases the chances of dosing errors. Most of the fevers are not harmful and the overuse of antipyretics can cause organ damage.

Conclusion

The evaluation of a child with fever should be driven by a careful history and meticulous physical examination. The clues to the cause often lie therein, but can be missed. A symptom-focused approach is far superior to a 'shotgun' or 'running-the-list' approach. The overall condition of the child should be the guide to the pace of work-up, rather than the degree of anxiety of the family or the physician.

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Investigations in fever

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Acute onset fever is a sudden elevation in the body temperature as a symptom of an underlying medical condition. The scope of the present paper is investigations to be carried out in children withacute onset fever. The major challenge confronted by the pediatrician is to differentiate bacterial infection and to identify other pathogens requiring specific treatment (eg.malaria).Another challenge is thediagnostic and management dilemma associated with fever in children without an identifiable focus.

Salient factors to be considered in a case with fever

The following factors need to be considered in a child presenting with acute fever:

- Presence of any risk factor (eg: receiving chemotherapy or having immunosuppression)
- Any danger signs
- Presence of diagnostic focus
- Age group to which the child belongs (0-28 days, 1-3 monthsand 3-36 months or above)

The general rule followed in clinical practice is that if the fever >105°F, the most probable cause is a bacterial infection. However, there are exceptions like influenza and adenoviral infections, which can cause fever >105°F.[1]

Risk stratification in children with fever

There are many risk stratification criteria, which have been developed to help clinicians decide on the course of management of an infant orchild with fever. The commonly used criteria for risk

stratification in children are given below:

- Yale observation scale for children
- Rochester criteria for infants <2 months
- Boston & Philadelphia criteria for premature infants/infants up to <3 months

For using any of the above scales or criteria, it is important to remember that those who qualify for the low-risk criteria have a high negative predictive value for serious bacterial infections or, in other words, have a low chance of having a serious bacterial infection.[2]

Danger signs

It is paramount to identify life-threatening signs such as reduced level of consciousness, difficulty in breathing etc. The ABCD red flag signs to be noted in child with fever are[3]:

A- arousal, alertness, activity

B-breathing difficulty

C-color and circulation

D- decreased intake and urine output

Focus of infection

If the focus is present, all investigations are directed towards the confirmation of the focus of infection. Some of the examples are listed below:

- X-ray for chest findings in suspected case of pneumonia or respiratory distress
- Urine routine and culture analysis for urinary symptoms
- Splenomegaly, especially in an endemic area – peripheral blood smear/ rapid test for malaria

Fever without the focus is the most confusing and difficult situation. Bacteremia, urinary tract infection (UTI) and pneumonia are the most common severe bacterial infections in infants that may not be clinically apparent. The choice of the work-up depends on the pace and severity of the illness. Investigations must be done in all the sick children with and without focusby72 hours, if the fever does not subside.

Investigations

The following are the common investigations carried out in pediatric patients with acute fever:

- Complete hemogram
- Inflammatory markers: C reactive protein (CRP), procalcitonin
- Chest X-ray
- Blood culture
- CSF exam for sick infants without localization
- Serology
- USG/Echo
- Urine analysis and culture
- Reassessment and revaluation in children not responding to medications

1. Hemogram

The white blood cell (WBC) count with differential count is the most commonly performed test in the hemogram. Values<5000 &>15,000/cumm suggest an abnormal finding. If the band forms ≥0.2% (> 1500 cells) and the absolute neutrophil count falls between<1500 or >10,000, the findings suggest a severe bacterial infection. The exceptions include leukopenia in patients with *N meningitidis* infection and leukocytosis noted in a small minority of patients with Salmonella infection and eosinopenia in Salmonella infections. A direct association has been noted between WBC count and prevalence of bacteremia. In addition, higher values of band forms help in identifying children with elevated risk for of severe bacterial infections and bacteremia.

However, some limitations have been noted in the clinical use of hemogram. For example, in nearly 50% of the children with bacteremia esp. with *Hemophilusinfluenzae* type b (HIB), WBC range is between 5000- 15000/cumm. Moreover, it may not be predictive in infants <8 weeks.[4] A study by Dharmalingam *et al.,* published in the *International Journal of Contemporary Pediatrics*, has noted that the mean WBC count was between 15016 ± 5801 in children of age between 1 month to 5 years. Among these children, only 49.3% had severe bacterial infection, comprising mainly of UTI and pneumonia. The researchers have noted higher WBC values in UTI infection.[5]

2. Acute phase reactants

CRP and procalcitonin are the commonly used acute phase reactants. However, there are certain disadvantages associated with their clinical use, hence both are not useful as standalone tests. Both CRP and procalcitonin have high sensitivity, but low specificity. The corresponding sensitivity, specificity and net predictive value for procalcitonin are 95-96%, 23-26% and 96%.The increased CRP levels are noticeable only after 12 hours after the onset of fever, and the elevated levels are noted both in viral and bacterial infections.[6,7] The use of acute phase reactants as adjunct screening tools helps in ruling out sepsis, rather than ruling in. CRP >80mg/L and procalcitonin >2ng/L help in identifying severe bacterial infection with 40-50% sensitivity and 90% specificity. CRP <20 mg/L and procalcitonin < 0.5 ng/l assist in identifying low risk of serious bacterial infection with >80% sensitivity and 20% specificity.

3. Urine analysis and culture

It is necessary to inform the patients to catch the clean, mid-stream urine. Urine collected from one-time bladder catheterized sample and suprapubic puncture is also used for analysis. Whereas, bag collected sample should be avoided, as the chances of false positive findings are higher.[8] Urine sample should be obtained before starting empiric antibiotic treatment. The urine analysis is considered as one of the gold standard tests for acute fever evaluation. The findings to be noted, while interpreting the results are WBC > 5 per hpf, positive leukocyte esterase test, presence of nitrites and a positive urine culture.

4. Chest X-ray

Usually, chest X-ray may appear normal in children with fever without focus. In infants with WBCs> 20,000/cumm, it may be suggestive of indolent pneumonias. It is also useful in detecting complications such as effusions and empyema.[9] ChestX-ray is indicated in the following scenarios: children <3

months, oxygen saturation<95% in room air, respiratory distress, tachypnea, rales temperature>39.5 deg C, and WBC > 20,000/cumm.

5. Blood culture

Blood culture is another gold standard test in acute fever management and it should be done prior to the initiation of antibiotic treatment. Preliminary results are available by 24-48 hours of culture.

Negative blood culture may result from prior antibiotic use, missing the bacteremic episode, inoculation of too little blood (<1ml) or too much blood (>5 ml), and false positive due to contamination.[10] For antibiotic stewardship, it is important to know the bacteria prevalent in a particular area and the sensitivity pattern therein. Therefore, sending a blood culture prior to the initiation of antibiotics should be implemented in routine practice. Blood culture is usually negative in subjects who are already on antibiotics. In such patients, one suggested way to improve the culture yield is to give a couple of hours break from the antibiotic before sending a sample for blood culture.

6.CSF exam

CSF exam is indicated in children<28 days, without any signs and symptoms of neurologic complications. It is also recommended in children with sepsis and signs localized to the CNS.

7. Serology

Several serology tests are available. For dengue, the commonly performed diagnostic tests are NS1 antigen, IgM, and IgG. However, it is not recommended to perform these tests on day 1.

Despite the wide spread use of Widal agglutination test in clinical practice for more than 100 years, it is still plagued by controversy. Inherent variability and lack of reproductivity are the major limitations of the test. The possibility of false positive findings is higher due to the repeated exposures to *Salmonella typhi* in endemic zones and cross-reactiveness of the non-salmonella antigens.[11] Even if Widal test has to be performed, it should be done after 1 week of exposure, keeping in mind that it is neither sensitive nor specific. It is no longer acceptable as a clinical method of diagnosis and the test has to be repeated after 4 weeks to demonstrate a rise in titers.

With regard to other serology tests for typhoid, rapid tests like Typhoid IgM or Typhidot are no longer recommended. For malaria, as per the government of India policy, only IgM test has to be performed. The findings should be corroborated by conducting a peripheral blood smear, which is still considered to be the gold standard.

The gold standard tests for rickettsial diseases are indirect immunoperoxidase test, immunofluorescence test and PCR. However, the increased cost limits the use of these tests in general practice. IgM capture is also used in diagnosing rickettsial diseases. Though Weil-Felix test lacks specificity and sensitivity, it is still considered as a useful inexpensive tool in areas where the disease is common. It should be carried out 5-7 days after the onset of the fever.[12]

Microagglutination test (MAT) is considered as the gold standard for leptospirosis.

8. Stool analysis

It is recommended only if diarrhea is present and is considered as a focus of infection. Presence of blood in the stool is indicative of a bacterial infection in the presence of fever.

9. Radiology

Ultrasonography (USG) of abdomen assists in identifying hidden findings, even in the early stages of the disease, especially in patient with localizing signs and symptoms. In patients with atypical or incomplete Kawasaki disease, it is wise to perform an early echocardiography to detect coronary artery abnormalities.[13]

The clinical investigation steps, to be followed in children ≤ 36 months with fever <1 week, are given in figure 1.

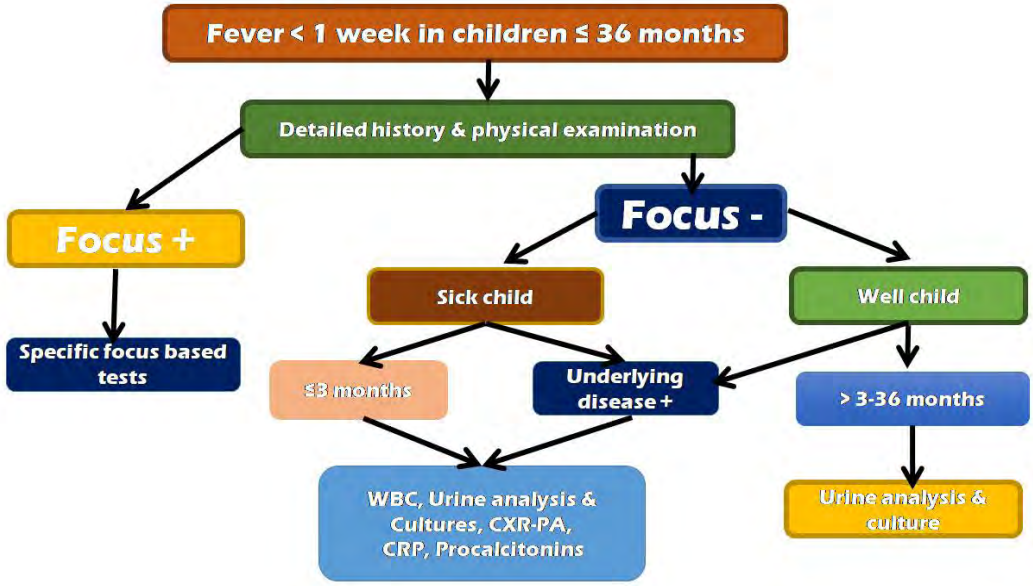

Fig. 1: Flow chart depicting the clinical investigation steps to be followed in children ≤ 36 months with fever <1 week

Conclusion

A battery of tests are available for the evaluation of acute fever in children, however the judicious selection of the appropriate test is mandatory. All children of >3 months old need a detailed first-line investigation. In most cases, clinical and investigative re-evaluation at the end of 24 hours gives a better understanding of the associated problem.

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Fever without focus

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Introduction

The fever can be broadly classified as fever with localizing signs, fever without localizing signs or focus, and fever of unknown origin (FUO). Fever without focus is also termed as fever without source (FWS). FWS is defined as an acute febrile illness with a fever of 1 week or less, without an apparent cause of the fever even after a thorough history and physical examination.[1] Approximately 20% of the febrile episodes in children do not demonstrate any localizing signs or focus, despite eliciting the best history and conducting a through clinical examination.[2] The most common cause for FWS is viral infections. A small percentage (7%) of the FWS is caused due to serious bacterial infections (SBI). In developed countries with better immunization coverage with *Hemophilus influenzae* and pneumococcal vaccines, the incidence of SBI has dropped to <1%.[3]

FWS and FUO are two different entities, which many clinicians fail to differentiate. FWS may progress to FUO if no underlying cause has been identified after 1 week of illness. The differences between FWS and FUO are listed in table 1.[1]

Table 1: Differences between FWS and FUO

FWS	FUO
Fever of </=1 week	Fever of at least 8 days
Warrants immediate intervention	Requires timely but not urgent intervention
Expectant antibiotic treatment is recommended in certain cases	Expectant antibiotic treatment not generally indicated

Causes of FWS

The common causes of fever are given below:[3]

- Infection: Bacteremia/sepsis, most viruses (HHV-6), UTI, malaria (tropical countries)
- Autoinflammatory disorders: Juvenile idiopathic arthritis
- Post vaccination: Triple vaccination, measles
- Drug fever: Most drugs
- Dehydration fever in <1-month-old child

Among these infections, SBI is the most serious cause of FWS. The incidence is more in <3 months old children (6-10%) when compared to 3-36 months (5-7%).[4, 5] The increased incidence noted in <3 months old children is mainly due to immature immune system. They have reduced opsonin activity, macrophage function and neutrophil activity.

A though clinical history and physical examination are crucial for the early identification of FWS. The history should collect the following details: onset and duration of fever, degree of temperature recorded, temperature taking method, similar symptoms in other family members, pattern of feeding, degree of activity, playfulness at home, overclothing, pre-existing disease, previous administration of antibiotics (</=90 days) and immunization status.

Signs and symptoms in SBI

The following are the common signs and symptoms noted in a child with SBI:[3]

- General: Reduced activity, weak cry, poor eye contact and absence of smile
- Body temperature: Instability, fever and hypothermia
- Signs of shock: Clammy, mottled skin and reduced CRT
- Respiratory: Apnea, tachypnea, shallow respiration and grunting
- Gastrointestinal: Poor feeding, vomiting, abdominal distension and diarrhea
- CNS: Altered sensorium and meningeal signs

SBI in children can also be due to occult bacteremia, urinary tract infections, pneumonia, meningitis and in tropical countries, it can be due to malaria, dengue, and enteric fever. These children do not present with classical history or clinical signs as given above, hence the chances of missing SBI in such children are high. The likelihood of capturing these children can be maximized by assessing the risk factors, lab screening tests and clinical decision rules.

Occult bacteremia

This condition is defined as the presence of bacteria in the blood of an otherwise well-appearing febrile child, in the absence of an identifiable focal bacterial source of infection.[4] In children aged <1 month, the risk of bacteremia is 12%, while it is 3-4% in 1-24 months of age. Degree of temperature also gives a clue for occult bacteremia. If the temperature is >41°C, the risk is 26%; whereas, it is 7% at 40 to 40.5°C and 13% at 40.5 to 41°C.[6] Clinical and demographic risk factors that are indicative of bacteremia are given in table 2.[1]

Table 2: Clinical and demographic factors that predict risk of occult bacteremia

Factor	High Risk	Low Risk
Age	</=3 months	>3 months
Immunization status	Incomplete	Complete
Magnitude of fever	>/+40 C(104°F)	</= 39.4°C (103°F)
WBC count	>15,000/cumm	<15,000 /cumm
Peripheral blood smear	Toxic granulation /vacuolization of PMN, thrombocytopenia	Unremarkable
Underlying chronic disorder	Sickle cell disease, immunodeficiency, malnutrition	None
H/O contact with bacterial disease	Contact with *N. meningitidis* or *H. influenzae*	None
Clinical appearance	Appears ill, toxic, inconsolable, irritable not eating and drinking enough	Looks well, playful, eating normally, not irritable

Other parameters suggestive of occult bacteremia

Peripheral blood smear showing toxic granulations and vacuolization in <24 months increases the positive predictive value of having bacteremia by 0.76. Febrile children, aged 2 months to 6 years, not responding to acetaminophen by reduction of temperature by <0.8° C in 2 hours have increased risk for occult bacteremia. Thrombocytopenia is another important predictor of occult bacteremia.

However, these factors may not hold good in predicting occult bacteremia in >3 months old children.[1] In such children, the positive predictive value of WBC and temperature for occult bacteremia is only 14%. Most of these children with occult bacteremia have transient infection and recover completely even without antimicrobial therapy. However, the primary concern in these children is meningitis and not bacteremia. The risk of developing meningitis is 1.8% in children with occult pneumococcal bacteremia. The risk is 15 times greater for *Hemophilus influenzae* type b (Hib) and 81 times greater for *N. meningitidis*. There is no test to identify or predict meningitis but conjugate vaccines have been proven to be most effective in preventing these infections.[7]

Vaccination is the ideal strategy to prevent such infections. In developed countries, the incidence of occult bacteremia has reduced to 0.17-0.36% after the introduction of conjugate vaccines, when compared to 11.6% in pre-vaccine era.[4] This was possible with vaccination coverage of >80% with pneumococcal vaccines. The present etiologies for occult bacteremia in developed countries are nonvaccine serotypes of Streptococcus pneumonia and *H. influenzae*, *S. pyogenes*, *Enterococcus* spp, *N. meningitidis*, *M. catarrhalis*, *Salmonella* spp, and *S. aureus*.[4]

Risk factors suggestive of UTI

Any child presenting with a temperature ≥39°C, a fever >24 hrs duration and without any obvious focus of bacterial infection should be investigated for UTI. The risk is higher in girl child of <12 months of age.[8]

Factors suggestive of pneumonia

Pneumonia is another possibility of FWS. The chest X-ray may not be always suggestive of underlying pneumonia, due to the presence of inter- and intra-person variabilities in interpreting chest X-ray. However, there are certain factors that may increase the likelihood of radiological pneumonia. Murphy et al. have suggested that fever >5 days, cough >10 days, and WBC> 20,000/cumm assist in predicting radiological pneumonia.[9] Mintegi and colleagues have suggested that age >12 months, CRP > 100 mg/L and absolute neutrophil count (ANC) > 20 x 10(9)/L may increase the likelihood of radiological pneumonia.[10]

Viral illness

Viral infections account for 76% of the incidence in children with FWS. Among them, 57% of the children have infections due to adenovirus, human herpesvirus 6, enterovirus, and parechovirus. PCR is the widely used rapid testing method available for detecting viral pathogens. The advantages of using PCR are: turnaround time of around 1 hour, decreased ancillary testing, decreased use of antibiotics and shorter hospital stays.[11]

Screening tests

A combination of tests should be performed for diagnosing SBI. Total WBC's of 15,000-20,000/cumm has a low sensitivity (50-69%) and specificity (53-80%) with PPV of 1.5-3.2%. CRP and interleukins (IL-6, IL-1, IL-8) cannot be used as a single screening tool. Serum procalcitonin increases more rapidly in bacterial infections and correlates well with severity of disease and mortality, but it is not sufficiently sensitive in < 3yrs of age.[4]

There is no single /combination of clinical findings and tests to reliably identify the SBI in a febrile child. Hence, the clinical decision or prediction rules have been formulated to diagnose SBI early in these children.

Clinical decision / prediction rules for predicting SBI

Several criteria are available for risk stratification in management of febrile infants of age ≤3 months.

Among these, Boston, Philadelphia and Rochester criteria are well accepted (Table. 3). Both Boston and Philadelphia criteria recommend compulsory CSF analysis in all the febrile children of age ≤3 months. But according to Rochester criteria, in a child with WBC count 5000- 15,000/cumm, band count <1500/cumm, spun urine specimen <10 WBCs/hpf and stool (if diarrhea) with <5 WBCs/hpf; the chances of serious bacterial infection is very less. The negative predictive value of this criteria is 98.9%.[4]

Table. 3: Boston, Philadelphia and Rochester criteria used for risk stratification

Low-Risk Criteria	Boston[a]	Philadelphia[a]	Rochester[a]
Age (d)	28-89	29-56	0-60
Temperature (°C)	≥38.0	≥ 38.2	≥ 38.0
Clinical appearance or YOS	Well	Well	Well
CBC	>5000 or <20,000	<15,000	>5000 or <15,000
Band counts	NA	<0.2 B:N ratio	<1500
UA	<10 WBC/hpf	<10 WBC/hpf	<10 WBC/hpf
Urine Grarn stain	NA	Yes	NA
CSF	<10 WBC/mm^3	<8 WBC/mm^3	Not required
Stools	If diarrhea	If diarrhea	If diarrhea
Chest radiograph	If done	All	If done

Lab score

Lab score also has a good negative predictive value (98%) in ruling out SBI. The parameters considered are CRP, serum calcitonin and urine dipstick test (leukocyte esterase and /or nitrite). Scores are given for each parameter, which range from 0 to 4. CRP of >100 mg/L and procalcitonin of >2 ng/ml are given a score of 4 each. If the total lab score is ≥3, the chance of SBI is high.[13, 14]

Step-by-step approach

The step-by-step approach is indicated for well appearing and previously healthy infants of >28 days of age. As per the approach, no leukocyturia, PCT <0.5ng/ml, CRP ≤20 mg/L and ANC ≤10,000/cumm indicate no serious bacterial infection. This approach has an NPV of 99.3 (Table 4).[15]

Table 4: Comparison of criteria for predicting SBI[15]

Criteria	Sensitivity%	Specificity%	PPV%	NPV%
Rochester	81.6	44.5	5.7	98.3
Lab- Score	59.8	84	13.4	98.1
Step by Step	92	46.9	6.7	99.3

Management guidelines

The consensus guidelines on evaluation and management of child, put forth by Indian Pediatrics, are outlined in fig. 1 and 2.[16]

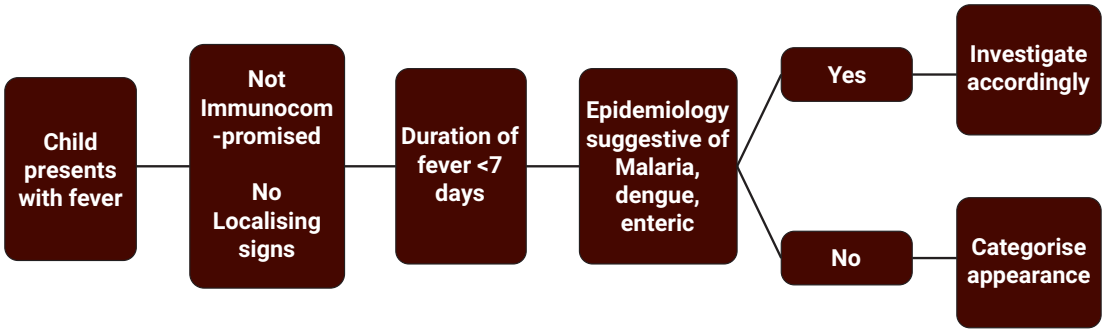

Fig. 1: Algorithm for evaluation and management of febrile child

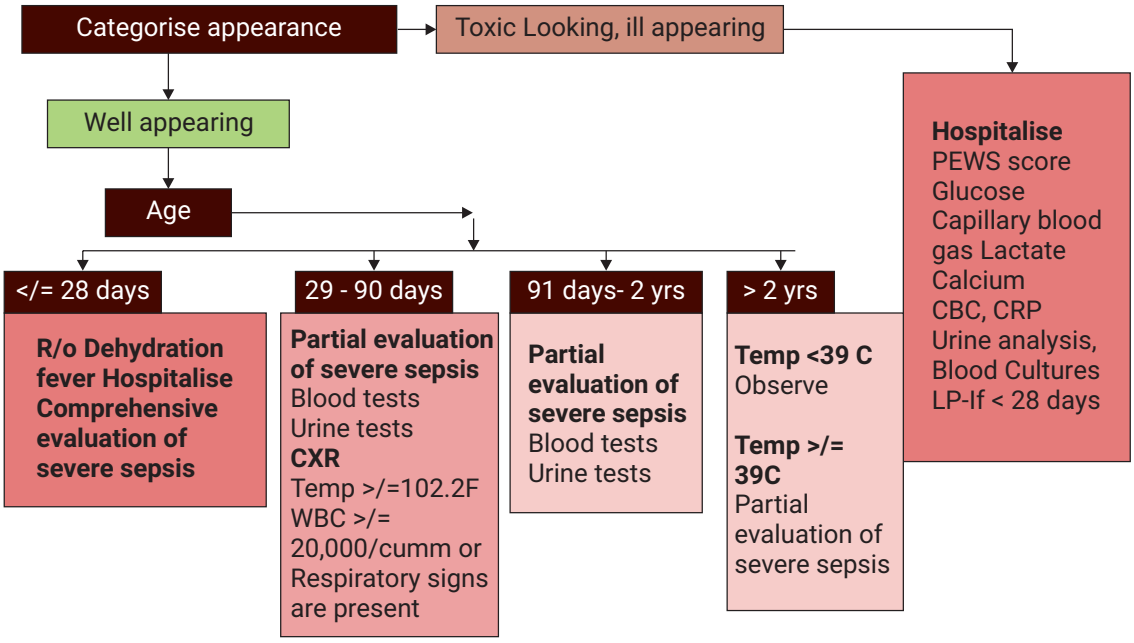

Fig. 2: Management of febrile child based on appearance

Comprehensive evaluation of severe sepsis in children ≤28 days of age includes blood tests (CBC, CRP, band cells, I/T ratio, toxic granules, vacuolization in WBC, and blood culture) urine analysis and culture, and others tests (lumbar puncture and chest X-ray).[16]

If the child is at high risk for SBI based on above evaluation, the therapeutic coverage for *S. pneumoniae*, *N. meningitidis* and *H. influenzae* should be provided based on the vaccination status of the child. If infant is <90 days old, additional coverage for *Group B streptococcus*, *E. coli*, and *Listeria monocytogenes* should be given.

Conclusion

In children of <3 months of age presenting with FWS, the possibility of SBI should be considered. Clinical prediction rules and lab scores have good negative predictive values and can be used to rule out SBI and avoid unnecessary antibiotics. Rapid testing for viral pathogens can be done for better

antibiotic stewardship. Parents should be counselled regarding the use of conjugate vaccines and completion of immunization to reduce the incidence of SBI.

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Fever in ICU

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Introduction

The etiology of fever in ICU can be infectious or non-infectious.[1] Patients with traumatic brain injury and cardiac arrest often present with fever. The present review discusses whether the fever in ICU is good or bad, and how to deal with the infection-related fever in ICU. The study also focuses on how to evaluate fever or late-onset fever in ICU.

Is fever good or evil?

Fever persists across various range of species and all organisms tend to mount fever. Mice can mount fever. If mice are not able to mount fever after the inoculation of *Klebsiella* into the peritoneum, the mice tend to die. Snake is a cold-blooded animal. However, when there is an infection, the snake warms up the body. If the warming process is prevented, the snake would succumb to the infection. This suggests that immunological system seems to work better in the febrile range. Blue gill sunfish can mount fever, but the fever decreases upon administration of NSAIDs. The normal body temperature of a pigeon is 41°c. This higher body temperature provides intrinsic immunity against *pneumococcus* infection to the pigeon. *Pneumococcus* can multiply easily in normal human body temperature, however, during physiological fever, *pneumococcus* finds it difficult to multiply. Likewise, when the culture temperature is increased/agar is warmed up to 40°C, the bacteria tend to die. Moreover, the concentration of antibiotics, required to inhibit bacterial growth, is much reduced when the temperature of the culture plate is increased. When yeast cells are inoculated into the honey bee larvae present in the bee hives, the honey bees fly in the area where the infected larvae are present

to increase the local temperature, thereby to protect them from yeast infection. These observations indicate that fever is a common response to infection in various animal varieties. The conservation of metabolically expensive response to fever, possibly suggests its evolutionary advantage.[2]

A good example in humans can be cited from the work of the Austrian neuro-psychiatrist, Julius Wagner-Jauregg (1857-1940) who received Noble prize in 1927 for treating dementia paralytica patients with malaria inoculation.[3] He noted that, in some patients, there was a spontaneous remission in paralysis after developing febrile illness, and 1:3 patients responded to the treatment. Similarly, Owens CA adopted a method of creating artificial fever to treat gonococci infection.[4] The patients with gonococci infection were asked to sleep in a chamber having a raised temperature of 41.6°C (Kettering hyperthermia therapy, Fig. 1). The aforementioned examples show that fever is good, as it helps in fighting against infection. Literature evidence also suggests that blood cells such as monocytes and neutrophils work better when a febrile response is mounted.[2]

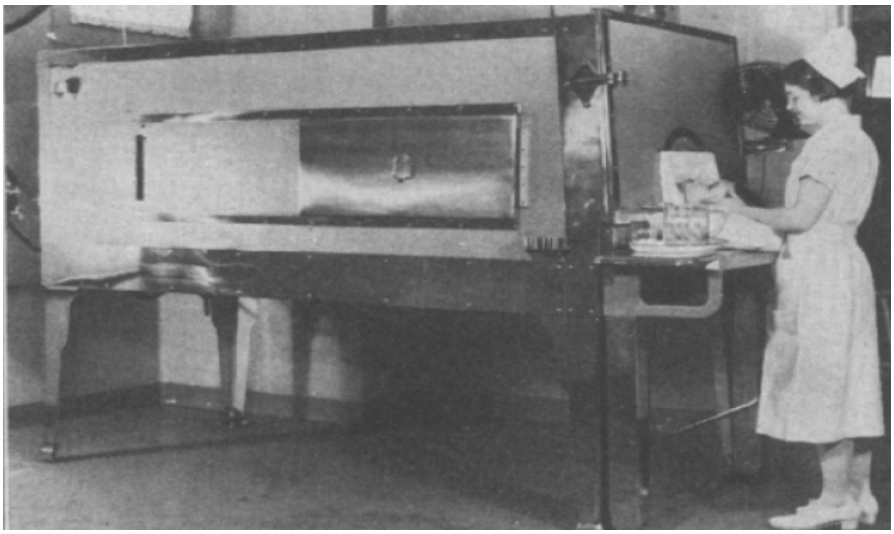

Fig. 1: Kettering hyperthermia therapy with patient in place

Young et al. (2012) conducted an observational study on ICU patients with and without infections. The study noted that subjects with higher degree of fever were more likely to be below the yellow line (better outcomes), whereas it was contrary in subjects without fever. It was demonstrated that a good fever response during the first few days of illness had a protective effect.[5] This study paved way for an interesting study conducted in adults, called the 'Heat-trial'.[6] The study, which compared IV paracetamol with placebo in ICU patients with fever and infections, hypothesized that among ICU patients with likely infection, the use of paracetamol to treat fever may decrease ICU-free days by 2.2. The study design is given in figure 2.

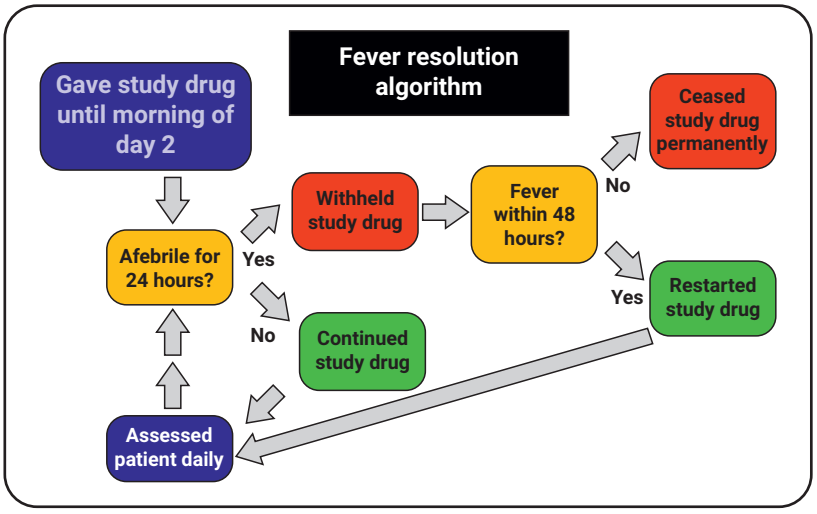

Fig. 2: Algorithm for fever resolution followed in 'heat-trial'

A total of 3601 subjects met the inclusion criteria, out of which 1674 had contraindications to paracetamol and acute brain pathologies. In addition, content was not obtained for 174 subjects and 1053 could not be followed up. Hence the study could randomize only 700 subjects. The study demonstrated that the ICU free days did not differ significantly between the paracetamol-treated and the placebo groups (P 0.07). Likewise, the mortality rates at day 28 (P 0.94) and day 90 (P 0.84) did not show significant difference between the placebo and the paracetamol-treated groups. However, the duration of hospital stay showed significant difference between the groups among survivors (P 0.01) and non-survivors (P <0.001). Subjects who received paracetamol died much later when compared to those who did not receive paracetamol, and they had a shorter stay in ICU. This indicated that paracetamol confer a modest antipyretic effect in critically ill patients.

Fever is bad

Fever is challenging, as it increases the metabolic and physiological demands.[7] Critically ill patients are not normal, as they are out of the physiological limits. The survival chance of such patients can be improved by adopting adequate supportive measures to recover. Tolerance of the physiological demands created by the fever may be poor and one potential way to protect patients from the physiological demand of fever is to systematically prevent and treat fever.

Schortgen *et al.* (2012) conducted the 'Sepsiscool' study, where patients with septic shock were cooled physically using cooling machine.[8] The study noticed that the outcomes and survival were much better in the group with tight fever control. Bernard *et al.* (1997) also documented that sepsis patients treated with ibuprofen had better outcomes.[9] Fever has beneficial response in a least sick patient and has less benefits in a sicker patient.

Trauma

During a trauma such as a cardiac arrest or a road traffic accident, the patient suffers a primary insult. The brain is injured at one moment, and subsequently sets off signals that leads to secondary injury, causing apoptosis and inflammation. The key objective of ICU care is to salvage the patient by

reducing or preventing secondary injury. The normal brain tissue receives 75-100 ml/100 g of cerebral blood flow (CBF) in a minute.[10] A drop in the flow to 20 can impair the function and a CBF beyond 10 leads to complete failure of NA-K pump mechanism, leading to neuronal death. In the presence of fever, the CBF drops drastically beyond 20 (Fig. 3). Therefore, even one degree of rise in fever can cause significant neuronal death and loss. Hence, it is highly challenging to manage both children and adults presenting with brain injury and fever in the ICU.

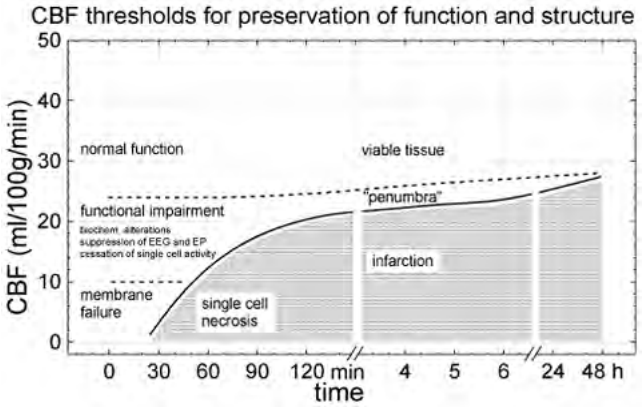

Fig. 3: Effect of fever on cerebral blood flow

How to monitor temperature

Fever can be measured as core temperature or peripheral temperature. Core temperature is generally measured in two ways: rectal route and esophageal route. Peripheral temperature is measured through axillary and tympanic routes.[11] Studies have demonstrated lack of correlation upon comparison of different routes of measurement such as: tympanic vs. bladder, axillary vs. bladder and nasopharyngeal vs. bladder. In fact, recommendations clearly state that monitoring core temperature is important and peripheral surface temperature monitoring is not reliable to treat patients.[12]

Physical cooling

Cooling blankets are commonly used for physical cooling. Server-controlled machines are preferred over physical cooling, as temperature swings are minimum and are tightly controlled in machines. They regulate temperature between 35-36°c. Fever in pediatric patients with cardiac arrest or traumatic brain injury is very harmful and documented evidence suggests that aggressive controlling of fever in such patients is very beneficial.[13]

In a patient presenting with fever, it is necessary to document the following details:

- Is the fever infection related?
- Does it impose significant metabolic demand on the patient?
- Does the patient suffer from brain injury?

In patients with brain injury or very high fever, physical cooling should be considered.

Take home message

- It is important to understand that peripheral temperature does not always correlate with core temperature in ICU patients.

- The conversion of peripheral temperature to core temperature by adding 0.5°C is not substantiated by literature evidence.
- A peripheral temperature >39°C, is an indication to start continuous monitoring of core body temperature.
- When dealing with infection-related fever, the patients are initiated with paracetamol. Physical cooling or serve cooling is opted, in case of high fever and acute brain injury.
- Aggressive management of fever may benefit patients with limited physiological reserves, particularly in the absence of infection.

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Recurrent fever in an immunocompetent host

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Introduction

Fever is one of the most common symptoms noted in an infection. Acute fever is mostly due to self-limited infections like viral and uncomplicated bacterial and resolves within a week or less.[1] In a small number of cases, fever may prolong or reappear after a particular time interval and such fevers are of deeper concern. The current review focuses on recurrent fever, which is characterized by febrile episodes and periods of normal temperature.[1]

Recurrent or periodic fever syndromes are defined by 3 or more episodes of unexplained fever in a 6-month period, occurring at least 7 days apart.[2] The discussion of the following case-based scenarios assists in better explaining recurrent fever in immunocompetent patients.

Case Scenario 1: PFAPA syndrome

A 5-year-old boy with a history of recurrent fever of 3 days duration within an interval of 3-4 weeks, presented with sore throat, tonsillar congestion and cervical lymphadenopathy. He was also suffering from occasional oral aphthous ulcers for 2.5 years. Except for leukocytosis and elevated CRP, all other lab parameters were normal. The pediatric periodic disease with these classical features is termed as 'Marshall's syndrome or 'Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome'.

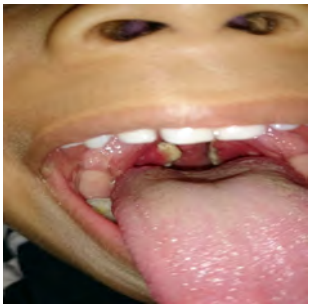

Fig. 1: Oral aphthous ulcers

These symptoms usually develop in <5 years of age and recurrent fever is the most prominent symptom of PFAPA. The frequency of fever is every 3 to 6 weeks, while the fever lasts about 3 to 5 days. Children may complain of pain in the throat, difficulty in swallowing due to pain, and painful mouth ulcers. The lymph nodes in the neck may be enlarged.[3] In a child with PFAPA, the test result will show elevated inflammatory reactants during acute phase and normal levels between the fever attacks. There is no specific medication to treat PFAPA. Administration of prednisone at the beginning of an attack may help in shortening the duration of the attack. However, it has been noted that the frequency of attack is more often in prednisone treated children.[3] The frequency of attack reduces gradually and stops by late childhood.

Case scenario 2: Juvenile idiopathic arthritis

A 5-year-old boy presented with second time febrile illness of 2 weeks duration within an interval of 2 months. He had evanescent skin rashes over body for the past 10 days (Fig. 2), generalized lymphadenopathy, hepatosplenomegaly, and transient pain in the right wrist (subsided in 2 days). There was no other significant finding on musculoskeletal system examination. Except for AST/ALT, all other lab parameters were high. Serum ferritin was 2000 ng/ml. Based on the findings, the disease was concluded as juvenile idiopathic arthritis (JIA).

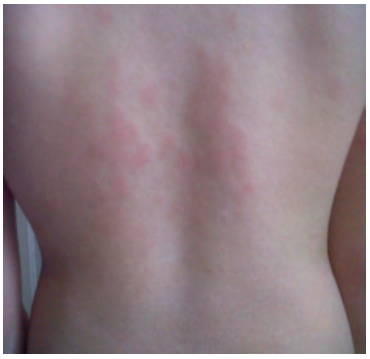

Fig. 2: Evanescent skin rashes over body

Systemic JIA, an autoinflammatory disease, is characterized by inflammation in one or more joints, high spiking and quotidian fever that lasts for at least 2 weeks, and skin rashes.[4] The diagnosis if JIA is mainly clinical. Other conditions that may mimic JIA include infections, childhood cancer, and bone disorders.[5] It can be complicated by macrophage activation syndrome.

Case scenario 3: SLE with diffuse alveolar hemorrhage and class 4 lupus nephritis

An 8-year-old girl presented with the following complaints: fever since 6 weeks with 2 weeks afebrile period in between, skin rashes since 2 weeks, respiratory distress since 24 hours, and 2 episodes of blood in sputum. Physical examination revealed fever, tachycardia, tachypnea, borderline hypertension, petechial to purpuric spots over the lower limbs, bilateral crepitations, and hepatosplenomegaly. Laboratory values showed anemia, borderline leucopenia, thrombocytopenia, and elevated ESR, but normal CRP. Urine examination showed 3+ proteinuria and hematuria. The X-ray showing lung involvement is given in figure 3.

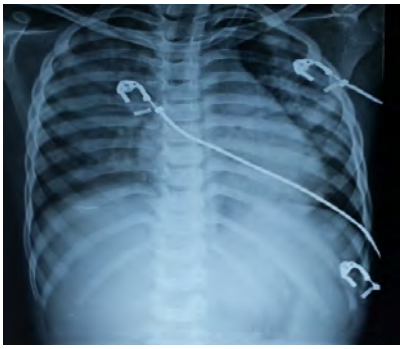

Fig. 2: Evanescent skin rashes over body

The following specific tests results assisted in diagnosing the disease: ANA- 1: 1280 titer, anti-dsDNA antibodies- positive, C3- 50 (80-160), C4- 7 (16-40), and renal biopsy- class 4 lupus nephritis. The final diagnosis was SLE with diffuse alveolar hemorrhage and class 4 lupus nephritis. The child was salvaged with repeated plasmapheresis, cyclophosphamide and steroid.

Case scenario 4: Enteric fever by *Salmonella Paratyphi*

A 12-year-old boy presented with fever since 1 month and treated periodically with multiple antibiotics. He had weight loss of about 3 kgs, but no history of TB contact. The child was appearing toxic and had hepatosplenomegaly. Urine routine was negative and USG abdomen revealed no focal collections. No significant lab findings were noted and ANA was negative. Histopathology of bone marrow revealed erythroid hyperplasia and culture demonstrated the presence of *Salmonella paratyphi*. The child had enteric fever caused by *Salmonella paratyphi* and the fever recurrence was due to the suboptimal use of antibiotics.

Case scenario 5: TRAPS

A 4-year-old boy was brought with complaints of recurrent fever, periorbital redness with swelling, painful skin rashes over trunk and thighs, and occasional abdominal pain. Laboratory tests of blood counts reveled leukocytosis, thrombocytosis, elevated ESR and CRP. Urine routine and blood culture were normal. The disease was diagnosed as tumor necrosis factor **α** receptor-associated periodic fever syndrome (TRAPS).

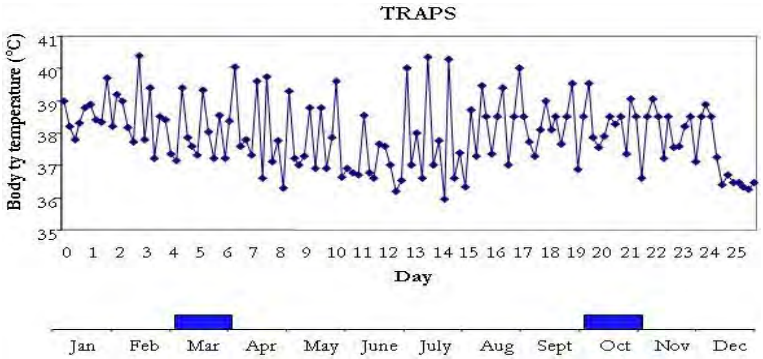

Fig. 4: Fever pattern in TRAPS

TRAPS is a condition characterized by recurrent episodes of fever. The fever typically last about 3 weeks, but can persist for few months.[6] During episodes of fever, people with TRAPS can have additional signs and symptoms. These include abdominal and muscle pain and a well demarcated spreading skin rash, typically found on the limbs. Affected individuals may also experience puffiness or swelling around the eyes (periorbital edema) and conjunctivitis.[6]

Case scenario 6: Juvenile dermatomyositis

A 6-year-old girl presented with complaints of recurrent fever since 6 months, difficulty in walking and climbing stairs, inability to squat and pain on being lifted up. The child was irritable with normal vital signs. Physical examination revealed weakness of proximal muscle of both upper and lower limb, truncal muscle and neck flexor muscle, and the presence of heliotrope rash. Laboratory examination showed that all counts and enzymes were normal, except LDH. Significant muscle edema in MRI along with clinical picture helped in the diagnosis of juvenile dermatomyositis (Fig.5).

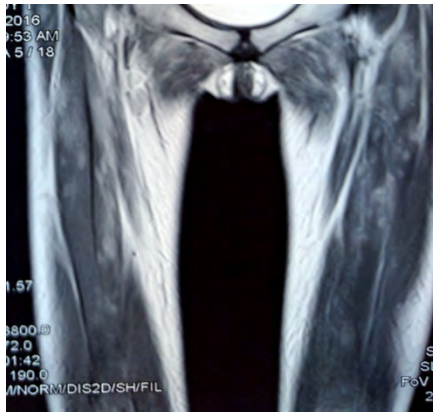

Fig. 5: MRI showing muscle edema in juvenile dermatomyositis

Case scenario 7: Brucellosis

A 7-year old girl, from an agrarian family, presented with symptoms of recurrent fever since 3 months, weight loss, and joint pain. Physical examination showed mild pallor, hepatosplenomegaly, and monoarthritis of the right knee. Laboratory values revealed moderate anemia, leucopenia, and elevated

ESR. Further evaluation revealed that the child was positive for Brucella IgM and was successfully treated with doxycycline and rifampicin.

Case scenario 8: Behcet's disease

A 7-year-old male child presented with complaints of recurrent fever and oral and genital ulcers since 1 year (Fig 6 &7). Physical Examination revealed stable vital signs, hepatomegaly, oral aphthae and penile ulcer.

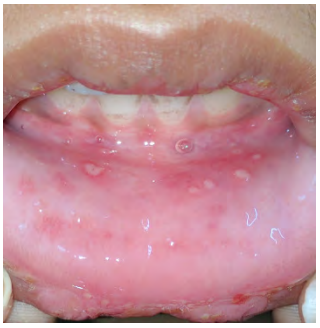

Fig. 6: Oral Aphthae

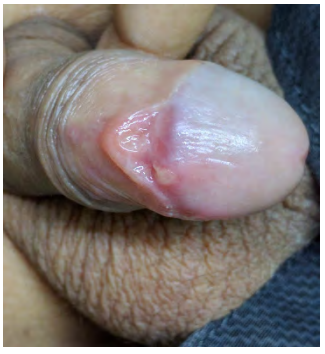

Fig. 7: Penile ulcer

This is a classic case of Behcet's disease. Further evaluation showed anemia and elevated ESR, and 2D echo revealed intracardiac thrombosis, which is a complication of Behcet's disease.

Case scenario 9: Infectious mononucleosis

A 14-year-old adolescent boy presented with complaints of recurrent fever since 6 weeks, sore throat at onset of fever for 7 days, and weight loss. Examination revealed generalized lymphadenopathy and splenomegaly. Blood counts were nearly normal. But differential counts showed predominant lymphocytes and peripheral smear showed plenty of atypical lymphocytes. Heterophile antigen test was positive. This is a case of infectious mononucleosis. This case highlights the need of considering infectious mononucleosis even in adolescent patient.

Case scenario 10: acute lymphoblastic leukemia

A 4-year-old girl presented with recurrent fever and pain in upper and lower limbs since 4 months. Examination revealed irritability, body tenderness, pallor, generalized lymphadenopathy and

hepatosplenomegaly. The child had anemia, leukopenia, lymphocytic predominance, borderline thrombocytopenia, elevated ESR and lymphocytic predominance in peripheral smear. Histopathology of bone marrow revealed plenty of blasts and the diagnosis was concluded as acute lymphoblastic leukemia.

Take home message

- In an immunocompetent patient, recurrent fever is not uncommon.
- Meticulous history and good physical examination will give clues in 80-90% of the patients.
- Rational use of simple investigations is important.
- Avoid use of antibiotics if the patient is not very sick, and use appropriate dose, if needed.
- Periodic fever, though rare, is not uncommon.

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Fever with rash

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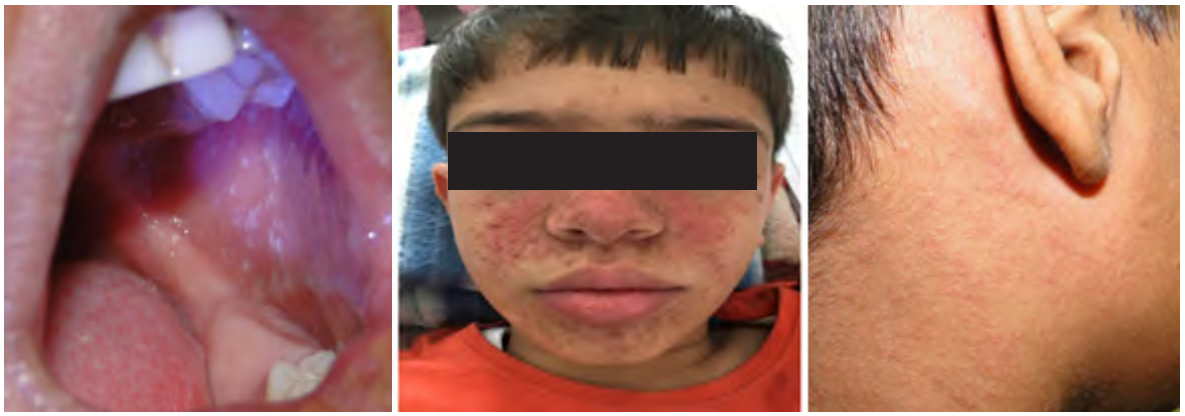
Introduction

Sir William Osler has underscored the significance of the skin as the mirror of the body. Many rashes that appear during febrile illnesses are manifestations of the underlying infectious diseases. Since infectious diseases range from mild infections to severe infectious diseases, basic knowledge of these diseases is integral for accurate diagnosis. The history collection on recent travel, exposure to animals, medications, forest and other natural environments, and time of onset of symptoms is essential for clinical diagnosis. It is also critical to understand the patient's history of specific diseases, including cardiovascular, sexually-transmitted, and immunodeficiency diseases.

Due to globalization and increase in travel and migration, imported infections with secondary local transmission are of greater concerns. Moreover, outbreaks in susceptible individuals may pose containment issues. The factors such as location, morphological pattern and their classification, rate of emergence, accompanying pruritus, and the association between the rash and fever play a paramount role in diagnosis.[1] In addition, the morphology of the primary skin lesions, seasonal occurrence, the distribution, arrangement of secondary lesions, and the presence of enanthem may assist clinicians in making an etiological diagnosis.[1]

Depending on the characteristic morphology, distribution, and accompanying symptoms; febrile rashes are broadly classified as maculopapular rash; generalized diffuse erythema; and vesicular, pustular, nodular, petechial, and purpuric rashes. The clinical vignettes discussed in this paper may help clinicians in better understanding the distributions and patterns of presentations of various

rashes, which may assist them to establish the diagnosis.

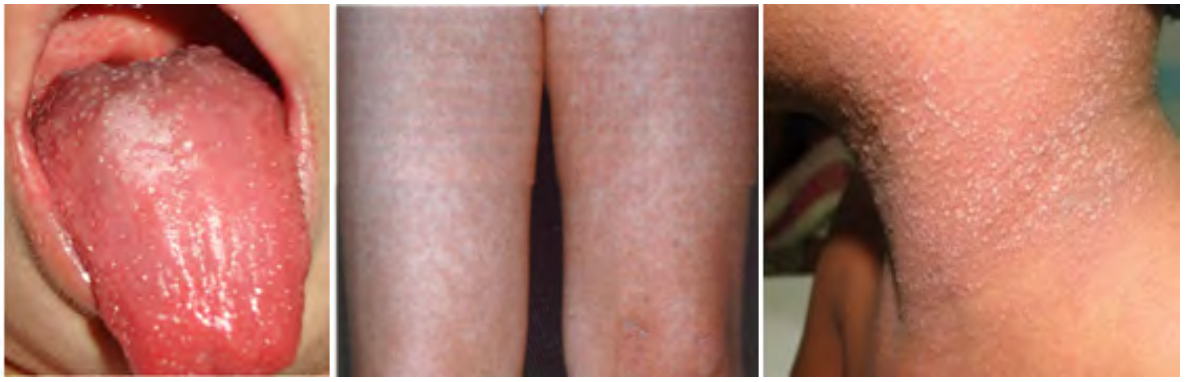


Case 1

An 8-year-old boy presented with fever for 4 days, cough, runny nose, and red eyes. Red maculopapular rash appeared on the 2nd day of fever.

CLASSIC CUPLIC SPOT MESEALES

Case 2

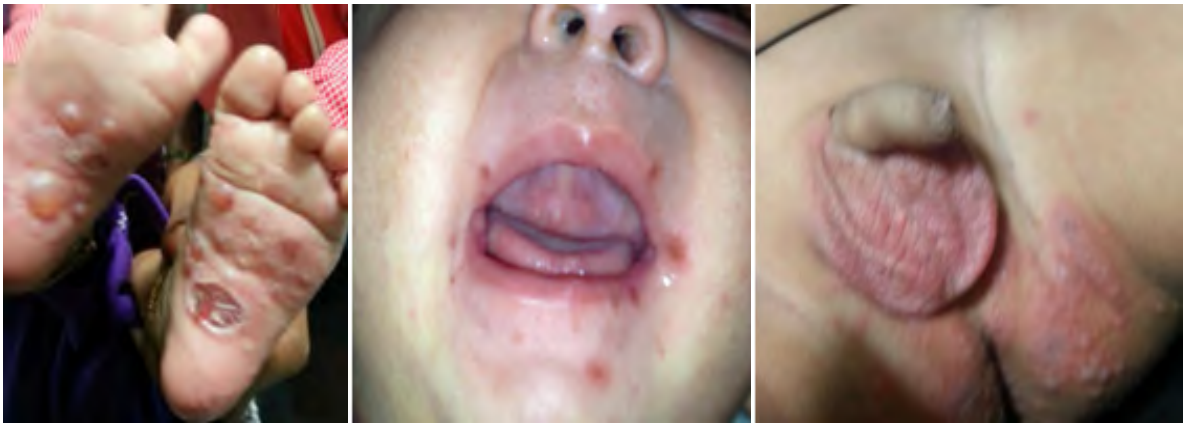


A 9-year-old girl had fever, sore throat and rash for 3 days.

SCARLET FEVER

It is caused due to the infection by erythrogenic exotoxin-producing group A *beta-hemolytic* streptococci. The characteristic presentations include acute febrile illness, sore throat, gooseflesh or coarse sand-paper rash within 12-48 hrs (most intense at pressure areas such as axilla and groin), Pastia's line, strawberry tongue, and pustule (staph scarlet). Desquamation begins towards the end of the 1st week.

Case 3

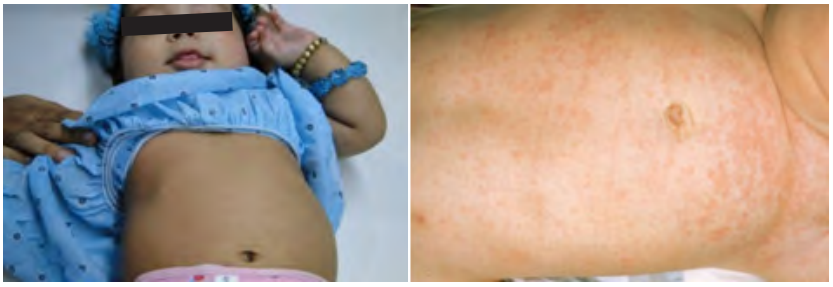


HAND, FOOT, AND MOUTH DISEASE

A common acute febrile illness of children caused by group A coxsackie viruses 16, which resolves in 2-7 days. Nowadays, the pattern of presentation has changed, and the rashes are appearing on the elbows, shoulder, buttocks and groin. In 5% of the cases, there in an increased risk for complications like encephalitis and pulmonary edema.

Case 4

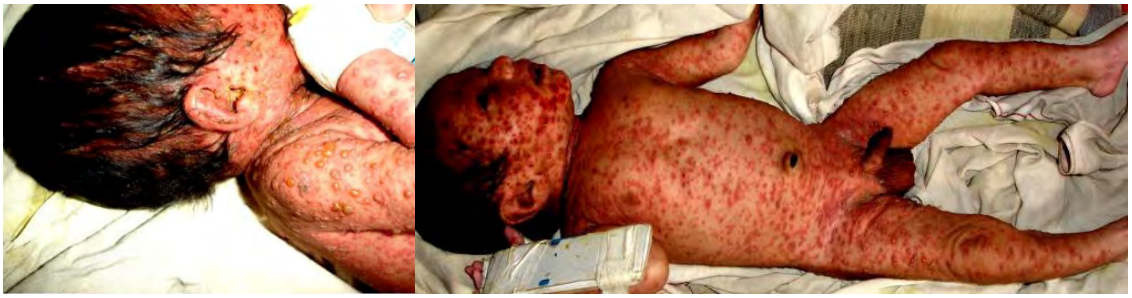
An 8-month-old baby had fever for past 5 days, but no other symptoms. Macular rash appeared on the second day of starting acetaminophen and the fever subsided.



ROSEOLA INFANTUM (EXANTHEM SUBITUM)

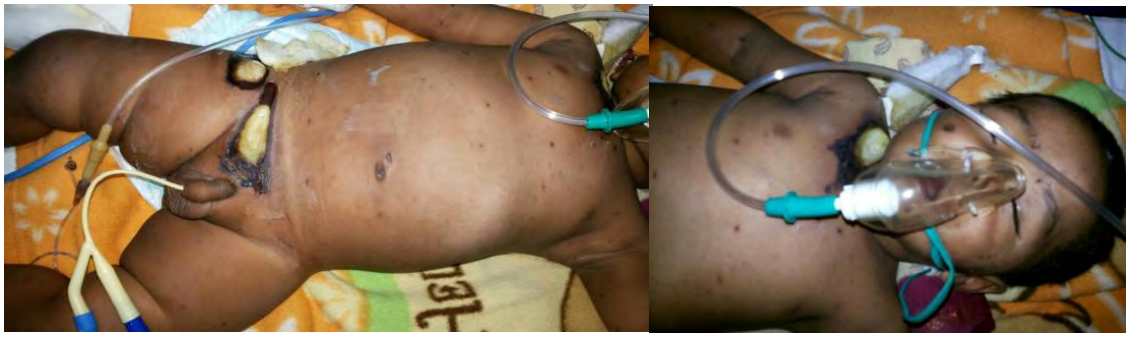
The disease is caused by human herpes virus 6 and 7. The characteristic features include high fever for 3-4 days, and the abrupt defervescence with appearance of rash. These is an increased risk for febrile seizures due to the infection.

Case 5



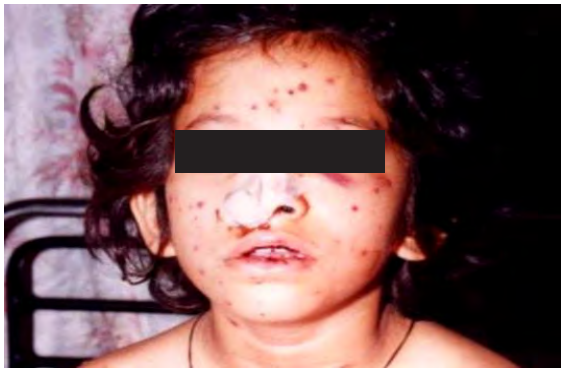
VARICELLA / CHICKENPOX

If a mother has infection 5 days before or 2 days after birth, the newborn will contract varicella infantum (mortality without treatment is 30%). The treatment options include varicella immunoglobulin and IVIg 400 mg.



GROUP A STREPTOCOCCAL INFECTION (Complication of varicella)

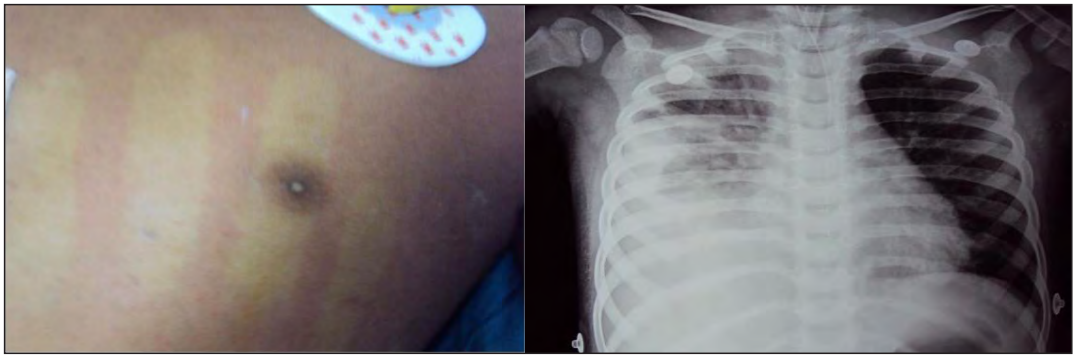
A 1.5-year-old child presented with shock, diffused erythroderma, necrotizing fasciitis over groin and upper chest and old chickenpox rashes.



HEMORRHAGIC CHICKENPOX

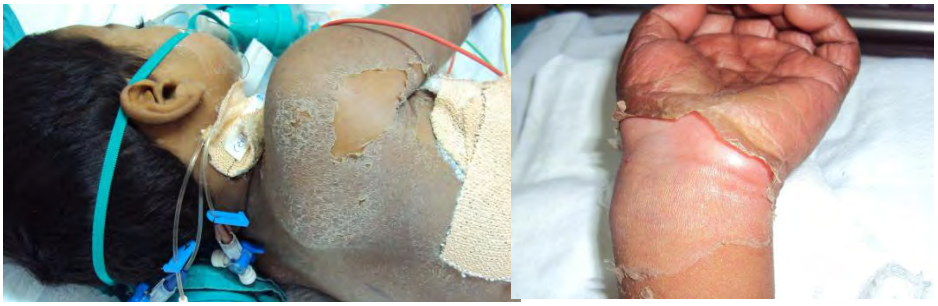
A girl had epistasis, hematuria, hematemesis, subconjunctival bleeding and lesions all over the body.

Case 6



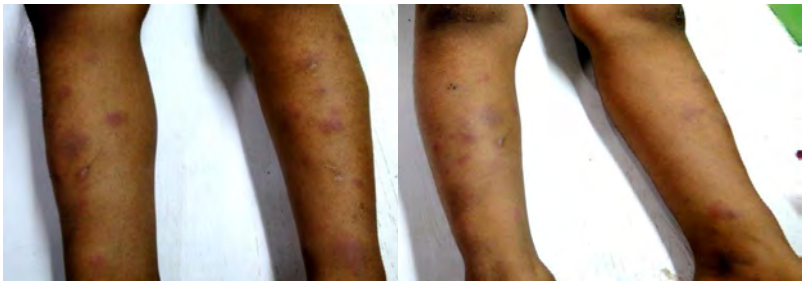
TOXIC SHOCK SYNDROME

A 4-year-old male child presented with fever and cough (4-5 days), vomiting (2 days), breathlessness (1 day) and irritability. On admission, the child had fever, drowsiness, tachycardia, tachypnoea, hypotensive, delayed CRT, flushing and feeble peripheral pulses. Physical examination revealed decreased air entry on right side lungs with B/L crepitations, hepatomegaly and diffused erythroderma. Thoracentesis indicated turbid pus and staphylococcal infection. The child had shock and was kept in ventilator support.



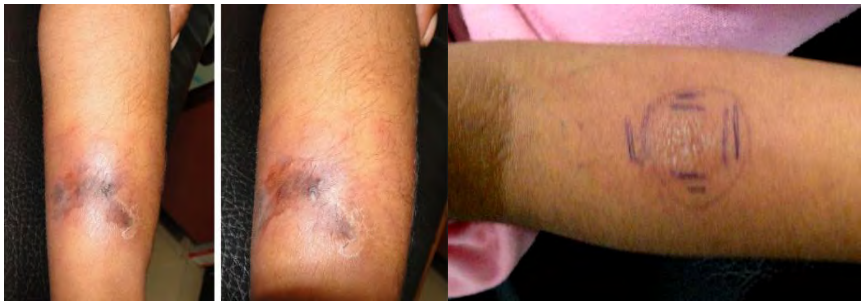
Toxic shock syndrome is a rare but life-threatening condition caused by *S. aureus*. After 7 days, the child started peeling.

Case 7



ERYTHEMA NODOSUM (Post streptococcal)

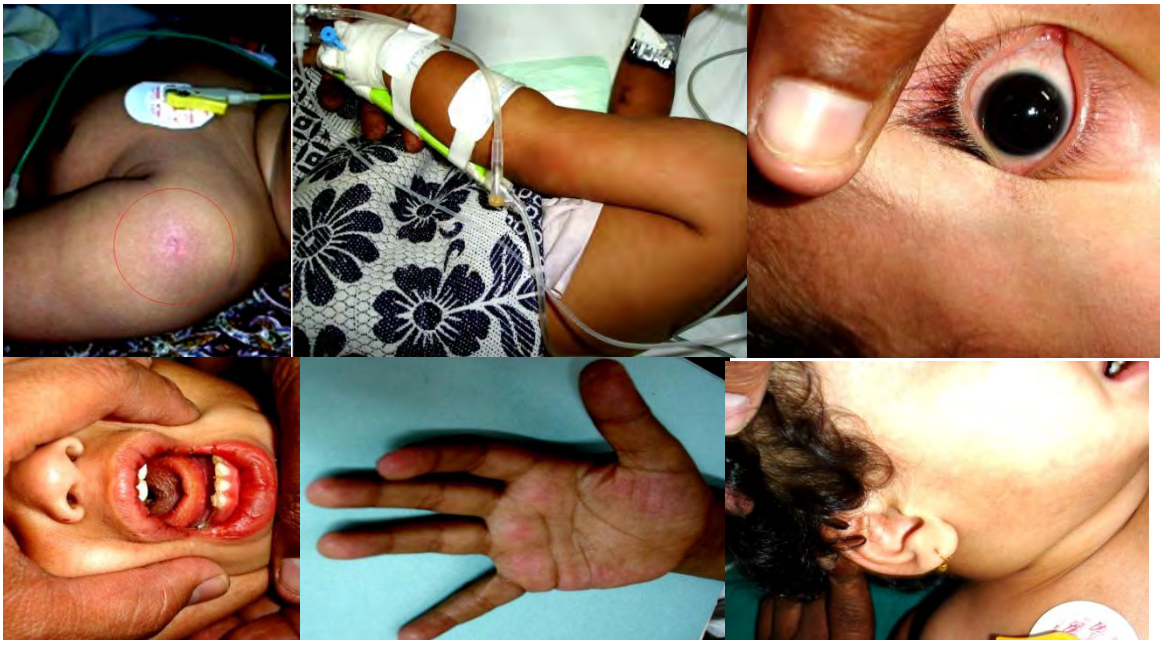
A 6-year-old male child presented with fever for 5 days, throat pain, and lesions on shin.



ERYTHEMA NODOSUM (Due to tuberculosis)

A 4 year-girl-child had fever for the past 3 weeks and violaceous lesions over tibia. She was positive for tuberculin skin test.

Case 8



STEVENS-JOHNSON SYNDROME (Drug induced)

A 3-year-old boy presented with fever and irritability for 6 days. Physical examination revealed maculopapular rash, non-purulent conjunctivitis, limbal sparing, cracked lips, strawberry tongue, enlarged cervical lymph nodes and redness of the palm. Peeling of the skin was noted after one week.

Case 9

A 2-year-old child was admitted with high-grade fever and convulsions. Treatment started with paracetamol and phenytoin. The child developed rashes on 3rd day. The symptoms improved after the discontinuation of phenytoin.

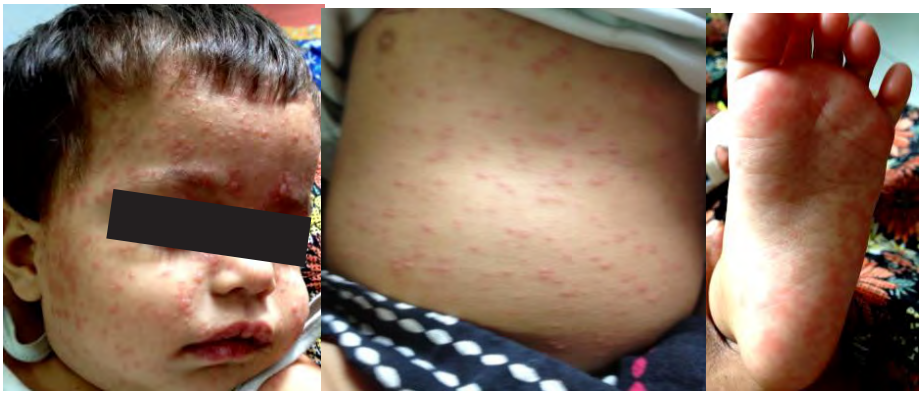


Fig. 1: Initial presentation

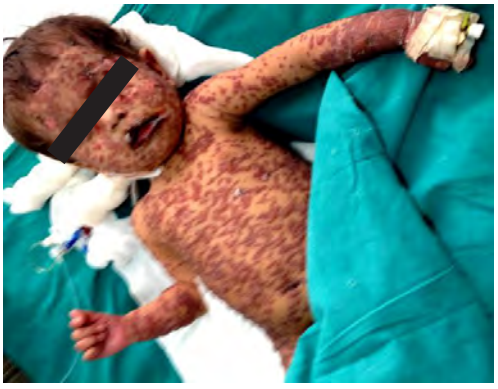


Fig. 2: Child on day 5 with rashes

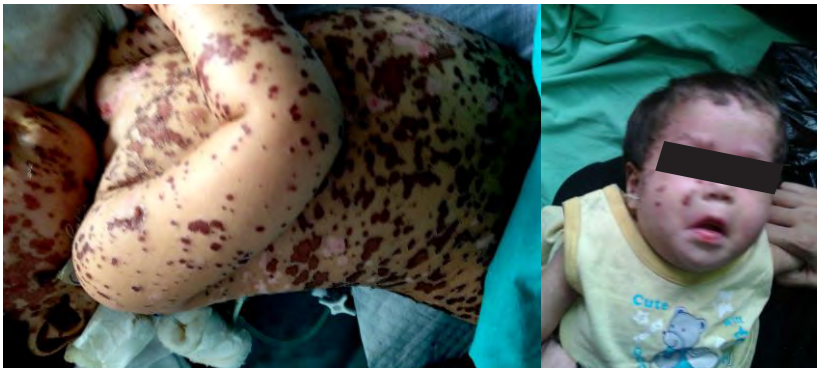


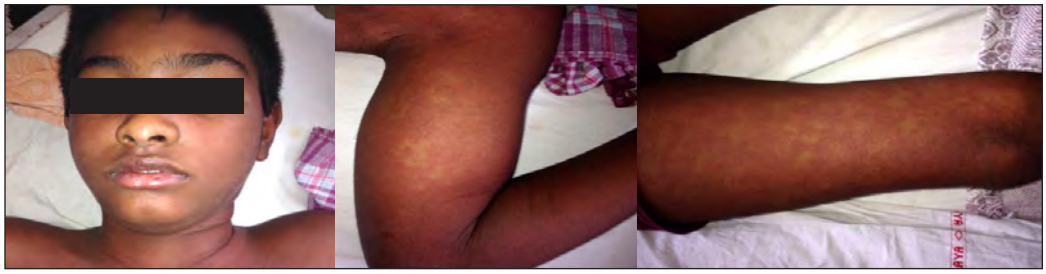
Fig. 3: Improvement after stopping phenytoin

The disease can be induced by medications such as NSAIDs, sulfonamides and anticonvulsants, and less commonly by mycoplasma pneumoniae and HSV. Burn protocol can be followed as treatment.

Case 10

A 9-year-old male child presented with high-grade fever (10 days) and rash over the body (5 days). He was not consuming anything orally for 2-3 days and had pain in chest and abdomen. Physical

examination revealed maculopapular rash over the trunk, lymphadenopathy and hepatomegaly. The child's condition improved after the cession of carbamazepine. Laboratory values showed TLC: 13500/µl (P 27%, L 64%, E 8%, M 1%) and SGPT: 110/L.

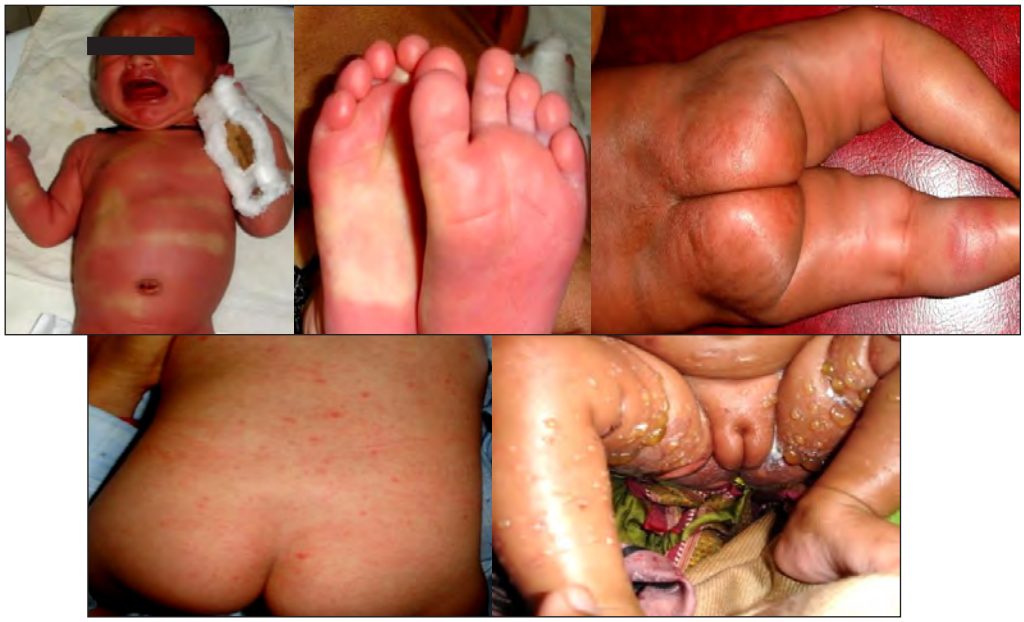


DRESS SYNDROME (Drug induced)

The presence of 3-4 of the following criteria assists in concluding DRESS syndrome: acute rash, fever >38°C, lymphadenopathy, involvement of at least one internal organ, and abnormal blood counts (lymphopenia or lymphocytosis, eosinophilia, and thrombocytopenia).[2]

Case 11

A newborn baby presented with diffused erythroderma, tachycardia, convulsions and encephalitis. Maculopapular rashes and bullous rashes are common in chikungunya.



CHIKUNGUNYA

Case 12

A 5-year-old girl presented with fever, rash, body ache, and flushing all over the body. Decrease in platelets and increase in hematocrit were noted. The following three types of rashes, characteristic for dengue, were noted.

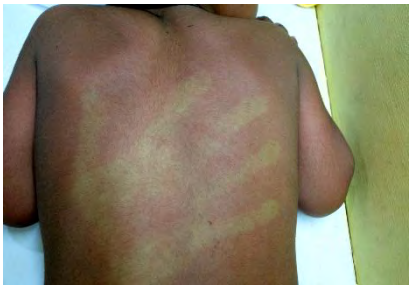


Fig.1: Presentation of diffused erythroderma on first 3 days

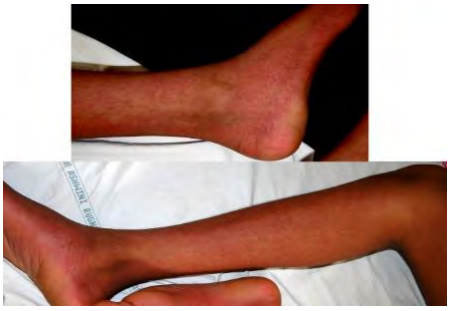


Fig.2: Purpuric rashes noted with decrease in platelets

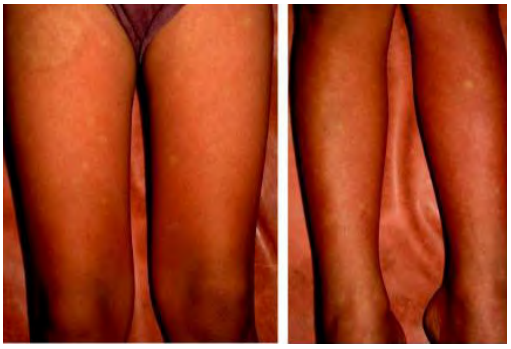
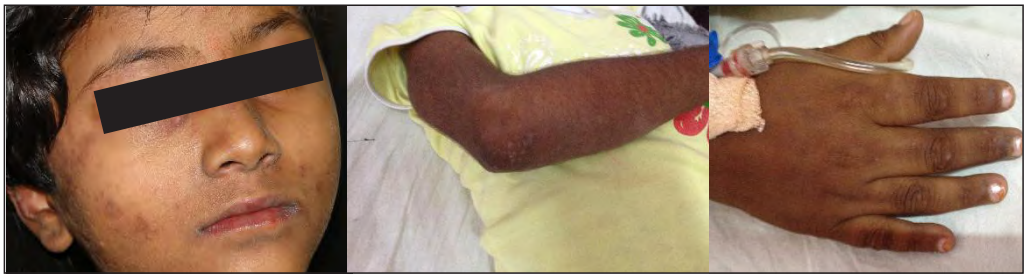


Fig. 3: White island in red sea rashes noted while recovering

Case 13

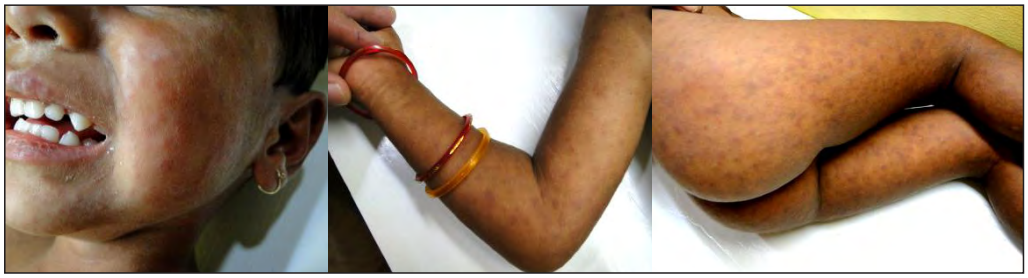
A child presented with weakness, body ache and Gottron's papules for the past 6 months.



DERMATOMYOSITIS

Case 14

A 5-years old female child presented with fever (6 days), palpable purpura rash (3 days), irritability (3 days) and pain in legs (2 days). She was treated with various antibiotics and lab values were normal.



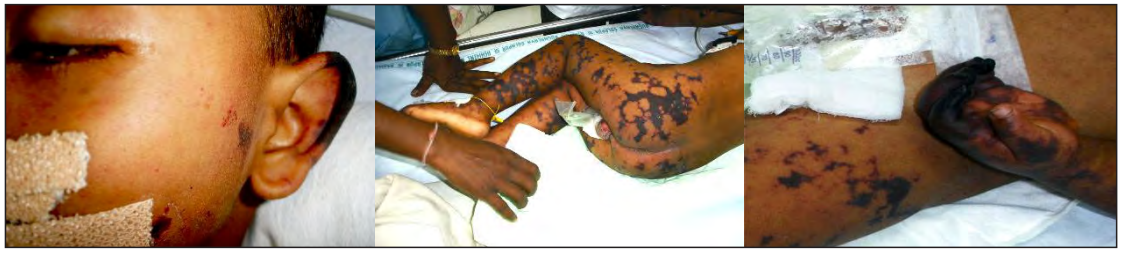
RICKETTSIAL FEVER

Rickettsial pathogens are transmitted through fleas, lice, mites, and ticks. If the disease is suspected, it is recommended to start the treatment immediately with doxycycline 2.2 mg/kg bid and acetaminophen, prior to the laboratory confirmation. ELISA may appear positive only on the second week of disease.

Case 15

A 4-year-old male child presented with fever (6 days), rash (4 days), convulsion (2 days), and altered sensorium (2 days). He resided in a rural area and had been exposed to animals. Leukocytosis, anemia and leukopenia were identified on laboratory investigations. He was treated with various antibiotics.

On admission, the child was febrile (103^0 F), unconscious, no response to verbal stimuli, decerebrating, and had irregular respiration (Spo2: room air 68 to 70%). The child was intubated and stabilized. Physical examination revealed gangrene over the ears and fingers, and extensive necrotic patches over the lower limbs.



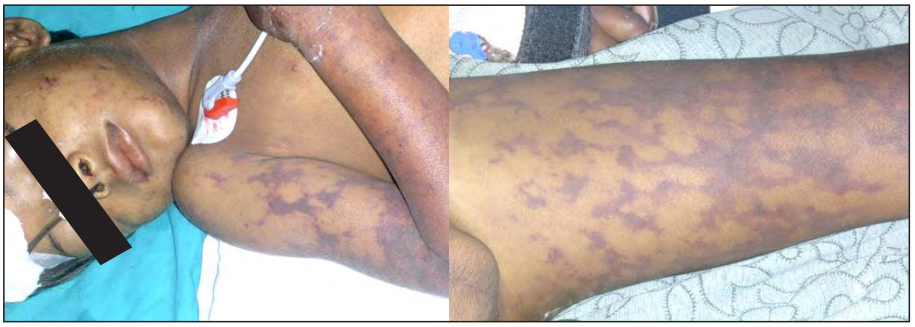
PURPURA FULMINANS

Weil-Felix test and ELISA for spotted fever were positive and started the treatment with doxycycline, chloramphenicol and mannitol. Child improved well. Unfortunately, he had to undergo amputation of left-hand fingers.

Case 16

A 10-year-old child presented with icterus and altered sensorium. He had taken some herbal medication earlier as a treatment for fever. Investigations showed anemia, thrombocytopenia, serum bilirubin 6.2 mg/dL and SGPT- 98/L. Child had continuous hematemesis and purpuric rashes.

Provisional diagnoses considered were sepsis with multi-organ dysfunction, meningococcal septicemia, and rickettsial encephalitis. Since the child's condition was deteriorating, peripheral smear was carried out and the results showed the presence of burr cells. The child was immediately treated with plasmapheresis and he progress well.



THROMBOTIC THROMBOCYTOPENIC PURPURA

Conclusion

Accurate diagnosis of fever with rash is important, because the treatment is decided on the basis of underlying etiology. Some rashes are life-threatening and require prompt medical attention. Categorizing the patients based on the distribution of rash, direction of spread, and the number and type of lesions may help in concluding the diagnosis.

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Approach to pyrexia of unknown origin

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Identifying FUO

Fever in children has different facets and fever not responding to treatment is a highly perplexing situation. Fever of unknown origin (FUO) in children is defined as the fever ≥ 38°C (101°F) occurring at least once per day for ≥ 8 days and no apparent diagnosis has been concluded even after conducting a careful inpatient and outpatient evaluation.[1] Moreover, the fever should be documented by a healthcare provider.

It is necessary to differentiate FUO from fever without source (FWS). Fever for ≤1 week without adequate explanation, even after a thorough history and physical examination, can be considered as FWS. In most cases, FUO may be a common presentation of an uncommon disease or an uncommon presentation of a common illness.

The below given real-life clinical scenario shows that the knowledge and understanding on FUO has changed over time. In 2001, A 27-month-old child, vaccinated as per the age, presented with high-grade fever of 7 days duration. The child was irritable and had glossitis, red tongue, red eye, macular rash, and cervical adenitis on the left side. CSF analysis revealed cell count of 20, protein 53 mg/dL and normal sugar level. Though it had been identified as a FUO at that period, the current clinical spectrum shows that it is a definite case of Kawasaki disease.

The majority of FUO are caused due to infections (60-70%), followed by rheumatological diseases (20%), malignancy (5%), and miscellaneous/ without diagnosis (5-10%).[2] Chronic sinusitis is the common, but often missed, cause for FUO. Other infectious causes are endocarditis, occult abscess

(abdomen, dental), viral infections (e.g. EBV), TB, brucellosis, UTI, typhoid, and cat scratch disease. The non-infectious causes include collagen diseases such as JIA and SLE; neoplasms like leukemia, lymphoma and neuroblastoma; and miscellaneous diseases like drug fever, IBD, immunodeficiency and hemophagocytic lymphohistiocytosis. The diagnosis of UTI as FUO is mainly due to the haphazard use of antibiotics and not sending the samples for culturing on time.[3]

The commonly noted zoonoses linked to FUO are: brucellosis, ornithosis, Japanese encephalitis, rickettsia, leptospirosis, trichinosis and toxoplasma

Evaluating FUO

The paramount part of FUO evaluation is understanding how sick the child is and this will help the clinician to decide where the child should be treated as in-patient or out-patient. Red flag signs that should be considered for identifying potentially serious diseases are listed in table 1.

Table 1: Red flag signs to considered in FUO

Clinical history	Clinical examination
Prolonged appetite loss	Organomegaly
Weight loss	Lymphadenopathy
Sleep disturbance	Rash
Focal complain	Clubbing
	Focal signs

Collecting a detailed history and conducting careful physical examination (including ENT examination) are mandatory for evaluating FUO. The evaluation approach should be sequential, by collecting the history as the first step, followed by conducting physical examination, making provisional diagnosis, conducting necessary investigation and managing the disease. Reassessment of history and investigations may be necessary until the disease gets resolved.

Fever documentation and maintain a fever diary are essential in history collection. The parents should be instructed to maintain a fever diary with the following details: date and time of recording, height and duration of fever, method of assessing the fever, and associated symptoms and response to antipyretics.[4]

If the child is not appearing ill or no other signs and symptoms have developed during the febrile episode, it may be necessary to consider the possibility of factitious fever or JRA.[5] The persistence of constitutional symptoms (eg, myalgias, headache, malaise, etc.), even after the abatement of fever, is suggestive of underlying systemic disease. During inter-febrile period, if the child is appearing toxic, the probable disease can be an underlying infection; whereas, if the child is not appearing toxic, the disease could be immune-mediated.

The patient-directed physical examination should include: documentation of fever, evaluation of vital signs and growth parameters, head to toe examination and systemic examination. Relative bradycardia is an important clue for typhoid fever, typhus, babesiosis, malaria, leptospirosis, yellow fever, and dengue fever. Weight loss may indicate TB, HIV, IBD, diabetes malignancy or other systemic illness/infection. Short stature or deceleration of linear growth may be suggestive of IBD or endocrine abnormalities.

Important diagnostic clues

In children with cervical lymphadenopathy, other lymph nodes and the draining area should be closely examined to rule out EBV, CMV, HIV, adenovirus, peritonsillar/paratonsillar abscess, TB, Kawasaki disease, hemophagocytic lymphohistiocytosis, autoimmune lymphoproliferative syndrome, and Kikuchi disease.

Pattern of rashes, and rashes with fever are diagnostic clues for exanthema, vasculitis, Langerhans cell histiocytosis, rheumatic fever JIA, SLE, IBD, sarcoid disease etc.[6]

Cardiovascular symptoms may be suggestive of pericarditis, pyopericardium, pericardial effusion, polyarteritis nodosa, and infective endocarditis. The presence of pneumonitis may be the diagnostic clue for sarcoid disease, Wegener's syndrome and polyarteritis nodosa.

The involvement of CNS may be suggestive of meningitis and meningismus. CSF analysis in such cases shows pleocytosis, increased protein and normal glucose levels.

Diagnostic clues related to common eye conditions

Some of the common eye conditions that may be suggestive of underlying FUO are listed below:

- Palpebral conjunctivitis: EBV
- Bulbar conjunctivitis: Leptospirosis, Kawasaki disease
- Conjunctival hemorrhage: Infective endocarditis
- Phlyctenular keratoconjunctivitis: TB
- Red eyes: Kawasaki disease, leptospirosis, infectious mononucleosis
- Absent tears and corneal reflexes: Familial dysautonomia (Riley-Day syndrome)

Abnormal funduscopic examination

- Choroid tubercles: Miliary tuberculosis
- Chorioretinitis (e.g. raised yellow-white, cottony lesions in a nonvascular distribution)
- Toxoplasmosis
- Perivascular sheathing: Vasculitis
- Slit lamp ophthalmologic examination: Uveitis

Diagnostic clues for musculoskeletal diseases

- Recurrent pharyngitis with ulcerations
- Periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome (PFAPA)

Diagnostic clues related to sinuses and oral cavity conditions

- Sinus tenderness in patients with persistent nasal discharge: rhinosinusitis
- Oral ulcers: IBD, SLE
- Pharyngeal hyperemia without exudate: Infectious mononucleosis (EBV or CMV), toxoplasmosis, tularemia, leptospirosis
- Dental abscess and other oral infections: May be complicated by other infections (e.g. sinusitis, brain abscess, mediastinal abscess)
- Anomalous dentition (hypodontia, anodontia or conical 'peg teeth'): Hypohidrotic ectodermal dysplasia
- Smooth tongue (i.e. without fungiform papillae) or excessive salivation: Familial dysautonomia

- Gingival hypertrophy or inflammation and loosening/ loss of teeth: Leukemia, Langerhans cell histiocytosis

Abdominal signs and symptoms suggestive of FUO

Gastrointestinal complaints are indicative of salmonellosis, leptospirosis, intestinal TB, intra-abdominal abscess, hepatosplenic cat scratch disease, and IBD. Hepatomegaly or splenomegaly is often noted in brucellosis, infectious mononucleosis, infective endocarditis, malaria, and salmonellosis. Tenderness on palpation of the liver may indicate hepatitis or liver abscess.

Laboratory investigations and findings

The initial screening tests to be conducted in FUO are listed below:

- CBC
- Peripheral smear
- Urine routine and culture
- Inflammatory markers
- Serum electrolytes, blood urea nitrogen, creatinine, and hepatic aminotransferases
- X-ray chest/Mantoux/sputum
- CSF analysis
- Blood culture
- USG

The following differential diagnoses should be considered while interpreting CBC and associated clinical symptoms in patients with FUO:

- Anemia: malaria, tuberculosis, infective endocarditis, JIA, SLE, and IBD
- Thrombocytosis: JIA, Kawasaki disease
- Thrombocytopenia: EBV, CMV, HIV, parvovirus, leptospirosis, tularemia, rickettsial infection, SLE, Kikuchi
- Fever, chills, aches, myalgia, and respiratory symptoms: Viral/ Flu illness
- Fever with or without chills, anemia, spleen+/- thrombocytopenia: Malaria
- Fever, retro-orbital pain, rash with muscle pains with rising hemoglobin and falling platelets: Dengue
- Fever beyond 4 days, sick looking, Liver and/or spleen +/- thrombocytopenia with leucopenia: Enteric fever
- Prolonged Fever, myalgia, multi-system involvement, thrombocytopenia: Brucellosis, leptospirosis, rickettsia, non-infectious diseases.

Apart from bacteremia, a positive blood culture may be indicative of infective endocarditis, typhoid fever, and brucellosis. Sterile pyuria along with pus cells in urine culture is suggestive of Kawasaki disease, adjacent intra-abdominal infection, and genitourinary tuberculosis. SLE, infective endocarditis, or leptospirosis should be speculated in hematuria and/or proteinuria.[3]

Extremes of the counts, pronounced thrombocytosis/thrombocytopenia, marked leukocytosis/ bandemia, elevated CRP, and reduced ESR, ferritin and fibrinogen are the red flag parameters of potentially serious conditions. For some disease/ conditions, the inflammatory markers may appear

normal, but the child may have persistent fever. Some of the conditions/disease are hyperthyroidism, hyperadrenocorticalism, neurological damage, cystic fibrosis, ichthyosis, dysautonomia etc.

Conclusion

Despite the access to newer diagnostics and management approaches, FUO remains a clinical challenge. detailed history and examination remain the cornerstone in concluding the diagnosis and guiding further investigation. Antibiotics or any other treatment, apart from supportive care, should not be initiated until the diagnosis is confirmed.

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Management of fever

Panel discussion

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A 2-year-old child weighing 11 kg, presented with fever 103°F of couple of hours and vomiting 2-3 times. How to manage the child?

This a common scenario noted in daily clinical practice. The child will be kept in observation and paracetamol and antiemetics can be prescribed to relieve the symptoms. It is also preferred to collect child's other history like irritability, weakness, headache etc. Ambient temperature and excessive clothing should also be considered while evaluating the cause of fever. If the fever is due to increased environmental pressure, the child should be encouraged to consume more fluids and to avoid excessive clothing.

Why paracetamol should be chosen instead of other more effective drugs like ibuprofen?

The child should be given paracetamol only to increase his comfort level and fever of 103°F for 2 days is not a serious matter of concern. Both the drugs are effective as antipyretics. In elderly patients, paracetamol is indicated for relieving the pain also. Paracetamol has a shorter duration of action, as it should be repeated every 4 hours. Whereas, ibuprofen should be given every 6 hours. In addition, paracetamol is safer when compared to the occurrence of side effects like gastritis with ibuprofen and mefenamic acid. Along with medications, parents can adopt other temperature relieving measures such as tepid sponging. Also, some children may develop gross hematuria, which may make the parents more panicky. If paracetamol is effective in managing fever, there is no need to switch to mefenamic acid or other drugs. At the onset of fever, it is preferable to manage only with paracetamol.

What is meant by 'doing well' in term of symptoms noted in the child?

In terms of symptoms noted, 'doing well' means the child is comfortable and paracetamol is helpful to bring down the temperature by 1 to 2°F. It is not intended to completely reduce the fever, as the fever is necessary to enhance the immune system functioning. This has to be clearly explained to the parents while prescribing the drug.

Since the child is having fever and vomiting. Whether paracetamol suppository can be used for managing the child?

If the child is vomiting and not responding to oral medications, paracetamol suppository can be used to manage the symptoms. The convenience of the parents must be considered while prescribing it.

What are the drawbacks of paracetamol suppository?

The main concern is convenience. Appropriate placing of the suppository is important. If placed outwards, it may fall off from the anus; and if it is placed too much interior, it may cause injury. In addition, the child may be scared of introducing a suppository and some elderly children may resist its use. At a very hot environmental temperature, there is an increased risk of softening and melting of the suppository.

What should be the ideal dose of rectal paracetamol to be prescribed?

The ideal daily dose of rectal paracetamol is 15 mg/kg and the maximum dose is up to 60 mg/kg. Since the absorption is erratic, some may prescribe a loading dose of 30 mg/kg.

Whether IV paracetamol can be prescribed, since the child is vomiting?

If the child is not eating and admitted to the hospital due to severe vomiting, IV paracetamol can be recommended. Otherwise, it is not necessary for a 2-year-old child. Analgesia in IV paracetamol is much higher when compared to the oral paracetamol.

Whether the parents should be instructed to perform tepid sponging?

Normal bathing water (warm), instead of cold water, is preferred for tepid sponging. The sponging should be done at interval to provide time for evaporation and heat loss. Tepid sponging should be performed along with the administration of antipyretic. Forehead tepid sponging will give more comfort to the child. However, recent evidence shows that it is not effective in bringing down the temperature.

For every 1 degree increase in temperature, should the fluid intake be increased by 12%?

The fluid intake can be decided based on the urine output and frequency. It also depends on the weather. There is no such guideline to increase the fluid intake for every one degree increase in temperature. Since the thirst is proportional to the dehydration, the fluid intake should be based on the child's acceptance level. Hydration is very crucial for reducing the temperature. Nowadays, due to the use of diaper and busy schedule of the parents, it may be difficult to assess the urine output. In such cases, the urine color is indicative of the child's fluid intake. The high-colored urine may be suggestive of the need of increasing the fluid intake.

What should be the recommendation on clothing for a child with fever?

The child should not be wrapped too much and it is necessary to loosen the clothes. Wrapping the

child with clothes conserves the heat and cause more heat production. Cotton clothing is preferred over the synthetic one and improving the ventilation will make the child more comfortable. Clothing may also depend on the climate. Overclothing may also produce fever in infants (not >101° F).

Is it preferable to switch on the AC to make the child more comfortable?

If it is a very hot summer month, the AC can be switched on to make the child more comfortable. It also depends on the mother's intelligence to judge the child's comfort zone. The room should not be too cold, as it may induce vasoconstriction. Too much warm may also cause perspiration. Hence, it is ideal to maintain the temperature at 25-26°C.

How effective is eau de cologne?

Eau de cologne should not be used due to the alcohol content.

How to manage the child having 101°F of fever, even after giving paracetamol?

It is one of the very common problems confronted by the clinician. In some children, ibuprofen may be more effective. If the child is comfortable, despite the elevated temperature, the parents need not worry regarding the temperature. The paracetamol reduces temp by 1-2 degree after 2 hours of administration.

The child developed swelling on his lips and rash after the administration of paracetamol. Is it necessary to discontinue the drug?

It is very rare with paracetamol. The medication should be discontinued and never be used if there is any anaphylactic reaction.

Should paracetamol and ibuprofen be prescribed as a plus syrup?

There are studies on the combined, individual and alternative uses of paracetamol and ibuprofen. But the combined use has not been found to be beneficial. Hence, they should not be prescribed as a combination drug. Either paracetamol or ibuprofen is sufficient to make the child comfortable.

Whether alternating the administration of paracetamol and ibuprofen is recommended?

It may cause more confusion and overdosing. Hence, alternating the drugs is not recommended. But, if one dose of ibuprofen is administered during a course of paracetamol, the duration between each fever episodes can be decreased.

Whether paracetamol toxicity can happen due to excessive dosing?

Paracetamol toxicity can happen due to the confusion on formulation. Comparatively it is much safer. However, there were cases of paracetamol toxicity due to overdosing and dehydration, which required ICU care. Paracetamol can be administered for longer duration at proper doses.

Whether mefenamic acid is still prescribed as an antipyretic?

Mefenamic acid has a good antipyretic profile and helps to bring down the temperature significantly, but it has severe adverse effects, predominantly renal. Hence the parents should be counselled not to use it for treating routine problems.

Two days later, the child develops a brief tonic clonic seizure. Whether the child requires more aggressive management of fever? Should the parents be counselled about more aggressive management in future?

Height of fever is not the reason for febrile seizures. It can occur even in cases with regulated fever. A child who gets febrile seizure is more prone to develop similar episodes in future till 5 years of age. It is also necessary to gather the child's family history regarding febrile seizures. The parents can be counselled regarding the measures to be adopted to manage seizures, and should be informed that there is no relationship between aggressive management and prevention of seizures. Medical books have clearly mentioned that management of fever does not have any impact on febrile seizure.

The child develops cough and wheeze. What is the effect of antipyretics in a coughing wheezing febrile child?

Both ibuprofen and paracetamol have equal propensity in worsening the wheezing in a susceptible child. The drugs should be contraindicated in child with a history of wheezing due to the drug administration.

The child is having a low-grade fever of 100.4°F on day 7. Should the parents continue the paracetamol?

Since the fever is only 100.4°F, there is no need of any medication.

Two weeks later, the child visits the clinic for vaccination and the parents are concerned about fever and convulsions. Should the child be prophylactically managed with paracetamol?

Depending upon the situation, on SOS basis, paracetamol can be administered for relieving fever and ibuprofen for reducing swelling/pain.

What is the opinion on use of antipyretics for managing fever associated with dengue?

In dengue cases, the child will be having persistent high-grade temperature, and it may be very difficult to manage the fever with antipyretics and may require change of drugs. Ibuprofen should be contraindicated in managing dengue fever due to the increased risk for bleeding.

What are the situations in which the clinician should start antibiotics along with antipyretic?

If the child is having high-grade fever and bacteremia is strongly suspected, antibiotics should be started along with antipyretics. Febrile neutropenia is another indication for starting antibiotics along with antipyretics.

Which is the safer antipyretic to be prescribed in a TB child receiving hepatotoxic drug?

Paracetamol is the safer drug in a child receiving hepatotoxic drug for TB.

Fever and immune deficiency: Eyes see only what mind knows

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Introduction

Immunodeficiency disorders occur when the body's immune response is compromised or absent. Primary immunodeficiency (PID) affects 1 in 500 individuals and many of them remain undiagnosed. Immunodeficiency should be suspected in children with persistent/recurrent fever and those with unusual infections, apart from the usually offered diagnosis of sepsis in children with fever in ICU.

The Jeffrey Modell Foundation (JMF) is a public charity devoted to early and precise diagnosis of immunodeficiency, and developing treatment and management strategies through clinical and basic research, physician education, patient support, advocacy, public awareness, and newborn screening.[1]

Warning signs suggestive of a PID

The following are the 10 warning signs recommended by JMF for suspecting immunodeficiency:[2]

1. Eight or more ear infections in one year
2. Two or more severe sinus infections in one year
3. Two or more months treatment of antibiotics with little effect
4. Two or more pneumonias per year
5. Insufficient weight gain or growth delay
6. Recurrent deep skin or organ abscesses (e.g. liver, lungs)
7. Persistent thrush in mouth or fungal infection on skin
8. Need for intravenous antibiotics to clear infections

9. >2 deep seated infections (e.g. septicemia, meningitis)
10. Family history of a primary immunodeficiency

If two or more aforementioned warning signs are present, primary immune deficiency can be suspected.

Real life scenarios will help in better understanding the diagnosis and management of PID and some of them are discussed below:

X- linked agammaglobulinemia

Case scenario 1: A 4-year-old boy presented with a history of recurrent hospitalization due to 3 episodes of pneumonia and 2 episodes of ear discharge. The chest X-ray revealed pneumonia. This case can be usually confused with other diseases like congenital heart disease, aspiration syndrome, cystic fibrosis, and anatomical defects. A thorough physical examination revealed the absence of tonsils (Fig.1) and cardiac murmurs. Absent tonsils with recurrent pneumonia in a boy are classic symptoms of X- linked agammaglobulinemia. Laboratory investigations indicated reduced IgG (<93 mg/dl), IgA (<16 mg/dl) and IgM (<11 mg/dl) and absence of β cells and immunoglobulins, thereby confirming the diagnosis.

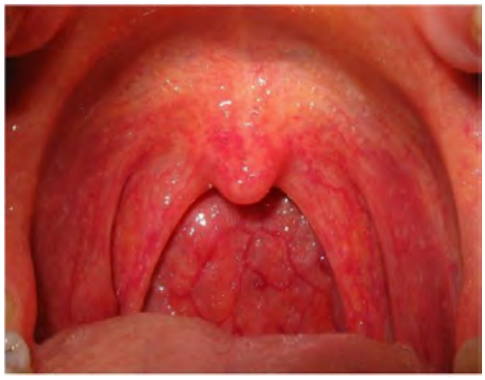

Fig.1: Absence of tonsils in X- linked agammaglobulinemia

Case scenario 2: A 3.5-year-old boy admitted with high-grade fever and neutropenia. The pediatric intensivist collected the child's previous history of recurrent illness (encephalopathy, hypotensive shock and pneumonia), multiple hospitalizations and treatment history. Immunoglobulin tests revealed low immunoglobulin counts and absence of β cells. This confirmed the condition as X-Linked agammaglobulinemia and his condition improved with monthly IVIG therapy.

X-linked agammaglobulinemia, a prototype of humoral immunodeficiency, occurs almost exclusively in males.[3] It is generally asymptomatic till the age of 6 months due to the transplacental transfer of immunoglobulin. Immunoglobulin profile showing near/ total absence of B cells (<1%) and panhypogammaglobulinemia assists in concluding the diagnosis. Small to absent tonsils and no palpable lymph nodes in boys are clinically suggestive of this condition.[3]

Immunodeficiency in adults are grossly underdiagnosed. In India only 5% of the cases are diagnosed; whereas, in western countries, the diagnosis of new cases of adult immunodeficiency account for around 60%. This discrepancy in diagnosis can be explained using below given examples.

Common variable immune deficiency (CVID)

Case scenario 1: A-41-year-old Guajarati male who had a history of 15-20 hospitalizations from the age of 15 presented with episodes of chest infections and diarrhea. He was seen by many physicians, pulmonologists, gastroenterologists and had undergone many tests and treatment, but none of them could treat him properly. He did a google search with frustrated mind, which helped himself to identify his condition as immunodeficiency. The patient presented to the physician with self-diagnosis, they checked his immunoglobulin profile and confirmed his condition as common variable immune deficiency (CVID) with low immunoglobulin counts and 10% B cells (Fig .2).

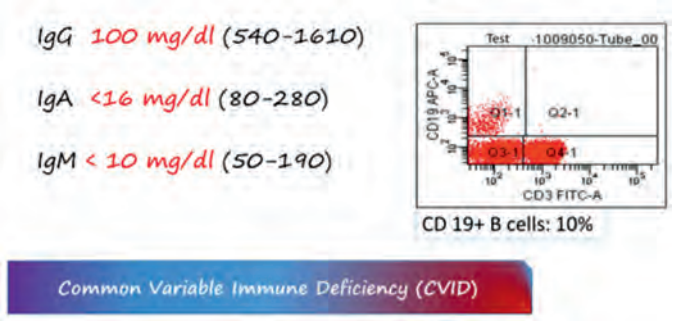

Fig. 2: immunoglobulin profile in CVID

CVID is a disorder that impairs the immune system with hypogammaglobulinemia with phenotypically normal B cells.[4] Most patients with CVID are diagnosed in their 20s or 30s and the presence of autoimmune manifestations may confuse the diagnosis. Most of them have normal or enlarged tonsils with 25% having splenomegaly.[4]

Case scenario 2: A 25-year-old female, presented with a history of recurrent chest infections from the age of 9 and polyarthritis treated by rheumatologists and orthopedicians. She also had bilateral ear discharge and her X-ray revealed bronchiectasis. The pulmonologist suggested an immunoglobulin profile, which helped in the diagnosis of CVID. Immunodeficiency should be suspected in patients with idiopathic recurrent bronchiectasis. The simple algorithm that can be followed in a suspected case of immunodeficiency is given in figure 3.

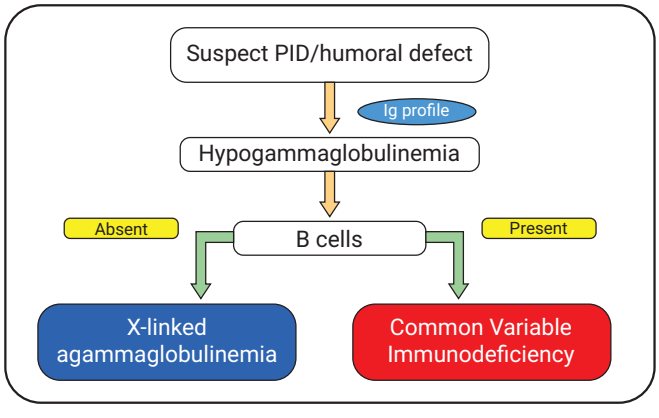

Fig. 3: Simple algorithm that can be followed in suspected immune deficiency

Hyper IgM syndrome

Case scenario 1: A 3-year-old boy presented with a history of ventilation for 17 days at the age of 6 months due to severe ARDS. But the pneumonia recurred at the age of 1.5 years and he was on treatment for the probable hyper reactive airway disease for the past one year due to recurrent wheezing and fever. The patient was referred to an immunologist and the lab findings revealed recurrent neutropenia. Immunoglobulin profile showed high IgM counts (> 542 mg/dl). The condition was diagnosed as hyper IgM syndrome. The disease is characterized by defective CD40 signaling, causing an elevated IgM levels, but decreased serum IgG, IgE and IgA (Fig. 4).[5]

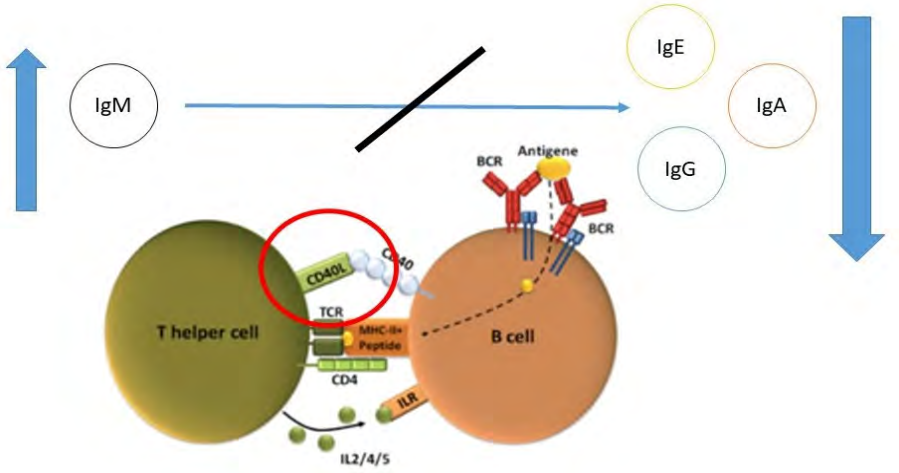

Fig. 4: Defective CD40 signaling in hyper IgM syndrome

Severe Combined Immune Deficiency (SCID)

Case scenario 1: A 7-month-old breast fed girl child presented with a history of ear discharge at 4 months of age, severe pneumonia, and oral thrush. HIV was negative. Chest X-ray revealed the absence of thymus shadow and the absolute lymphocyte count was only 1200/mm^3. Based on the findings, the diagnosis was concluded as severe combined immune deficiency (SCID).

SCID patients are usually affected by severe infections in infancy and often present with interstitial lung disease, chronic diarrhoea, and failure to thrive. Ear infections, recurrent pneumonia, and profuse oral thrush are common in such patients.6 A closed look at the absolute lymphocyte count and chest X-ray will give a diagnostic clue for SCID.

Case scenario 2: A 4.5-month-old male child presented with a history of first episode of pneumonia. The child was thriving well. Further clinical investigations revealed that T cells were absent and the diagnosis was concluded as SCID. The baby had undergone a stem cell transplant and became healthy.

Chronic granulomatous disease

Case scenario 1: A 4-year-old boy presented with unresolved patches on his chest (Fig.5) and high spiking fever. He was not responding to antibiotics. Lung aspiration indicated the presence of Aspergillus and CBC revealed neutrophilic leukocytosis and increased gammaglobulinemia. Based

on the clinical and lab findings, the diagnosis was confirmed as chronic granulomatous disease (CGD). This condition can be confirmed using NBT reduction test. Aspergillus is a signature pathogen for CGD.

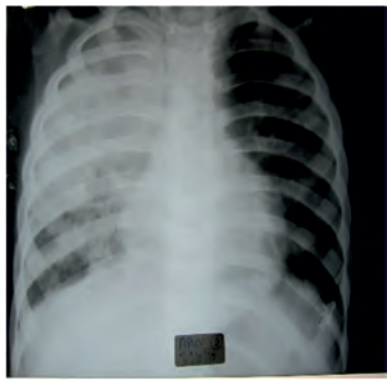

Fig.5: unresolved patches in chronic granulomatous disease

Case scenario 2: A 4-year-old boy presented with a history of recurrent pneumonia since 2 years of age, complicated with rib osteomyelitis and swelling over cervical spine. Rib granuloma, observed in rib aspiration, was treated thrice with anti-tuberculin therapy, before consulting an immunologist. MRI of spine revealed vertebral osteomyelitis. Based on the clinical and lab findings, the diagnosis was concluded as CGD. CGD should be considered as a part of differential diagnosis in all cases of granuloma.

Case scenario 3: A 2-year-old boy presented with a history of swelling of both the feet since one year. X-ray revealed osteomyelitis of meta tarsal bones, which was successfully treated with anti-microbial therapy. But the child revisited the clinic with suppurative lymph adenitis on one side, which did not respond to antimicrobials. Lab findings revealed thrombocytosis and leukocytosis, and immunoglobulin profile indicated hyper gammaglobulinemia. The diagnosis was confirmed as CGD. He had undergone stem cell transplantation and prognosed well. CGD should be suspected in cases with osteomyelitis involving small bones, accompanied by leukocytosis and thrombocytosis.[7] Repeated suppurative lymph adenitis, liver abscess, and recurrent pneumonia are suggestive of CGD.

Wiskott-Aldrich syndrome

Case scenario 1: A 3-year-old boy presented with pneumonia and the CBC showed thrombocytopenia. The death of his sibling at the age of 6 months due to dysentery gave a diagnostic clue to immunodeficiency. The low mean platelet volume and reduced platelet size indicated a diagnosis of Wiskott-Aldrich syndrome.

In every child with persistent thrombocytopenia, it is recommended to evaluate mean platelet volume.

Leukocyte adhesion deficiency

A 3-month-old girl presented with distended abdomen and the umbilicus appeared erythematous. CBC showed marked leukocytosis and high neutrophil counts. This condition was diagnosed as leukocyte adhesion deficiency. It is marked by the inability of leukocytes to adhere to the vessel

wall, so the counts are high in blood stream and there are no leukocytes in the cells to fight against infection.

Disseminated BCG: Atypical mycobacteria

A 6-month-old well-thriving boy, presented with fever, rashes and ulcerated BCG cite. He also had hepatosplenomegaly and the culturing of aspirated node revealed disseminated BCG strains. Further tests revealed *STAT1* gene mutation. Based on these findings, the diagnosis was concluded as Mendelian susceptibility to mycobacterial disease (MSMD).

Conclusion

Think common is a usual saying by all teachers. But immunology foundation says that when you hear hoof beats, they cannot be always horses, it can also be zebras. Primary Immunodeficiencies are like the zebras of the medical world.

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Panel on interesting problems in managing fever

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The present paper discusses the dilemmas confronted by clinicians in everyday clinical practice while managing pediatric cases.

CASE SCENARIO: 1

A 9-month-old infant presents with fever of one day without focus, not showing response to orally administered paracetamol in adequate doses. How aggressive should the approach be?

Regarding the fever per se, the baby should be made comfortable and the mother should be counselled regarding the necessity to wait. Additional measures should be taken to relieve fever such as removing the thick clothes, sponging the body with luke warm water and frequent small quantity of freshly prepared soft smashed foods. Danger signs to be looked for.

Does age influence the management? What should be the approach if the baby was of 2 months old or if 5 years old?

In both the situations, it is necessary to look at the vitals. Irrespective of the fever, if the baby is fine, the clinician can focus on consoling the baby and opt for watch and wait. However, if the vitals are not normal and/or if there is altered sensorium, a different management approach is required. Babies of <3 month with persisting high fever, should be investigated aggressively. In a 5-year-old child, we can wait and watch. The focus of the clinician should vary with the age of the child; younger the age more likelihood of serious bacterial infections (SBI) particularly <3 months old.

Any other history, which makes the approach aggressive?

In certain clinical situations, like if the child is on long-term steroids or has uncontrolled diabetes mellitus or other underlying disease lie leukemia, a cautious approach is required. If the immune functions are not normal either on its own or due to the treatment for other associated conditions (eg: the child who had measles 3 weeks ago), an aggressive approach is mandatory.

If this infant had a febrile seizure 2 months ago, does the management approach change?

No, there is no change in management.

Worried parents requesting for investigations, as their neighbor has been diagnosed with Dengue. The 9-month-old child has a fever of <12 hours. Does conducting NS1 antigen, platelet counts, or ELISA for Dengue IgM is relevant?

Since the fever is of <12 hours, none of the tests including NS1 antigen, platelet counts, or ELISA for Dengue IgM will come positive. The parents should be instructed to wait and observe. PCR test for Dengue mostly arrive positive on day 1, but it is ideal to do NS1 antigen on day 2. All NS1 positive children do not develop the serious manifestations of Dengue.

How early the malaria can be diagnosed? Which test should be done first, peripheral smear or rapid diagnostic test?

Generally, malaria tests do not show positive result on day 1. Theoretically, peripheral smear shows positive result after 24 hours. Rapid test may be positive on day 1. Hence, it is advocated to do both the tests.

Is it possible to arrive at a confident diagnosis on the first day of fever?

With only fever as symptom, it is difficult to arrive at a diagnosis.

In exceptional cases, if the patient is receiving chemotherapy or/is immunodeficient, the physician should be more aggressive to arrive at a diagnosis on the first day itself.

Any clinical situations wherein rapid reduction of fever is beneficial?

In exceptional cases like a child with cardiovascular compromise or with organ defect, in which situation increase in metabolism is not desirable, rapid reduction of fever may be beneficial.

The worried parents come back after 2 days and the infant is still febrile. What should be the management approach?

If the fever is persisting for >2 days, a urine analysis is recommended to rule out UTI particularly if the child has no other accompanying symptoms e.g., cough, cold, vomiting, diarrhea etc.

How early should screening tests detecting IgM antibodies to be performed? What is their relevance?

IgM presence is detected only after a few days of infection. For Dengue, it usually takes 4-5 days to show the presence of IgM in the peripheral blood. This is a valid parent education point. It is preferable to do an antigen detection test than an antibody detection test at the earlier stages.

If the parents come on the fifth day with a report of Typhidot Positive or a Widal reaction showing titers 1:120, What should be the next step?

It is necessary to look into other clinical parameters and symptoms like pattern of fever recurrence,

leukopenia etc., considering the possibility of false positive result. It is recommended to do a blood culture to corroborate the test result. Generally, it is not advocated to do Widal within the first week of illness. The endemicity of the disease in the area in which the child resides will also influence the WIDAL test report.

Do acute phase reactants help in diagnosis? How frequently they should be evaluated?

They are generally done as adjunct to other key tests. Acute phase reactants like WBCs are done at the first time of admission and they are not repeated, unless it is necessary. There is a common notion that if the CRP is >24 mg/L, it should be ruled as a bacterial infection. But it can happen in viral infection, inflammatory reaction, Kawasaki disease etc. Hence the cut off to be considered for CRP should be 60-80 mg/L. Moreover, it depends on the lab where the CRP is tested and method of quantification. Serial test may yield more information.

If the child is having persistent fever, whether chest-X ray is useful for diagnosis?

Yes, if the child is having leukocytosis and all other vital parameters and urine routine are normal, it is preferable to do X-ray. It is recommended to monitor the breathing and heart rates in a febrile child to conclude tachypnea, which may be a clue to pneumonia. It should also be remembered that the radiological manifestations of pneumonia are relatively late when compared to clinical manifestations.

If typhoid is suspected and IgM is positive, whether the antibiotic treatment should be initiated? What criteria to be adopted to choose the antibiotic? What should be the route of administration, oral or parenteral?

It is advocated to wait for a blood culture to confirm the diagnosis. In confirmed cases, cefixime of 20 mg/kg twice a day is recommended and a lower dose is recommended to treat other infections including bacterial and fungal.

CASE SCENARIO: 2

A child having fever for 4 days who is already on antibiotics, yet not responding. How to evaluate the child and what should be the treatment approach?

It is important to understand the cause of infection and the type of antibiotic administered. If the child is having throat infection due to acute tonsillitis, cefixime may not be the appropriate drug and it should be substituted with another antibiotic (eg: amoxicillin). If the child has UTI and cefixime has been initiated, it is essential to check the urine culture report for drug resistance to decide on substituting the antibiotic. The dosage and compliance of the antibiotic administered also need to be rechecked. Thorough examination and close monitoring are needed to rule out the possibility of other infections like rickettsia.

Antibiotic should be stopped before performing any culture report including standard blood culture and BACTEC culture. Moreover, it is necessary to look at other foci of infection by conducting X-ray and/or ultrasound.

Does height of fever always indicate serious infection?

No, it is recommended to look at the total clinical profile of the child including red flag signs.

NICE National Institute for Health and Care Excellence

Traffic light system for identifying risk of serious illness

	Green – low risk	Amber – intermediate risk	Red – high risk
Colour (of skin, lips or tongue)	• Normal colour	• Pallor reported by parent/carer	• Pale/mottled/ashen/ blue
Activity	• Responds normally to social cues • Content/smiles • Stays awake or awakens quickly • Strong normal cry/not crying	• Not responding normally to social cues • No smile • Wakes only with prolonged stimulation • Decreased activity	• No response to social cues • Appears ill to a healthcare professional • Does not wake or if roused does not stay awake • Weak, high-pitched or continuous cry
Respiratory		• Nasal flaring • Tachypnoea: – RR >50 breaths/ minute, age 6–12 months – RR >40 breaths/ minute, age >12 months • Oxygen saturation ≤95% in air • Crackles in the chest	• Grunting • Tachypnoea: RR >60 breaths/minute • Moderate or severe chest indrawing
Circulation and hydration	• Normal skin and eyes • Moist mucous membranes	• Tachycardia: – >160 beats/minute, age <12 months – >150 beats/minute, age 12–24 months – >140 beats/minute, age 2–5 years • CRT ≥3 seconds • Dry mucous membranes • Poor feeding in infants • Reduced urine output	• Reduced skin turgor
Other	• None of the amber or red symptoms or signs	• Age 3–6 months, temperature ≥39°C • Fever for ≥5 days • Rigors • Swelling of a limb or joint • Non-weight bearing limb/not using an extremity	• Age <3 months, temperature ≥38°C* • Non-blanching rash • Bulging fontanelle • Neck stiffness • Status epilepticus • Focal neurological signs • Focal seizures
CRT, capillary refill time; RR, respiratory rate *Some vaccinations have been found to induce fever in children aged under 3 months			
This traffic light table should be used in conjunction with the recommendations in the NICE guideline on Feverish illness in children. See http://guidance.nice.org.uk/CG160			

CASE SCENARIO: 3

A 3-year-old with fever for two days, clear urine, 8 to 10 puss cells and other normal parameters. The referring doctor has already informed the parents that the child has UTI and needs IP care. What should be the approach?

The infection may not be due to UTI. The chances of febrile pyuria should be considered. It is recommended to repeat the urine samples with Leukocyte esterase and urine culture. The Leukocyte esterase and nitrate can be evaluated simultaneously through dipstick test. If the child does not have any urinary symptoms, it is essential to consider alternate diagnosis.

CASE SCENARIO: 4

A 5-year-old with fever (4 days), swelling in neck (3 days, Fig. 1), difficulty to swallow (2 days, Fig. 2), and change in voice (2 days). Do these symptoms indicate a common upper respiratory tract infection noted in daily clinical practice?

No this presentation is unusual and other uncommon diagnosis have to be considered.

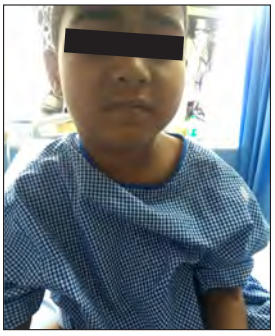

Fig: 1

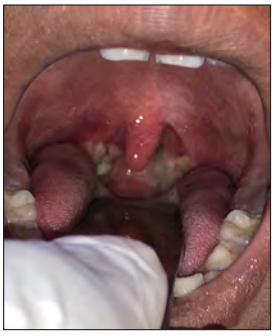

Fig: 2

It is a case of diphtheria and it indicates the resurgence of the disease in India. Epstein bar virus is a probable differential diagnosis, but it can be ruled out, since the child has neck swelling, swallowing difficulty and change in voice. The presence of epitrochlear lymph node is suggestive of EBV infection.

CASE SCENARIO: 5

A toddler presented with cold, cough and fever followed by wheezing. He had shown no significant response to treatment for fever and his respiratory distress persisted even after two days of IP care. What would be the treatment approach?

A viral-induced wheeze responds in 48hrs. It is recommended to do an X-ray to rule out the possibility of pneumonia with wheezing. Recent similar history in the family should be considered to rule out influenza virus. H1N1 patient may also mimic similar symptoms.

In such cases, the following may help to recognize bacterial infections:

i. history of fever at home,
ii. abdominal pain,
iii. triage temperature of >38°C and
iv. SpO2 of <92%.

In some cases, mycoplasma may trigger wheeze, which may be similar to viral-induced wheezing.

Fever: Parent education

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Introduction

Fever is one of the commonest symptoms requiring unscheduled visit to clinician. In 1800s, Dr. Carl Wundelich, a German researcher felt the need to document fever. In the field of clinical thermometry, he conducted a research involving 20,000 normal subjects of both genders to determine the actual normal body temperature. The normal body temperatures noted by the scientist in adult males and females were 98.2°F and 98.6°F respectively. He was the first person to determine diurnal variation in body temperature i.e. an increase of 1°F by evening.[1]

What parents anticipate from the pediatrician?

Most of the parents consult pediatrician for medicines to normalize the body temperature of their child. However, it is necessary to educate the parents that fever in the moderate range could be beneficial, and it is only a symptom and not an illness. About 5% of the parents consider 100.4°F as high fever and around 25% of parents start with the administration of antipyretics when the temperature is <100°F.[2] About 80% of the pediatrician feel that it is not necessary to wake up the child for giving medications. Some of the common parent concern and answers by the clinician are given in table 1.

Table 1: Common concerns by the parents and answers by the clinician

Parent's concerns	Answers by the clinician
100.4°F is high fever	Wait, fever could be beneficial and it is only a symptom.
Start antipyretics even if the fever is <100°F	Not necessary.
Should wake the child up for medication	Not necessary. Sleep is necessary for recovery.
The drug dosage is too much or too little (50% of the parents). Supranormal doses (15% of the parents)	The drug dosage should be determined based on the weight of the child and not the age. Accurate measuring of the drug is important.

Message to the parents on antipyretic therapy

The clinician should communicate the following to the parents regarding the benefits of antipyretic therapy:[3]

- To reduce the overall discomfort of the child
- To reduces water loss due to dehydration
- To buy time to investigate and diagnose the underlying problem

The potential benefits of fever include: retardation of bacterial or viral growth, proliferation of T lymphocytes, production of neutrophils, and elicit acute phase reaction. Limited data shows that not treating a viral fever may actually help in shortening the course of fever, as the high temperature may kill the viruses. The message that can be given to the parent is "*Paracetamol is there for your child, but not necessarily good for your child*".

Primary goal of treatment

The primary goals of treating a fever are the following:[4]

- Improve the overall comfort of the child.
- Ensure that the child is getting adequate sleep.
- Focus on the sufficient fluid and food intake of the child.
- Focus on the general wellbeing of the child.
- Lessen the child's irritability and improve the behavior.

What is fever phobia?

Fever phobia occurs when both parents and the pediatrician focus on the numbers of body temperature. In such scenarios, the clinician should try to calm down the parents, instead of making them too anxious about the high temperature range.[5] The main concern of most of the parents is that the high fever may damage the brain. The physician should clarify that most of the viral fevers do not cause brain damage or febrile seizures. It is also important to convey that there is nothing to worry if the child is getting a fever after vaccination and some studies show that prophylactic antipyretics may lower the efficacy of vaccination.[6]

What are the normal temperature ranges?

The normal temperature ranges, based on the routes of temperature assessment, are the following: rectal: 97.9 to 100.4°F, ear: 96.4 to 100.4°F, oral: 95.9 to 99.5°F, and axillary: 97.8 to 99.5°F.[7]

What temperature is bad, 40°C (104°F) or 41°C?

Simple febrile illness or hyperpyrexia due to endo or exogenous pyrogens causes the hypothalamus to reset at a higher temperature to activate the immune mechanisms of the body. Hence, it does not cause heat-related adverse effects. The fever begins to reduce as soon as the pyrogens start getting cleared off from the body due to the body's natural immune mechanism.[8]

Whereas, hyperthermia is a condition where the body temperature rises, since the outside temperature is too much for the body's cooling system to manage. There is a greater possibility of getting a heat stroke when the temperature is too high, as it is beyond the body's capacity to dissipate heat.[9] It is usually seen in north India, and in some parts of North Karnataka and Maharashtra. In addition, it is important to educate the parents not to leave the children alone in a car, as there is an increased risk for hyperthermia due to heat trapping.

Thermometers and accuracy

The most accurate thermometer is the digital thermometer. Whereas, the forehead strip, infrared emitting detectors, pacifiers/dummy, and apps with heat sensors are comparatively less reliable. Eardrum thermometers are good for quick screening. The accuracy of the eardrum thermometer is comparatively good, as it measures the temperature of tympanic membrane. Since the membrane lies close to the thermal regulatory center of the hypothalamus and both share the same artery, ear drum thermometers are considered to be more accurate.[10]

The ideal technique to be used for measuring temperature in children, based on the age is listed in table 2.[11]

Table 2: Recommended temperature measuring techniques based on the age

Age	Recommended technique
0 to 6 months	Rectal or axillary (for screening low risk children)
6 months to 2 years	Axillary or rectal
2 years to 5 years	Axillary or eardrum (or temporal artery if in hospital) (screening)
>5 years	Oral (definitive), axillary, tympanic (or temporal artery if in hospital) (screening)

How to use a rectal thermometer?

Make the child to lie across the lap with the face down. Apply a small amount of petroleum jelly at the tip of the thermometer and gently insert it into the child's anus until the silver tip is not visible (6 to 12 millimeters). Keep the thermometer for <1 minute for digital thermometer and for around 2 minutes for glass thermometer (Fig.1).[12] Otherwise, make the child to lie on the back. Hold the legs and insert the thermometer (Fig. 2).

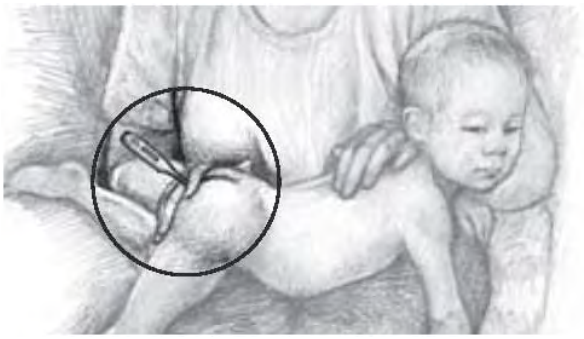

Fig.1: Measuring rectal temperature: method 1

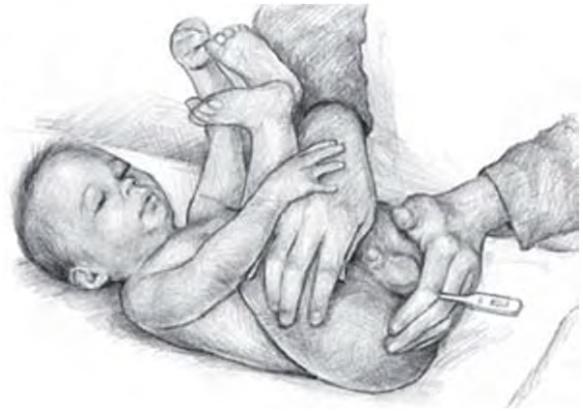

Fig. 2: Measuring rectal temperature: method 2

Educating on antipyretic medications

The following details should be conveyed to parents regarding antipyretic medications:

- Drug combinations have a higher risk of complications.
- Ibuprofen should be given only if the child's water intake is adequate and it is not recommended in <6 months of infants.
- Should not alternate between paracetamol and ibuprofen, though there are studies to prove that the medications can be altered.
- Should not give >5 doses of crocin within 24 hrs.

Do's and Don'ts for homecare

Do's

- Use tepid water for sponging, avoid alcohol.
- Make the child to wear loose clothes while taking rest.
- Keep room cool with overhead fan or a/c.
- Encourage the child to sip fluids in between medications.
- Watch for urine output and hydration.
- Medications may be given on empty stomach.
- Carry the medication while travelling to remote areas.

Don'ts

- Avoid wrapping child in wet clothes while sponging.
- Avoid overclothing (sweaters, blankets etc.) and synthetic garments.
- Do not wake the child up to take medications.
- Avoid home remedies with dubious benefits like oiling the scalp or umbilicus, light tea decoctions, herbal concoctions etc.
- Don't use adult medications for children.
- Don't use household cups and teaspoons for measuring drugs.

When to seek medical attention?

It is necessary to seek medical attention in the following situations:[13]

- Temp ≥103°F
- Child <6 months old
- Fever more than 24 hrs
- Fever combined with rashes, or if the child is looking 'sick', sleepy, lethargic or not responding
- Refusing to have food, excessively cranky, fussy and irritable
- Persistent wheezing or coughing
- Reduced activity
- Seizures

In the following special situations, it may be necessary to consult a clinician:

- Febrile convulsions
- Hyperthermia
- Pre-existing complex medical diseases (eg: ectodermal dysplasia)
- Children who refuse to take medications
- Vaccinations

Common recommendations

Fever in children is managed differently in different parts of the world. But there are certain common recommendations for managing fever in children. Some of them are given below:

- Antipyretics are indicated only in cases of discomfort associated with fever and not with the sole aim of reducing body temperature.
- Recommended antipyretics are paracetamol and ibuprofen, according to the child's age, weight, and characteristics.
- The use of antipyretics does not prevent either febrile convulsions or reactions to vaccines.
- Tepid sponging alcohol baths are not recommended for fever.
- The use of cough/ cold medications is discouraged due to the risks of overdosage and interactions.
- Caution is recommended while using antipyretics for managing chronic diseases such as pre-existing hepatic and renal impairment, diabetes, cardiac diseases and malnutrition.
- In asthmatic children with fever, paracetamol does not seem to worsen the asthma symptoms.

Conclusion

Further research is mandatory to improve the quality of present guidelines, to reinforce the messages of common recommendations, and to create consensus on discordant recommendations. Framing international guidelines to unify medical behavior is very essential. The parents need to be educated using various visual aids to avoid fear, distress, and unwanted calls and treatments.

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Notes

Notes

FEVER FOUNDATION

Vision

Strive towards imparting knowledge on the unmet needs and provide information on research, education and therapy updates on fever management.

Mission

- Independent, non-commercial foundation supporting the educational / academic activities to address the unmet needs in fever management
- The foundation is committed to conceive, build, and sustain programs and make scientific initiatives aimed at providing evidence based updates to the health care professionals.
- To run patient education programs on fever management

Objectives of Fever Foundation

- To address the unmet needs and provide updates on fever management
- To provide access to health care through evidence based programs that can reach to large audience
- To engage eminent doctors for various scientific activities

MICRO KNOWLEDGE ACADEMY