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FEVER

FEVER - PATHOPHYSIOLOGY AND TYPES

***Ashwath D**

Abstract: *The basic mechanisms of thermoregulation with specific reference to elevated body temperature is discussed. A distinction is made between fever and elevation of body temperature due to other causes like environment. The different types of fever based on etiology and clinical characteristics are briefly reviewed.*

Keywords: *Fever, Thermoregulation, Pyrexia, Pyrogens.*

Fever is elevation of core body temperature above the normal for age and species. In humans, this is traditionally defined as an elevation of core body temperature above 38° C or 100.4° F.[1]

Perhaps it is the most common symptom a pediatrician is consulted for and accounts for the most number of emergency consultations. Unfortunately, fever remains one of the most poorly understood and managed symptom of illness in children.

This article is a review of pathophysiology of temperature regulation and fever.

Physiology of temperature regulation[1]

It is very important that the body temperature is maintained within a narrow acceptable range of degrees so that the various physiological processes of the body function optimally. Heat is produced in the body by the following mechanisms i) basal metabolic rate of every functional cell and its exothermic reactions, ii) specific dynamic action of ingested foods and iii) muscular activity. Heat is lost by radiation and convection (70%), vaporization of sweat (27%), respiration (2%), defecation and urination (1%).

The body temperature is regulated by the hypothalamus as a master control centre. This centre lies in the area called organum vasculosum lamina terminalis (OVLT) which is one of the circum ventricular structures at the base of the brain. This thermoregulatory centre lies outside the blood brain barrier and constantly is updated about the core body temperature by the rich vascular supply as well as neural inputs from the cold receptors in the skin and other receptors in the deep tissues, spinal cord, non hypothalamic portions of the brain. The thermoregulatory centre then directs a response by the body that is appropriate to the need.

Whenever there is a disturbance in the temperature of the body, a set of neurobehavioral and endocrine processes are initiated to bring back the temperature to normal. There are distinct response patterns activated by heat and cold injury.

Mechanisms activated by heat leads to increased heat loss, through cutaneous vasodilation, sweating and increased respiration. Similarly heat production is decreased through anorexia, inertia and apathy. Mechanisms activated by cold include shivering, hunger, increased voluntary activity, curling up, increased appetite, cutaneous vasoconstriction and horripilation (hair standing up as in goose pimples). Fever results from an elevation of a set point in the hypothalamic thermostat which drives various body processes that either increase heat production or decrease heat loss or both.

One needs to understand the difference between fever and hyperthermia. In hyperthermia, there is elevation of the body temperature above normal without involving the resetting of the hypothalamic thermostat system and a common example is heat stroke.

Pathogenesis of fever

Fever involves resetting the hypothalamic thermostat system to a new higher level by prostaglandins especially PGE2. PGE2 mediates its actions by any of the four receptors Endogenous Pyrogen (EP) 1, 2, 3 or 4. The PGE2 works on the pre-optic area of the hypothalamus which, in turn, directs various processes which together raise the body temperature.[2] This prostaglandin production is stimulated by one of the two sets of chemicals namely endogenous or exogenous pyrogens.

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Endogenous pyrogens: These include interleukin 1 beta (IL1β), interleukin 6 (IL6), tumour necrosis factor alpha (TNF α) and the beta and gamma interferons (IFN β and IFN γ). These chemical signals are chiefly derived from the monocytes, macrophages, natural killer (NK cells) and Kupffer cells. The stimulation of these cells of the immune system is most commonly mediated by interaction between the invading microbes and the toll like receptor (TLRs) molecules on the host immune cells. As mentioned above, these endogenous pyrogens stimulate the prostaglandin E2 production at the hypothalamus.

Exogenous pyrogens: The most well characterised exogenous pyrogen is lipolysaccharide (LPS) of the Gram negative bacterial cell wall. Microbial toxins like toxic shock syndrome toxin (TSST) and microbes themselves can also serve to initiate the production of endogenous pyrogens. Another unique feature of the microbial LPS is its ability to directly activate the hypothalamic thermostat without prostaglandin production. Of late, neural mechanisms for the initiation and maintenance of fever and role of ceramide as a secondary mediator of thermostat resetting have been suggested. The pathogenesis for fever in sepsis is shown in Fig.1.[2] Stimulation of sentinel cells by exogenous pyrogens produces endogenous pyrogens which stimulate fever production in the pre-optic area (POA) of the hypothalamus by the second messengers prostagland in E_2 (PGE_2) and ceramide. PGE_2 is also produced from Kupffer cells in the liver in response to stimulation from lipopolysaccharide (LPS), which additionally stimulates the POA via the vagus nerve.

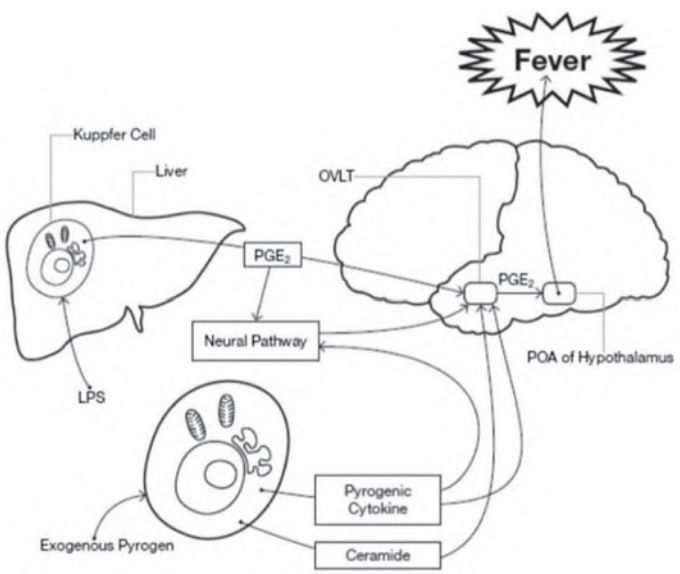

Fig.1. Fever in sepsis-Proposed mechanisms[2]

Pathogenesis of hyperthermia

In hyperthermia, there is elevation of body temperature because of either increased heat production or defective heat loss mechanisms without reset of the thermostat.

Hyperthermia caused by increased heat production occurs in catabolic states like malignancy and hyperthyroidism, massive muscle necrosis as occurs in electrical shock injury and malignant hyperthermia. In neuroleptic malignant syndrome and central fevers (results from complex disturbances of central mechanisms of thermoregulation), the hypothalamic injury directly activates heat producing mechanisms.

Hyperthermia caused by decreased heat loss occurs in altered sweating capacity typically seen in ectodermal dysplasia, as an atropine side effect and datura poisoning, occlusive clothing which interfere with sweat evaporation, hot and humid environment where radiation and convection mechanisms of heat loss are decreased, dehydration (reduction of the ECF volume) typically seen in renal salt and water wasting states like diabetes insipidus and dysautonomia wherein autonomic regulatory functions of vital body functions are impaired e.g. scorpion envenomation, Guillain Barre syndrome.

Consequences of fever

Whether fever is a friend or a foe continues to be a matter of debate. Apart from alerting us to a change in homeostasis, fever, is purely a symptom of disease and not a disease unto itself.[2,3] The fact that fever has been retained by the human species across millions of years of evolution suggests that there might be an advantage in the process to the survival of our species. The possible beneficial effects of fever on the biological responses of an organism include i) immunological responses such as antibody production are upregulated and help tackle the infectious disease more effectively, ii) neutrophil functions such as chemotaxis, phagocytosis and intracellular killing are more efficient at higher temperatures and iii) the high body temperature directly inhibits the microbial survival.

However, at higher than normal temperatures the following ill effects are possible:

i) Direct cellular damage: Elevated temperature is directly cytotoxic, affecting the plasma membrane, ion channels, cytoplasmic proteins especially enzyme systems and both DNA and RNA structures disrupting cellular structure and function. Direct cell death occurs at temperature above 41°C, with the rate of cell death rising rapidly even with minor elevations thereafter.

ii) Local effects on tissues: The changes at tissue level induced by fever are mediated by various inflammatory agents and cytokines. The most important of these mediators of tissue injury are the prostaglandins and the interleukins especially IL1 and IL6. Interferons and neutrophil derived products play a supporting role in promoting the inflammatory effects. Together, these agents induce tissue level inflammation characterised by edema, vascular injury and extravasation of fluids and edema.

iii) Systemic effects on organ systems: In the gastrointestinal tract, there is altered gut permeability allowing gut bacteria to translocate and cause bacteremia. Splanchnic visceral free radical production is increased, which augments the systemic inflammatory effects.

In kidneys, there is a reduction in the GFR with fever. Further renal injury occurs by activation of the renin angiotensin system and the resulting renal vasoconstriction. With very high fever, there is a risk of rhabdomyolysis which can further contribute to tubular injury. The insensible water loss in hot and humid conditions accompanied by refusal to increase fluid intake during febrile episodes makes matters worse for the kidneys.

In heart, elevation of temperature leads to tachycardia and increased oxygen demand at the cellular level because of the increase in the basal metabolic rate of the cells. While the oxygen needs of the tissues are increased, there is simultaneously an effect on the cardiac output and systemic vascular resistance which can have profound effects on the blood pressure. In most cases, there is an increase in the stroke volume and cardiac output but the effect of the cause of the fever on the systemic vascular resistance is very variable. Considering that infections and sepsis are the most common causes for fever in children the effect of sepsis on the vascular system is very important and determines the type of clinical presentation. With a high cardiac output and low systemic vascular resistance, one can see a classical picture of 'warm' shock with bounding pulses, wide pulse pressure and flash capillary refill. More commonly, the picture is of low blood pressure and cold clammy peripheries and narrow pulse pressure with prolonged capillary refill which characterise 'cold' shock. Both types of shock contribute to the significant morbidity and mortality that accompanies sepsis in children.

The neurological system is very vulnerable to the ill effects of fever. These include febrile fit and fever triggered seizures in epileptic children. Irritability, alterations in states of consciousness, mood disturbances and delirious behaviour are other effects of fever. Alterations in blood brain barrier and perturbations in the neuronal cell membranes brought on by elevated temperature may be the reasons for the ill effects of fever.

Other systems include involvement of the liver which can present with just elevated liver enzymes as a simple derangement to acute liver cell failure with coagulopathy. The hemostatic system can be affected by the direct effect of fever on platelets function and coagulation system as well as the effects mediated by liver injury resulting in bleeding diathesis.[2]

Fever - Clinical patterns[4]

i) Continuous fever or persistent fever: Here the body temperature fluctuates by less than 0.5^{O}C in a day, without touching the baseline.

ii) Remittent fever: Here the body temperature fluctuates by more than 0.5 C, but the temperature does not touch baseline.

iii) Intermittent fever: Here the temperature frequently touches the baseline but rises and falls over a 24 hour cycle. Double quotidian (two paroxysms of fever daily) fever is a special type of intermittent fever, seen typically with systemic onset juvenile idiopathic arthritis (SOJIA).

iv) Relapsing fever: Here, within the same disease syndrome there are both febrile and afebrile phases over the course of the disease.

v) Camel back fever (biphasic fever): Here in a single disease course there are two distinct peaks of the fever response with a valley of lower grade fever between the two peaks. This pattern is typically seen with dengue, leptospirosis, viral hemorrhagic fevers, poliomyelitis and other enteroviral diseases.

vi) Hyperpyrexia is defined as a temperature more than 41^{O}C. Typically seen with non infectious causes of fever like heat stroke. This is also seen in malignant hyperthermia, neuroleptic malignant syndrome and other diseases that directly affect the hypothalamus or the musculoskeletal system causing sustained and excessive muscle contraction.

With a proper understanding of the basic mechanisms underlying elevation of the body temperature, one can direct the evaluation and diagnostic processes more to etiology based approach rather than mindlessly reacting to the reading on the thermometer.

Points to Remember

- ***Fever is elevation of core body temperature above the normal for the age and species.***
- ***The body temperature is regulated by the hypothalamic thermoregulary center.***
- ***The ill effects of fever are multisystemic.***
- ***The clinical patterns of fever may help in suspecting the etiology.***
- ***Hyperpyrexia (temperature > 41 °C) is typically seen with non infectious causes.***

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CLIPPINGS

Vitamin D status in full-term exclusively breastfed infants versus full-term breastfed infants receiving vitamin D supplementation in Thailand: a randomized controlled trial.

Many international medical organizations recommend vitamin D supplementation for infants, especially exclusively breastfed infants.

In a study in Thailand full-term, exclusively breastfed infants were randomized into two groups at 2 months of age to continue exclusive breastfeeding either without vitamin D supplementation (control group, $n = 44$) or with vitamin D_3 supplementation at 400 IU/day (intervention group, $n = 43$) until 6 months of age. At 6 months, the serum vitamin D (25OHD) of the infants and their mothers, serum bone marker and infants' growth parameters were compared between the two groups.

The infants' serum (25OHD) concentration was lower in the control group than intervention group (20.57±12.66 vs. 46.01±16.42 ng/mL, $p < 0.01$). More infants had vitamin D sufficiency (25OHD of >20 ng/mL) in the intervention group than control group (93.0% vs. 43.2%, $p < 0.01$). There were no significant differences in the maternal (25OHD) concentrations between the control and intervention groups (25.08±7.75 vs. 23.75±7.64 ng/mL, $p = 0.42$). Serum calcium, phosphorus, intact parathyroid hormone, alkaline phosphatase and infants' growth parameters were comparable between the two groups. After adjustment for the confounding factors, (25OHD) concentration in the intervention group was 25.66 ng/mL higher than the control group (95% confidence interval, 19.07-32.25; $p < 0.001$). Vitamin D supplement contributed to an 88.7% decrease in the prevalence of vitamin D insufficiency/deficiency (relative risk, 0.11; 95% confidence interval, 0.04-0.35; $p < 0.01$).

In this study breastfed infants without Vit D supplementation had serum vitamin D concentration below sufficiency level at 6 months of age compared to the breast fed infants with Vit D supplementation.

However, vitamin D supplementation (400 IU/day) improves their vitamin D status and prevents vitamin D deficiency.

Ruangkit C, Suwannachat S, Wantanakorn P, Sethaphanich N, Assawawiroonhakarn S, Dumrongwongsiri O. Vitamin D status in full-term exclusively breastfed infants versus full-term breastfed infants receiving vitamin D supplementation in Thailand: A randomized controlled trial. BMC Pediatr 2021; 21:378. https://doi.org/10.1186/s12887-021-02849-z.

FEVER

FEVER IN NEONATES

***Srinivas Murki**
****Deepak Sharma**

Abstract: *Fever in a neonate is one of the symptoms causing concern and requiring admission to NICU. Fever in neonates is defined as rectal temperature ≥38°C. It is important to differentiate between environmental exposure hyperthermia and fever in neonates. Neonates with environmental hyperthermia are usually active, alert and have stable vital parameters. Once the environmental factors causing hyperthermia are corrected, their body temperature normalizes rapidly without any other treatment being required. After ruling out hyperthermia due to environmental causes, all neonates with fever should have complete sepsis work up including cerebrospinal fluid analysis to rule out serious bacterial infection. When there is no apparent focus of fever, empiric antibiotics should be started in these neonates based on local antibiogram without waiting for other laboratory reports.*

Keywords: *Hyperthermia, Neonate, Serious Bacterial Infection, Fever without focus.*

Fever is seen in nearly 20% of newborns admitted to the neonatal unit and approximately 10% of hospitalized newborns with fever have a serious bacterial infection.[1] Fever, in itself is not a disease but a manifestation of underlying pathology. The primary aim of evaluation should be to identify underlying etiology and treat it rather than focusing on normalization of body temperature. Fever in neonates is defined as rectal temperature of ≥38°C.[2-4] However, rectal thermometry, the gold standard method of temperature measurement is more invasive and has therefore been replaced by less invasive axillary method for neonates and infants.[5] World Health organization defines normal body temperature as axillary temperature between 36.5°C to 37.5°C.[6] So, whenever axillary temperature in neonates exceeds 37.5°C (99.5°F), every attempt should be made to identify etiology and manage accordingly. All newborns with fever need admission and should be submitted for a detailed history, examination and baseline investigations to rule out serious bacterial infection (SBI). A practical and step wise approach to fever in newborns would be to differentiate fever from hyperthermia and then grouped into one of the three: 1) fever with rash, 2) fever with focus and 3) fever without focus.

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Fever versus hyperthermia

In neonates, it is important to differentiate between elevated body temperature caused by fever and an elevated body temperature caused by hyperthermia. Hyperthermia is not due to resetting of hypothalamic thermostat and is characterized by an uncontrolled increase in body temperature that exceeds the body's capacity to lose heat, in contrast to fever which is caused by resetting of thermostat to a higher level by the release of endogenous pyrogens secondary to infection/inflammation. In neonates, hyperthermia mostly occurs due to hot environment and/or excessive swaddling. These neonates are usually active, alert, accept feeds well, have normal perfusion with pink and warm extremities and normal neonatal reflexes. When they are shifted out of hot environment or excessive swaddling is removed, their body temperature normalizes rapidly without any other treatment. Hot and dry environment may cause dehydration in these neonates especially those who are receiving inadequate breast milk. Dehydration fever usually occurs during first or second week of life. It can sometimes lead to severe complications like hypernatremic dehydration and hence needs to be identified early and treated promptly.

1. Fever with rash

Fever with rash in neonates can be observed in viral illnesses like neonatal dengue, chikungunya, neonatal varicella, herpes simplex infection; bacterial infections such as staphylococcal scalded skin syndrome (SSSS), congenital syphilis, congenital tuberculosis and fungal infections like candidiasis.

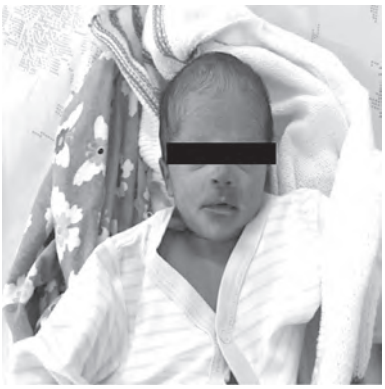

Fig.1. Neonatal chikungunya: Perioral hyper-pigmentation

Chikungunya : Neonates can present at 3 to 5 days of life with fever, irritability, varied dermatological manifestations like erythematous maculopapular rash, generalized or perioral hyperpigmentation (Fig.1) and other manifestations like recurrent apnea, seizures and shock with disseminated intravascular coagulation (DIC) if the infection occurs through vertical transmission. Maximum risk of transmission occurs if mother is viremic at the time of delivery.[7] Clinical symptoms in mother usually are high grade fever with severe joint pains and maculopapular rash. Diagnosis is by chikungunya serology. Treatment is mainly symptomatic in the form of antipyretics, supportive care and ensuring adequate volume status.

Neonatal dengue : Onset of fever in congenital dengue varies from day 1 to day 11 after birth and signs and symptoms last for 1 to 5 days.[8] Neonates can have generalized erythematous rash and can develop petechiae, edema, hepatosplenomegaly, coagulopathy and disseminated intravascular coagulation. Dengue in late pregnancy predisposes to neonatal dengue. In neonates, vertical transmission of dengue infection can result in symptoms ranging from fever with thrombocytopenia to shock with multiorgan dysfunction and rarely cerebral hemorrhage.[9] Diagnosis is usually made by maternal history, dengue serology (IgM and IgG antibodies) and NS1 antigen. Babies should be monitored for thrombocytopenia, coagulopathy, intracranial bleed and liver dysfunction. Management is usually in the form of supportive care including fluid therapy to maintain adequate intravascular volume.

Neonatal varicella (Fig.2a and b): Neonates with varicella have fever, vesicular rash with variable degrees of crusting and can develop pneumonia, hepatitis or encephalitis. Neonates can suffer varicella infection either by vertical transmission or exposure to varicella positive person in

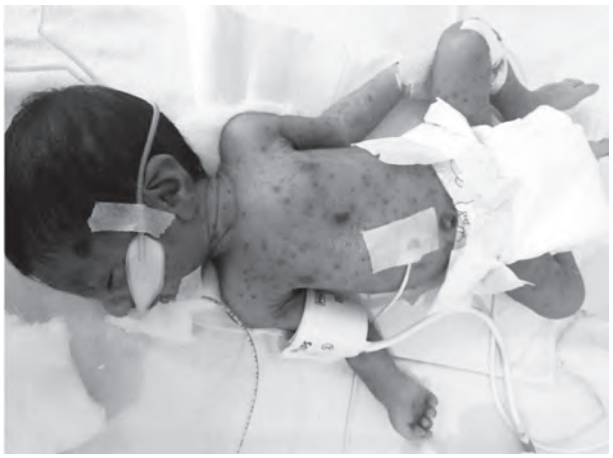

Fig.2a. Congenital varicella - Acute phase

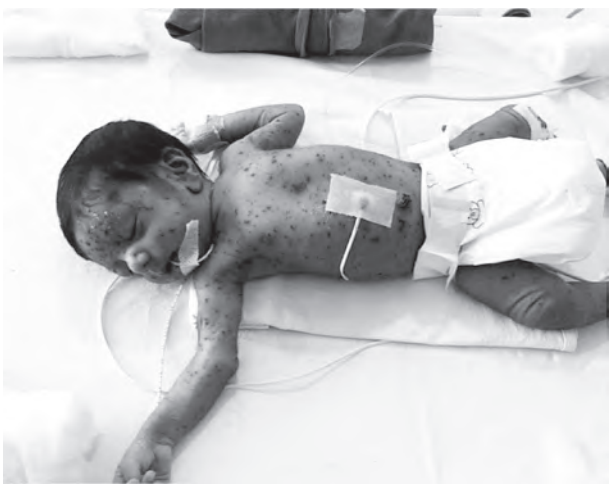

Fig.2b. Resolving phase

postnatal life. If neonate develops signs and symptoms of varicella during first 10-12 days of life, then it is a trans-placentally transmitted infection. Varicella infection occurring after that time, is most likely acquired postnatally. Neonates are at highest risk of severe disease if mother develops varicella rash within 5 days before delivery and within 2 days after delivery. Diagnosis of neonatal varicella is based on clinical features, history of varicella in mother, or contact with varicella positive person. Differential diagnosis includes congenital herpes simplex infection and enterovirus infection. Confirmation can be done by detecting IgM/IgG varicella antibodies or by amplification of viral DNA in skin swabs using polymerase chain reaction (PCR). Neonates with active varicella should be treated with IV acyclovir. Neonate whose mother develops varicella within 5 days before delivery or within 48 hours after delivery should receive varicella zoster immunoglobulin. If it is not available, IVIG can be a substitute.

Neonatal herpes: Most neonates are normal at birth and symptoms develop after first 72 hours of life. Skin lesions begin as erythema that rapidly evolve into isolated or grouped vesicles with erythematous base on the skin and around the eyes and mouth that burst, crust over and heal. Primary genital infection in pregnant mother late in pregnancy can cause neonatal mucocutaneous herpes, disseminated disease or CNS disease. Diagnosis should be based on maternal history of genital herpes, clinical features in neonate and PCR of fluid swab from skin lesions in case of mucocutaneous herpes or PCR of blood in case of disseminated herpes. All neonates with any kind of herpes simplex infection should also undergo CSF analysis. Treatment includes acyclovir and supportive care.

Impetigo: Impetigo is a superficial skin infection caused by *Staphylococcus aureus*, *Streptococcus pyogenes* or both. Bullous impetigo caused by *S. aureus* is one of the most common skin infections in neonates which presents as flaccid vesicles/ bullae or pustules on an erythematous base. Rupture of these bullous lesions, leaves behind a moist red base and collarette of scales. In bullous impetigo, lesions are not close to each other which differentiates it from herpes, in which vesicles are in groups. Diagnosis is supported by presence of Gram positive cocci in the vesicle fluid. Definitive diagnosis is by bacterial culture taken from skin or blood.

Staphylococcal scalded skin syndrome (SSSS): Neonates with SSSS initially present with temperature instability, irritability, lethargy followed by generalized skin tenderness and erythema associated with significant periorificial crusting. After these initial symptoms and signs, neonate develops widespread flaccid bullae which undergo subsequent desquamation. It is important to remember that mucus membranes are spared in SSSS.

Congenital syphilis: Early congenital syphilis may present with rash, fever, low birth weight, jaundice, hepatosplenomegaly, desquamation of the palms and soles, watery nasal discharge, hair loss, symmetrical metaphyseal and periosteal lesions in long bones and anemia. Cutaneous findings of early congenital syphilis include a copper red maculopapular rash, sometimes acral vesicles or bullae, petechiae and mucous patches. Evaluation for congenital syphilis usually involves quantitative non-treponemal tests venereal disease research laboratory / rapid plasma reagin (VDRL/RPR) or polymerase chain reaction (PCR) of lesions or body fluids, complete blood count (CBC), liver function tests (LFTs), long bone radiographs and CSF analysis. Treatment is by using aqueous crystalline penicillin or procaine penicillin or benzathine penicillin.

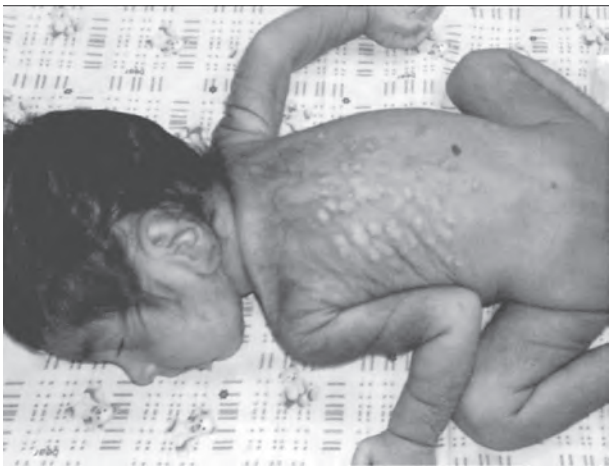

Fig.3. Candidal rash in a neonate

Disseminated candidiasis: Cutaneous manifestations include scaly and erythematous patches, papules, pustules with intense background erythema and accentuation in intertriginous area, back and extensor surface of extremities (Fig.3). Hematogenous spread can lead to involvement of kidney, CNS and eyes. The heart, liver, spleen, bones and joints may get involved. Diagnosis is usually based on potassium hydroxide preparations and culture of skin scrapings. Blood, urine and CSF fungal cultures should be done in disseminated disease. In addition, chest X-ray, ophthalmological examination, echocardiogram and abdominal ultrasonography should also be considered. Fluconazole and amphotericin B are the drugs of choice to treat candidiasis.

2. Fever with focus

In some neonates with fever, a focus of infection may be apparent like omphalitis, thrombophlebitis, abscess, cellulitis, septic arthritis or osteomyelitis.

Omphalitis: Omphalitis is infection of umbilical stump. It is characterized by erythema and induration of the periumbilical area with accompanying purulent discharge from stump site. Risk factors include delivery conducted in an unhygienic environment, umbilical cord catheterization, maternal chorioamnionitis, prolonged rupture of membranes and unhygienic cord care. Omphalitis can sometimes progress to diffuse abdominal wall cellulitis, peritonitis, hepatic vein thrombosis and liver abscess. To prevent omphalitis, one need to follow aseptic precautions like clean hands, clean delivery surface, clean cord care, clean blade for cord cutting, clean cord tie and no application on cord stump. All neonates with omphalitis should be evaluated with CBC, blood culture and lumbar puncture and treated with intravenous (IV) antibiotics directed against both Gram positive and Gram negative organisms.

Thrombophlebitis: Septic thrombophlebitis occurs at intravenous infusion site. It is characterized by swelling, erythema, induration, tenderness or a palpable cord and rarely purulent discharge at indwelling intravenous catheter site. Sometimes neonates with thrombophlebitis can develop fever. Causative organisms are usually Gram positive but sometimes Gram negative organisms can also be isolated. Treatment is removal of IV catheter, appropriate antibiotics and surgical intervention.

Septic arthritis and osteomyelitis: Neonate will have restricted mobility of involved limb, apparent pain on passive movement of limb sometimes associated with localized erythema and swelling. They usually result from hematogenous seeding in the setting of systemic sepsis or by direct extension from a skin lesion. Evaluation should be as for systemic sepsis. X-ray, ultrasound, other imaging modalities of involved joint and needle aspiration can aid in diagnosis. Treatment is by IV antibiotics and surgical drainage, if required.

Mastitis neonatorum: It is an uncommon condition caused by infection of breast tissue predominantly occurring in neonates mostly resulting from bad child rearing practice like squeezing of breast tissue to remove the milk (witch's milk). Neonates have fever, local erythema, swelling and induration of breast tissue. Treatment is with analgesics and IV antibiotics.

3. Fever without focus

Among neonates and infants less than 3 months of age with fever without a source (FWS), 5% to 15% have a serious bacterial infection (SBI), like bacteraemia/sepsis, meningitis, pneumonia, urinary tract infection (UTI), soft tissue and bone infection.[10] Although difficult, the differentiation of neonates and young infants at risk of SBI from those without significant clinical problems is considered crucial. The previous Rochester criteria suggested a low risk of SBI in infants who appeared well (i.e., absence of tachypnea, dyspnea, tachycardia, bradycardia, lethargy and decreased activity/ appetite), had no evidence of ear, soft tissue, or skeletal infections and had WBC counts between 5000 and 15,000/mm^3, bands less than 1500/mm^3 and $\leq$10 WBC/HPF in urine. In cases with diarrhea, SBI could be excluded if stool examination shows $\leq$5 WBC/HPF. Subsequent studies suggested addition of CSF studies and chest X-ray to identify infants at risk of SBI.

The previous Rochester criteria and the protocols derived from this, remain effective for identifying young infants between 29 and 60 days old who do not have SBI. With reduced incidence of bacteremia and meningitis, the risk of missing out an invasive disease is very low, as most of the SBIs are UTIs. However, a more complex approach including the use of C reactive protein (CRP) and procalcitonin (PCT) helps to identify a greater number of young infants who really have SBI and need immediate prompt hospitalization and adequate therapy. The approach in evaluating neonates is significantly more complicated, as their risk of SBIs, including bacteremia and meningitis, remains relevant and none of the suggested approaches can reduce the risk of dramatic mistakes. The approach in the evaluation of febrile neonate is more complicated and available criteria are not reliable. Hence, all neonates with fever without focus should undergo full sepsis workup consisting of CBC with differential counts, blood culture, urine analysis, urine culture, CSF analysis and X-ray chest.

Management of a newborn with fever

1. Is this fever or hyperthermia: For environmental hyperthermia, it is important to adjust environmental conditions. Neonate should be moved away from the source of heat and should be undressed partially or completely. If the neonate is under radiant warmer (RW), temperature probe functioning, probe position, set mode and set temperature should be checked and fixed accordingly. For neonates in incubators, check probe position, air temperature and skin temperature, relative humidity (RH) and if required decrease air temperature and RH. Check temperature every 15-30 minutes till temperature reaches normal range. Never turn off the incubator or radiant warmer to cool the neonate. Cooling devices are not recommended. Ensure adequate feeding for neonates so that adequate hydration is maintained and for those who are unable to breastfeed, tube feedings or IV fluids should be given as appropriate.

2. Evaluate for focus - Once environmental hyperthermia is excluded, any obvious focus of fever like omphalitis, thrombophlebitis, abscess, cellulitis, septic arthritis and osteomyelitis should be looked for and managed accordingly.

3. Investigate for unknown focus - if there is no obvious cause of fever, full sepsis work up should be done to rule out serious bacterial infection.

4. General management: Immediate management of airway, breathing, circulation, control of fever, hydration, correction of electrolyte and acid base disturbances, ventilation if needed and empiric antibiotics.

5. Specific management: Specific management should be tailored according to underlying etiology of fever. All neonates with fever should be admitted to hospital and started on empiric antibiotics after sending full sepsis work up. Choice of initial antibiotic therapy should be based on local sensitivity pattern. Once blood culture, urine culture and CSF analysis reports are available, antibiotics should be changed accordingly. Neonates with sepsis/bacteremia should receive 10 to 14 days of therapy with sensitive antibiotics whereas neonates with meningitis should receive a minimum of 3 weeks of antibiotic therapy. Neonates with strong clinical suspicion of sepsis but with sterile blood culture should complete full course of IV antibiotics for 10-14 days. For neonates who responded to initial antibiotic therapy, there is no need to repeat investigations before stopping antibiotic therapy. Neonates with sepsis should also be monitored for blood counts as these neonates can develop severe neutropenia and thrombocytopenia. Appropriate supportive therapy should be instituted.
6. Another important cause of fever in neonates is urinary tract infection. Diagnosis of UTI is made by urine analysis and urine culture. Urine culture should be obtained by bladder catheterization or by suprapubic aspiration with sterile technique. Antibiotic choice and antibiotic duration is based on urine culture, blood and CSF culture reports.

Conclusion

Fever in neonates is an emergency. Once environmental hyperthermia is ruled out, all these neonates should be admitted to hospital and managed aggressively. Complete sepsis work up including CSF analysis should be done to rule out serious bacterial infection. When there is no apparent focus of fever, empiric antibiotics should be started in these neonates based on local antibiogram without waiting for laboratory reports. Once underlying etiology of fever is identified, treatment should be tailored accordingly.

Points to Remember

- ***Fever in neonates may be a manifestation of underlying serious bacterial infection.***
- ***Detailed history and examination should be done for all neonates with fever.***
- ***Environmental hyperthermia is one of the important reasons for increased body temperature in neonates and should be ruled out in stable, well looking neonates.***
- ***Dehydration is an important cause of fever and is often associated with hypernatremia.***
- ***All neonates with fever and rash must be evaluated.***
- ***Neonates having fever without focus should undergo full sepsis workup.***
- ***All neonates with fever should be admitted and started on intravenous antibiotics after sending investigations.***

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FEVER

APPROACH TO FEVER WITHOUT LOCALIZING SIGNS IN CHILDREN AGED 1 TO 36 MONTHS - INDIAN CONTEXT

Rajesh Chokhani

Abstract: *Fever without localizing signs is a common symptom in children. It can be due to mild self limiting illnesses or serious causes. A pediatrician should be able to discriminate the mild from the serious causes by using a systematic approach that involves detailed history, careful examination and select laboratory tests. While the disease process evolves, symptomatic treatment and careful follow up are essential to recognize any clinical deterioration. At the same time, one should avoid unnecessary investigations and inappropriate antibiotics.*

Keywords: *Fever without focus, Well looking febrile infant, Serious bacterial infection.*

Fever is a symptom that almost always evokes anxiety in the minds of both parents and doctors alike. Until the cause is figured out, it remains a point of significant concern. This is more so when the affected patients are children of 1 to 36 months of age. This article aims to provide a systematic approach to the diagnosis and management of such fever, with a special focus on fever without localizing signs in this age group which is traditionally considered in two further sub groups: 1 to 3 months and 3 to 36 months.

1 to 3 months

One might encounter three categories of presentations.

1. Febrile infants may present with localizing symptoms and signs. The common bacterial infections seen in this age group with suggestive symptoms and signs include, meningitis, pneumonia and sepsis. Less commonly, one may encounter other infections from bacterial causes like gastroenteritis, osteomyelitis, septic arthritis, cellulitis, etc. These babies need to be managed as per diagnosis.
2. Some febrile infants may present without any localizing signs, but are sick looking because of the presence of non-specific symptoms and/or signs (lethargy, irritability, refusal to feed or clinical signs suggestive of circulatory impairment). Though these symptoms may not localize the disease process to a particular organ, they may indicate an evolving serious illness needing admission. This category of patients can be identified by using the pediatric assessment triangle.
3. The third category of infants are those who are febrile but 'well-looking' i.e., they have no other symptom or sign except fever. Though a large number of these infants maybe suffering from a self-limiting viral infection, a tiny percentage of them do turn out to have a serious or invasive bacterial infection. This is the category where decision making can be quite challenging. While not wanting to miss an infant developing a serious bacterial infection, one runs the risk of over investigating or treating such infants. Trying to strike a balance is an art everyone is still trying to perfect.

3 to 36 months of age

One can be more confident of managing febrile children without localizing symptoms and signs in this age group, largely on the basis of the clinical picture as it evolves, with very few investigations in select situations.

Clinical approach

Detailed history and thorough clinical examination are mandatory to identify if a febrile infant or young child has any localizing symptoms or signs.

Is it a documented fever?

Infants and young children are often brought to the doctor because their head or body feels warm to touch. If the parents have not documented fever with a thermometer, this may or may not represent fever. Infants and young children usually do exhibit some change in behavior when they have fever becoming irritable or less active. So, one way to confirm the presence of fever even

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when it was not documented, is to ask for such corroborative history.

The head may feel warmer than the rest of the body due to its larger surface area; the baby may be otherwise normal. At times, the baby may be overclothed or the surrounding environment may be hot. Both these situations do not merit a search for an infection.

Duration and progress of fever

If the fever has been only of few hours duration, it is too early to expect any localizing symptoms or signs and hence it may be prudent to carefully wait and watch. A worsening trend obviously calls for urgent evaluation, while an expectant approach is rational when there is an improving trend.

Accompanying symptoms

Lethargy/irritability: A change in behavior of the infant is one of the most important indicators of the presence of a significant illness. History needs to be correctly elicited. In the initial months, most babies would sleep for a large part of the day. If the baby gets up regularly and feeds well, then sleeping for rest of the time may be normal. So, it is the mother (caretaker) who can correctly identify a 'change' from the pre-illness routine and needs to be carefully questioned regarding the same. Similarly, babies can cry for a variety of reasons (hunger being the commonest, at this age) and an overwhelmed mother may consider the baby 'irritable'. When a baby cannot be pacified by the mother/caretaker, even after satisfying the regular needs of the baby, the 'irritability' can be considered to be significant. A recent onset irritability that accompanies the fever indicates a significant illness.

Poor feeding/refusal to feed: Reluctance or refusal of the infant to feed and /or a reduced vigor of sucking at breast suggests that the infant is sick. In bottle fed infants, a sudden reduction in the quantity of feed consumed could be an additional indicator. In slightly older children, reduction in food intake during an illness is often non-specific.

Vomiting /loose stools: Many infants regurgitate routinely and pass stools frequently; in contrast, vomiting suggests an illness. Besides an increase in frequency, it is the character of the stools that indicates disease - sticky and foul-smelling stools as against the normal golden yellow, semi solid, sour smelling stools.

Other symptoms: The presence of any other symptoms like cough, fast or labored breathing, excessive crying or ear discharge should also be elicited. Other localizing symptoms in slightly older children could be a rhinorrhea, skin rashes, abdominal pain, decreased or increased frequency of micturition, etc.

Contact history: History of contact with a close family member suffering from symptoms suggestive of a viral infection must be sought.

Clinical examination

While a thorough general and systemic examination is mandatory, the following things should be particularly focused on. At times, the temperature recorded may be only minimally raised. But the presence of disproportionate tachycardia may be a clue to underlying myocarditis, shock or increased core temperature. The adequacy of the peripheral circulation is assessed by the peripheral pulses and capillary refill time. Ideally, the blood pressure should also be recorded. Any tachypnea or respiratory distress should be noted. The anterior fontanel must be carefully examined with the infant supported in the upright position to look for any bulging. A pulsatile anterior fontanel is reassuring. The skin should be carefully examined for rashes, such as petechiae or eschar after undressing the child. The ears should be checked with an otoscope and the oral cavity should also be carefully examined. Bronchial breathing, rales and rhonchi should be looked for in the respiratory system examination. One should examine the abdomen for distension, absent bowel sounds, hepatosplenomegaly, etc. The genitalia should be examined for vulval synechiae and phimosis.

The crucial next step - triage

If nothing abnormal is found on history and examination as discussed above, further course of action needs to be decided in managing a febrile infant or young child who has no localization.

1 to 3 months

After a careful history and examination, if a febrile infant is assessed to be otherwise 'well', there are very high chances that it is a mild illness.[1] So, a good clinician would carefully follow up this infant on an outpatient basis. In order to further narrow down the possibility of serious bacterial infection, screening investigations have been proposed. Various criteria have been designed namely, Boston, Philadelphia and Rochester criteria - to try and identify babies in this group who are at low risk of serious bacterial infection. In addition to an unremarkable history and a normal clinical examination, these criteria depend

on a normal CBC, urinalysis and chest X-ray to label the infant as 'low risk'. Some criteria include a normal CSF examination as well. A clinical prediction rule identified infants younger than 60 days to be at low risk of serious bacterial infection using a combination of a negative urinalysis result, an absolute neutrophil count of 4090/µL or less and serum procalcitonin of 1.71 ng/mL or less, with a sensitivity of 97.7%.[2]

In the Indian setting, it may not always be easy to get all these screening investigations done. Further, CBC in isolation, is not so specific, while X-ray chest has a poor yield in the absence of any tachypnea. Similarly, there have been conflicting reports about the utility of serum procalcitonin.[3,4] In other words, these tests perform well when used as a battery of tests. Also, whenever a well looking febrile infant is later diagnosed to have a bacterial infection, urinary tract infection is the commonest. Therefore, the single most useful test in such infants is a urinalysis.[5] A clinically well febrile infant whose urinalysis is normal, has an extremely low chance of being detected with a serious bacterial infection later; ensuring a good follow up can further safeguard against this risk.

Ability to follow up closely

A close follow up is crucial, to identify a minority of infants in whom a serious bacterial infection evolves over the next 12-24 hours.[6] Failing this, at least a telephonic follow up is essential.[6] The treating pediatrician should always carefully assess the ability of the caregiver to follow up, whether they have the level of understanding and also access to communicate with the pediatrician.[7]

Obtaining other investigations to establish an alternative diagnosis of a viral infection and thereby ruling out a bacterial infection is an unrealistic option in most Indian settings.

To summarise, ideally, a clinically well febrile infant should undergo screening investigations to rule out evolving serious disease. If abnormal, the infant should be admitted and commenced on appropriate antibiotics after sending relevant investigations, including blood and urine cultures. If normal, the infant can be closely followed up on an outpatient basis.

If there are limitations to performing screening investigations, at least a urinalysis must be performed. If follow up cannot be ensured, admission for observation has to be considered. There is no role of presumptive antibiotic therapy intended to treat an unknown, undiagnosed infection. Similarly, when the infant is being followed up on an outpatient basis or is admitted for observation, only symptomatic treatment is to be offered, till the disease evolves or the infant settles.

3 to 36 months

In this age group, if the febrile infant or young child is looking well, it is extremely unlikely that one will miss a serious bacterial infection. Hence, a sound clinical approach can be used as a guide to take decisions.

Localizing symptoms and signs can take at least 24 - 48 hours to appear. The focus during this period, is to rule out serious illness by a diligent history and clinical examination, while providing symptomatic treatment. Investigations done too early in the course of the illness can either mislead or be non-specific. Only if the child is sick, admission and empirical antibiotics are indicated, after sending relevant investigations.

After 48 hours, if the infant or young child continues to have fever without localization, one has to clinically decide if they are dealing with a viral or bacterial infection. Fever that is moderate or high at the onset but responds well to an antipyretic in a child who is playful in the interfebrile period is most likely to be a viral fever. If, by 3-4 days there is a downward trend of temperature, it may just be a self - limiting viral fever. A fever that is moderate to high at the onset and responds poorly to an antipyretic, with the child remaining 'sick' or 'not playful in the interfebrile period is likely to be a bacterial infection. Such children and also those who have fever beyond 3- 4 days need relevant investigations. Further management would depend on the results of these investigations. The need for a constant follow up till the diagnosis evolves or the fever subsides, cannot be overemphasized.

Points to Remember

- ***Confirm the presence of fever.***
- ***A detailed history and careful clinical examination are vital to pick up localizing symptoms and signs.***
- ***Even when a febrile infant 1 to 3 months of age is assessed to be otherwise 'well', screening investigations to rule out a serious bacterial infection are ideal with urinalysis being a must.***
- ***In older infants and young children, a sound clinical approach can safely guide decision making on further management.***
- ***The need for a constant follow up is essential until fever subsides or a clear diagnosis is made.***

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CLIPPINGS

Six Month Follow-up of Patients With Multi-System Inflammatory Syndrome in Children.

Myocardial dysfunction and coronary abnormalities are prominent features of multisystem inflammatory syndrome in children (MIS-C). Persistent coronary aneurysm and/or low-normal or mild left ventricular dysfunction has been reported after hospitalization.

This is a longitudinal 6-month cohort study of all children admitted and treated for MIS-C from April 17 to June 20, 2020. Patients were followed ~2 weeks, 8 weeks, and 6 months post admission, with those with coronary aneurysms evaluated more frequently.

Acutely, 31 (62%) patients required intensive care with vasoactive support, 26 (52%) had left ventricular (LV) systolic dysfunction, 16 (32%) had LV diastolic dysfunction, 8 (16%) had coronary aneurysms (*z* score $\geq$2.5) and 4 (8%) had coronary dilation *(z* score <2.5).

A total of 48 patients (96%) received immunomodulatory treatment. At 2 weeks, there was persistent mild LV systolic dysfunction in 1 patient, coronary aneurysms in 2, and dilated coronary artery in 1.

By 8 weeks through 6 months, all patients returned to functional baseline with normal LV systolic function and resolution of coronary abnormalities.

Cardiac MRI performed during recovery in select patients revealed no myocardial edema or fibrosis. Some patients demonstrated persistent diastolic dysfunction at 2 weeks (5, 11%), 8 weeks (4, 9%) and 6 months (1, 4%).

Children with MIS-C treated with immunomodulators have favorable early outcomes with no mortality, normalization of LV systolic function, recovery of coronary abnormalities, and no inflammation or scarring on cardiac MRI. Persistence of diastolic dysfunction is of uncertain significance and indicates need for larger studies to improve understanding of MIS-C. These findings may help guide clinical management, outpatient monitoring, and considerations for sports clearance.

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FEVER

APPROACH TO A CHILD WITH FEVER LESS THAN ONE WEEK DURATION

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*****Varun Govindarajan**

Abstract: *Fever, a thermo regulated elevation of body temperature above normal daily variation, is the most common reason for parents to seek medical care. The disease spectrum in Indian children is more diverse than western countries, with tropical diseases and serious bacterial infections being more common. Since most short duration fevers are self-limited, the primary goal of treatment is to keep the child comfortable, while looking for the localizing signs. Fever without localizing signs pose a unique challenge, especially in young infants who are prone to a wide spectrum of viral and serious bacterial infections. While a well appearing infant needs only parental reassurance and adequate follow-up, an ill appearing infant needs further investigations based on local epidemiology. A thorough clinical assessment and prudent selection of laboratory tests identify at-risk children, aiding in prompt management.*

Keywords: *Febrile illness, Short duration, Antipyretics, Serious bacterial infections, Tropical infections.*

"Humanity has three great enemies: fever, famine and war, of these by far the greatest and by far the most terrible is fever" - Sir William Osler.[1]

Fever -a friend or a foe?

Fever is an elevation of the core body temperature as part of a specific biological response, mediated by cytokines and controlled by the central nervous system. Elevated temperature inhibits bacterial and viral replication, enhances mobilization of polymorphonuclear leukocytes (PMNs), increases phagocytosis and activity of T-helper cells and hence is beneficial. Temperatures over 41.5°C (107°F) are harmful, lead to irreversible organ damage and termed hyperpyrexia.[2,3]

Fever may present as an initial/isolated symptom along with an undifferentiated illness or with localizing signs that suggest etiology. Though a concerning symptom for parents, majority of children have a viral etiology and can be managed by ensuring adequate hydration and judicious use of antipyretics. Comprehensive evaluation of the young febrile infant (<3 months) and even hospitalization maybe necessary to rule out serious bacterial infections (SBI), while a less conservative approach can be employed for older infants and children. Use of antibiotics in short duration fever in children must be discouraged unless there is clinical / laboratory evidence of bacterial infection.[4]

In the evaluation of fever, both instinctive (Type-1 thinking, like Integrated Management of Childhood Illness) and reflective or analytical (Type-2 thinking, like Yale Observation Scale) thinking are important, which assists the clinicians to achieve a balance between efficiency and effectiveness.[5]

Decoding the Indian dilemma

The fever profile of Indian children is different from that of the western world, with a predominance of tropical diseases and bacterial sepsis, apart from viral illness (Table I). Dengue, malaria, typhoid, scrub typhus, along with complicated pneumonia, urinary tract infection (UTI) and meningitis contribute significantly to etiologies of fever in Indian children. There exists a diversity in the trends and occurrence of tropical fevers as they are greatly influenced by the seasons and the geography. Tropical fevers have overlapping clinical presentations and it is important to understand the local epidemiology for accurate management of these diseases.[6]

Western medicine focuses mainly on microbiological diagnosis, categorizing children into high and low risk for serious bacterial infection utilizing criteria-based approach (Table II) and is more investigation based.[7] Laboratory investigations are inaccessible, unreliable and expensive

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Table I. Comparing western and Indian scenarios

Western scenario	Indian scenario
• Age, risk status and microbiological diagnosis are the criteria for categorization.	• More reliant on history taking and clinical examination as laboratory investigations are usually not accessible, unreliable or expensive.
• Presence of an uniform standardized approach from home care to emergency room (ER), wards and critical care units	• No uniform or standardized protocols but totally individualized among health care providers.
• Duration of time spent on individual patients is more	• More number of patients and hence time spent on individual patients is less.
• Higher prevalence of influenza and pneumonia	• High prevalence of tropical disease like dengue, malaria, typhoid, scrub typhus

Table II. Low risk criteria for young infants (1 to 3 months)

Rochester criteria	Milwaukee criteria	Philadelphia criteria
Normal examination and well-appearing Born at term and previously healthy Labs- • WBC count 5,000 to 15,000/mm^3 • Absolute band count ≤ 1500/mm^3 • Urine: ≤10WBC/HPF, no bacteria on Gram stain • No infiltrates on chest X-ray • Stool: ≤5WBC/HPF	Well appearing infant - • Alert and active • Normal respiratory status Normal muscle tone • Reassuring examination - • Not dehydrated • No signs of focal infection - otitis media, soft tissue, bone or joint infection Labs - • WBC <15000/mm^3 • Urinalysis <5-10 WBC/HPF • Urine Gram stain negative for bacteria • Urine leukocyte esterase, nitrite negative • CSF <10 cells/mm^3 • CXR without infiltrate	Well appearing infant • No skeletal, soft tissue, skin or ear infections • No confounding factors • No immunization in preceding 48 hours • No antibiotics in preceding 48 hours • Not dehydrated Normal labs - • CSF <10 cells/mm^3 • Urinalysis <10 WBC/HPF • WBC <20000/mm^3 • CXR without infiltrate

in most parts of India, hence this approach fails in the Indian setting. A tailored clinical approach is more suitable for evaluation of an acute febrile Indian child.

Acute febrile Indian child - Evaluation

Short duration fevers are usually infectious in origin, due to viruses, bacteria or protozoa. Most of these children recover completely, even before a precise diagnosis is made or treatment is instituted. Steps in evaluating such a child are as follows (Fig.1).

1. Assessment of vitals and emergency stabilization
2. Identifying high-risk factors in the host
3. Actively searching for the focus of infection
4. Considering contacts in family or environment

A. Eliciting history -

- Fever - onset, intensity, duration, frequency and pattern
- Localizing symptoms of fever (Table III)
- Rash - when and where did the rash start? how it evolved and progressed? type and distribution of rash, and whether there is mucosal involvement? any treatment received for different disease?.[8]
- Immunization history: recent vaccination or a history of inadequate immunizations
- History of exposure to sick contacts and any treatment (including antibiotics) received in recent past
- Recent travel history, local epidemiology or any exposure to natural calamities.

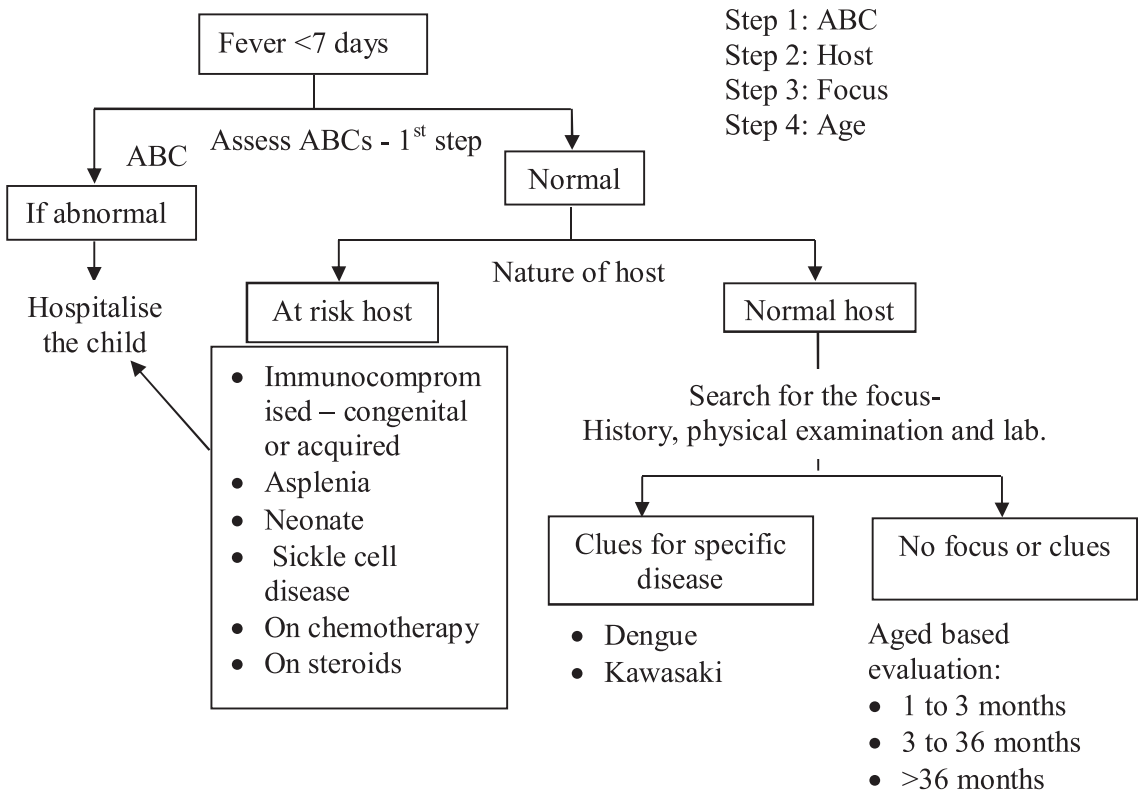

Fig.1. Algorithmic assessment of short duration fever in Indian children

- Any exposure to animals or insects
- History of previous hospitalization, prolonged ICU stay, prematurity, or immunocompromised states
- History of change in mental status, change in eating and/or behavioral patterns such as irritability, lethargy or apnea

B. Focused examination -

- Assessment of vital signs: Fever is associated with tachycardia and tachypnea, with 1°C rise in temperature increasing the heart rate by 10 approximately. Relative bradycardia can be seen in typhoid fever, brucellosis and Mycoplasma pneumonia.
- Assessment of growth parameters: Serious bacterial infections may present only as fever without localizing signs in malnourished children.
- Quality of the cry: Is it abnormal, high pitched or weak?
- Skin color: Are there areas of cyanosis or jaundice?
- Degree of hydration: Are tears present during crying? Are oral mucosa/lips or tongue moist? Severity of dehydration assessed by checking the skin turgor and palpating the anterior fontanelle.
- Response to caregiver or examiner: whether appropriate, irritable or consolable can provide valuable clues to the child's well being.

C. Classification into fever syndromes

1. Fever with focus
2. Fever without a focus -
   a. Fever without localizing signs
   b. Fever of unknown origin
3. Fever complicating chronic illness

Short duration fever of less than 1 week duration, can be with focus or without localizing signs. Site of infection must be identified by asking for relevant symptom, looking for signs in the child and by targeted laboratory evaluation.

Fever without localizing signs[2]

Temperature elevation may be the only sign of sepsis in young infants. Children less than 36months of age, presenting with fever without localizing signs have high probability of occult bacteremia and serious bacterial

Table III. Localizing features in short duration fever

Cough, coryza, sneeze, headache, sore throat, cervical nodes	Rhinitis, rhinosinusitis, pharyngitis, tonsillitis, undifferentiated viral fever
Cough, sore throat, loss of smell or taste, diarrhea, vomiting	COVID-19, MIS-C
Membrane over tonsils, neck swelling	Diphtheria, Ludwig angina
Ear pain, discharge, headache	Acute otitis media, otitis externa
Rash	Measles, rubella, chickenpox, erythema infectiosum, roseola infantum, herpes simplex, meningococcemia, dengue, Henoch - Schonlein purpura, Kawasaki disease, infectious mononucleosis
Stridor, dysphonia	Laryngitis, tracheitis, croup, epiglottitis, diphtheria
Fast breathing, cough, chest indrawing	Pneumonia, bronchiolitis, pleural effusion
Vomiting	Viral gastritis, gastroenteritis, viral hepatitis, meningitis, enteric fever, urinary tract infection (UTI)
Diarrhea	Gastroenteritis, enteric fever, dysentery
Jaundice	Hepatitis, cholecystitis, malaria
Chills, pallor	Malaria
Altered sensorium, seizures, neurological deficits, meningeal signs	Meningoencephalitis, cerebral malaria, enteric encephalopathy, brain abscess
Abdominal pain, bowel disturbances	Appendicitis, liver abscess, hepatitis, cholecystitis, intra-abdominal/pelvic abscess, peritonitis
Frequency, urgency, dysuria, hematuria, lower abdominal pain	Lower UTI, cystitis
Dysuria, loin pain, vomiting, constipation	Upper UTI, pyelonephritis
Hepatomegaly	Hepatitis, dengue
Splenomegaly	Malaria, enteric fever, infectious mononucleosis
Hepatosplenomegaly	Scrub typhus, leptospirosis
Joint swelling, pain, reduced movements disorders	Septic arthritis, rheumatic fever, connective tissue
Skin boils, redness, pain	Abscess, pustules, cellulitis, impetigo
Conjunctival injection, mucocutaneous erythema, Periungual desquamation, BCG reactivation	Kawasaki disease

infection (SBI) (Table IV). The risk of SBI is variable in different age groups and these children are usually sub-classified into the following age-based categories:

- Neonates, up to 1 month of age
- Young infants, 1to 3 months of age
- Young children, 3 to 36 months of age
- Older children, >36 months of age

In young infants (1 to 3 months), self-limited seasonal viral illnesses are the most common cause of fever without localizing signs. The possibility of SBI should always be entertained in any febrile young infant and the following conditions should be ruled out- otitis media, pneumonia, meningitis skin and soft tissue infections, omphalitis and urinary tract infections especially in uncircumcised boys and children with urinary tract anomalies. Sick children and those with localizing signs require admission and

Table IV. Common etiologies of acute fever[9]

Infectious		
Age group	**Pathogens in order of frequency**	**Frequency of SBI**
1-3 months	RSV, Influenza A, *Enterobacter*, Group B streptococci, *Listeria monocytogenes*, *Salmonella enteritidis*, *E. coli*, *Neisseria meningitidis*, pneumococci, *Haemophilus influenza* type b, *Staphylococcus aureus*	5%
3months to 3 years	Viruses, Pneumococci, *Haemophilus influenza* type b, *Neisseria meningitidis*, Salmonella	0.5% to 1%
>36 months	Viruses - RSV, influenza, parainfluenza, enterovirus, varicella; bacteria - streptococcus, pneumococcus, staphylococcus, hemophilus, mycoplasma;	<0.5%
Noninfectious		
Kawasaki disease		

Table V. Criteria for hospitalisation and discharge

Hospitalisation	**Discharge**
All acutely ill children in need of airway stabilization, ventilation or continued O_2 requirement Age <28 days Prolonged seizures/status epilepticus Altered sensorium Electrolyte imbalance Signs of severe dehydration Not feeding well Respiratory distress SpO_2<90% in room air Drug toxicity or drug reaction Unknown or undetermined cause Concern for non-compliance or inability to follow-up	No emergent need for airway, ventilation or circulatory support Stable vitals Child tolerating oral feeds Definitive management plan worked out Compliance ensured Follow up ensured

initiation of empirical antibiotics (Table V). Well appearing infants can be closely followed up for any signs of developing SBI. In recently immunized infants having fever without focus, close follow-up is needed to ensure that the fever resolves within 48 hours of vaccination. Toxemia should be suspected when there are clinical clues such as altered mental status, poor eye contact, inappropriate response to stimuli, abnormal vital signs, poor skin perfusion, cyanosis and grunting.[2,7]

Viral infections are responsible for majority of young children between 3 to 36 months age having non-localizing fever. SBI can also occur due to *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Hemophilus influenzae*. Important bacterial infections include otitis media, pneumonia, sinusitis, enteritis, urinary tract infection, osteomyelitis and meningitis. Yale observation scale is used in assessment of these children. Scores of 10, 11-15 and >16 correspond to SBI incidence of 2.7%, 26% and 92.3% respectively (Table VI).[2,10]

In older children with fever, pediatricians can rely more readily on symptoms and physical examination findings to establish a diagnosis. Assessment of oral intake and urine output is critical because associated dehydration increases morbidity. Social history inquiring about attendance to school, recent travel or exposure to sick contacts will aid the diagnosis. Overall appearance and vitals along with thorough history guides the physical examination.

Table VI. Yale observation scale for young children (3-36 months)

Score	1	3	5
Quality of cry	Strong or no cry	Whimper or sob	Weak cry, moan, high pitch cry
Reaction to parents	Brief cry or content	Cries off and on	Persistent cry
State variation	Awakens quickly	Difficult to awaken	No arousal or falls asleep
Color	Pink	Acrocyanosis	Pale, cyanotic, mottled
Hydration	Eyes, skin and mucus membrane moist	Mouth slightly dry	Mucus membrane dry, eyes sunken
Social response	Alert or smiles	Alert of brief smile	No smile, anxious or dull
Inference: Total scores of 10, 11-15 and >16 have SBI incidence of 2.7%, 26% and 92.3% respectively			

Examination should be directed to localize the cause for fever and the usual sites to look for are -

- Cervical region for presence of lymph nodes
- Throat for erythema or exudate and differentiate causative etiology
- Ears for bulging tympanic membrane
- Skin - for rashes, eschar, etc
- Neck signs of meningitis
- Lungs for presence of crackles or wheeze
- Abdomen for localized tenderness or organomegaly
- Joints - swelling or limitation in range of movements

Routine laboratory testing is not recommended in fully immunized children as the risk of occult bacteremia is very low. Unimmunized and under-immunized children are at a higher risk of occult sepsis. Screening for occult infections like UTI, should be guided by age, gender and degree of fever. Children who appear toxic, having signs of sepsis or bacterial meningitis require emergent treatment with parenteral antibiotics and adjunct therapies to support hemodynamics.[10]

Fever in children with special considerations

Children with cerebral palsy, cognitive impairment or disability have increased risk of fever due to pneumonia, UTI, dental infections or complications secondary to pressure ulcers, orthopedic prostheses, ventriculo-peritoneal shunts, or other device malfunction. They need specialized care with prompt identification of source and targeted treatment.

Immunocompromised children do not have the same capability to mount an immune response to control a disease. Any fever in such children requires hospitalization and detailed evaluation. Less virulent organisms including normal skin flora, commensal bacteria of oropharynx or gastro intestinal (GI) tract, environmental fungi and viruses of low level pathogenicity can cause severe life threatening illness in them. Use of empirical antibiotics is warranted, especially when there is neutropenia, to reduce risk of progression to sepsis. These children should receive all the recommended inactivated vaccines to prevent infection and live vaccines are contraindicated.[11]

Children with implanted synthetic and prosthetic devices are at constant risk of sepsis due to possible development of biofilms over the implants. Prevention of infection with strict aseptic handling is important and once infected, these implants may need replacement for complete clearance of infection.[12]

Pediatric COVID-19 and MIS-C

Children are less commonly affected with COVID-19, with majority being asymptomatic or mildly symptomatic. But 10%-20% need hospitalization and 1% to 3% require intensive care. Common symptoms include fever, cough, breathlessness, fatigue, myalgia, rhinorrhea, sore throat, diarrhoea, loss of smell and taste. Symptomatic treatment with case based decision on use of steroids and antivirals in severe illness are the suggested management options.

Aggressive treatment with steroids or IVIG maybe necessary in sick children with epidemiological link to SARS-CoV2 and multi-system involvement due to the newly emerging Multisystem Inflammatory Syndrome in Children (MIS-C), characterized by cytokine storm.[13]

Management of short duration fever

- Wait till 7 days for investigating a well looking child. Monitor for serious signs and treat fever only with paracetamol.

- Investigate early in a sick looking child. Even in an apparently well looking child, investigations can be attempted after 4th day, if there is high suspicion of tropical infection or COVID-19.
- Order for CBC, CRP, NS1 antigen, urine routine, X-ray chest and SARS-CoV2 RT-PCR, if the setting warrants.
- MP-QBC based on frequency of cases encountered or presence of rigors or pallor or splenomegaly.
- Before starting broad spectrum antibiotics always send blood and urine cultures.
- Any child with fever persisting beyond one week needs to be hospitalized.

A. Investigating an acutely febrile child

Investigations are necessary only in a sick child, or when fever is persisting beyond day 4-5. Screening tests include complete blood counts with differential, band cell counts, C-reactive protein (CRP), NS1 antigen for dengue, urine dipstick, microscopy, leukocyte esterase and nitrite test for UTI, malarial parasite smear with QBC test. (Table VII). During this pandemic of COVID-19 and MIS-C, any unremitting fever warrants evaluation with nasopharyngeal swab for SARS-CoV2 RT-PCR or rapid antigen test.

Blood culture is the gold standard for diagnosis of bacterial sepsis including typhoid fever and needs to be sent along with urine culture prior to initiation of antibiotics in fever without localizing signs. CSF analysis is prudent in young infants in following scenarios to rule out concomitant meningitis (Table VIII).[14,15]

Normal range of CRP is <6 mg/dL. Viral etiology can be suspected when it is <20 mg/dL and initiation of antibiotics can be postponed. It is strongly indicative of bacterial infection when CRP is >40 mg/dL. CRP levels that persist or continue to rise after 48hours of antibiotic therapy requires further evaluation.

Table VII. Clues from CRP and leucocyte counts

CRP	CBC	Possible diagnosis
Negative	Leucopenia	Viral infection
Negative	Leucopenia +Thrombocytopenia	Dengue
High	Leucocytosis	UTI, Pneumonia, Meningitis, Kawasaki disease, MIS-C
High	Low or Normal	Enteric fever

Table VIII. Indications for lumbar puncture in young febrile infants

Clinical	Altered sensorium, seizures
Total leukocyte count	<5000/mm^3 or >15000/ mm^3
Absolute band count	>1500
Immature to mature neutrophil ratio	>0.2
CRP	>20 mg/dL

Molecular methods are gaining grounds with PCR assays which can be employed on blood, sterile body fluids, respiratory samples, stool and CSF and utilized for detection of various bacteria like staphylococcus (Methicillin resistance), streptococcus and viruses like SARS-CoV2, enterovirus, dengue etc. GeneXpert and BioFire assays are available in India, but are expensive (Table IX).[15]

B. Treating an acutely febrile child

The primary objective of treating fever is to make the child comfortable and trying to identify the cause of fever.

Antipyretics are the main stay of treatment with either paracetamol or ibuprofen. Being inhibitors of the COX-2 enzyme, they reduce production of prostaglandin E2, an endogenous pyrogen.[2] Oral paracetamol is recommended at a dose of 10-15 mg/kg at 4-6th hourly intervals, not exceeding 60 mg/kg/day. Antipyretic effect usually begins within 30-60 minutes, reducing temperature by 1-2°C in 2 hours. Rectal suppositories maybe used in children when oral medication cannot be administered. Ibuprofen has a longer antipyretic effect with oral dose of 10 mg/kg at 6-8th hourly intervals. It is not routinely preferred in Indian children because of the endemicity of dengue infection.

Rules for judicious use of antimicrobials in acute febrile illness.[16]

- In acute illness, mere presence of fever doesn't justify use of antibiotics, as majority of infections are viral.
- Clinical differentiation between bacterial and viral infection is possible in most cases.
- Choose single oral antibiotic if feasible, covering suspected Gram positive or negative organism as per type of infection, site and age of patient.

Table XI. Fever with focus - Evaluation

Disease	Targeted investigations	Newer diagnostics
UTI	Urine routine, leukocyte esterase, nitrite, culture	Urine PCR
Acute gastroenteritis, dysentery	Stool routine, ova, cyst, culture (invasive organisms)	Stool PCR
Pharyngotonsillitis	Throat swab culture (suspicion of GABHS)	Throat swab rapid streptococcal antigen test
Pneumonia	Chest X-ray, blood culture	Sputum/blood PCR
Influenza	RT-PCR for H1N1	Rapid influenza diagnostic test
COVID-19	RT-PCR, RAT for SARS-CoV2, Serology	CBNAAT, TruNat
Meningitis, Encephalitis	CSF analysis and culture, Blood culture	CSF PCR
Dengue	NS-1, Serology ELISA	PCR
Malaria	PS-MP, QBC MP	RDT-Malaria
Typhoid	Blood culture, CBC, LFT	Typhidot-M
Scrub typhus	IgM ELISA, Weil Felix	PCR
Leptospirosis	IgM ELISA, dark field microscopy, culture	PCR

- Antibiotic combination is justified only in SBI with no proof of specific organism.
- Prescription of antibiotic at first visit (<48 hours) is justified only if bacterial infection is highly likely e.g. acute otitis media, streptococcal pharyngitis.
- Antibiotics may need to be modified based on cultures and their continuation at 48 hours to be re-evaluated.

C. Counseling the caregivers

Parents have many misconceptions regarding childhood fever, treatment and consequences, tend to self medicate with wrong doses at wrong intervals and seek medical opinion late. They regard fever, not merely as a symptom, but as a worrisome disease by itself. The goal of parent counseling is to enable them to observe the child effectively, paying close attention to potential signs of severe illness (e.g. child's breathing, skin, behavior and level of consciousness), rather than just worrying about defervescence.

Counteracting fever phobia[17]

- Educate caregiver about fever at every wellness visit
- Fever is a normal response to infection, a symptom not a disease
- Parents should treat for the child's discomfort rather than a specific temperature
- Fever will persist until the disease process resolves
- Well being of child is more important than the height of the temperature
- Use the term "fever therapy" rather than "fever control"

Points to Remember

- ***Short duration fevers are usually self-limiting and caused by common viruses.***
- ***Disease profile of Indian children is different from the western population and clinical examination with relevant investigation is important.***
- ***Fever maybe the only early sign of serious bacterial infections in young infants requiring hospitalization, where empirical broad-spectrum antibiotics and complete evaluation into the cause are required.***
- ***Undifferentiated, benign viral fevers presenting with rash need to be differentiated early from sinister entities like meningococcemia, scrub typhus, dengue fever and Kawasaki disease based on the pattern of rash appearance and distribution.***
- ***Older children usually have localizing signs for infection which need to be actively searched for and treatment instituted appropriately.***
- ***Undifferentiated fever in children with***

immunodeficiency or immunocompromised states need aggressive evaluation for source of infection and warrant early initiation of empirical antibiotics.

- ***Antibiotics in short duration fevers is justified only when a bacterial source of infection is conclusively identified.***
- ***Pediatricians play an active role in counseling the parents regarding danger signs of infection, when to seek medical care, allay fears and address common misconceptions regarding fever even during wellness visits of the child to the clinic.***

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FEVER

APPROACH TO A CHILD WITH FEVER OF 1-2 WEEKS DURATION

***Monjori Mitra**
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Abstract: *Fever is one of the common clinical symptoms seen in pediatric population diagnosed with an identified bacterial or viral infection. In several others, the fever may be prolonged for a longer duration commonly called fever of unknown origin (FUO). Common causes are infectious in nature such as viral, bacterial, fungal and parasitic. Non-infectious causes are immune-mediated and granulomatous diseases, periodic fever syndromes and autoinflammatory disorders and neoplasms. Important factors to be considered for diagnosis are periodicity of fever and associated signs and symptoms. When investigating prolonged fever, it is important to consider the age at onset, family history, duration of febrile episodes, length of the interval between episodes, associated symptoms and response to treatment. Along with case history data, a careful physical examination during and between febrile episodes may provide useful clues and guide laboratory investigations. A careful watch is mandatory in cases of prolonged fever because new signs and symptoms may appear over time which may help to approach the diagnosis.*

Keywords: *Fever of unknown origin, Fever etiology, Fever periodicity, Relapsing fever.*

Fever is a common presenting complaint for many clinical conditions in children. Most febrile illnesses either resolve before a diagnosis can be made or may show distinguishing characteristics that lead to a diagnosis.[1] The most difficult clinical scenario is when the fever is prolonged for more than one to two weeks which is defined as fever of unknown origin (FUO), when the etiology cannot be ascertained despite thorough evaluation.[2]

A consensus definition for FUO in children is lacking. For clinical purposes, FUO can be defined as fever >38.3°C (101°F) at least once per day for ≥8 days with no apparent diagnosis after initial outpatient or hospital evaluation that includes a detailed history, thorough physical examination and initial laboratory assessment.[3,4] But this article describes basic approach to a child with fever of one to two weeks duration which requires evaluation for a diagnosis or cause, before it is labeled as FUO.

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Etiology

The most common etiologies of fever persisting for one to two weeks include infectious and noninfectious causes such as connective tissue disease and neoplasms. Among infectious causes, viral, bacterial, fungal and parasitic diseases are included and among noninfectious causes, there are immune-mediated and granulomatous diseases, periodic fever syndromes, auto inflammatory disorders and neoplasms. In addition, there are causes of prolonged fever with no definite etiology, such as drug fever, factitious fever, central nervous system dysfunction, and others, that do not fit into the above categories. In many cases, a definitive diagnosis is never established and fever resolves while undergoing many investigations, treatments with antibiotics and other means.

A) Infectious causes: Common causes for fever of 1-2 weeks duration may be due to infectious or non infectious etiologies. Common infectious causes are described in Box 1. Order of frequency varies based on the region, time period and immune status of the individual.

B) Non-infectious causes: Non-infectious etiological factors are considered only next to infectious etiology in this duration of fever of 1-2 week duration, but beyond two weeks duration, they form the major group. They are discussed in Box 2. Showing specific differences between some autoinflammatory disorders, infectious diseases and immune-mediated conditions.

Approach to the disease conditions

Fever periodicity and associated signs and symptoms may guide the pediatrician towards the correct diagnosis. Sometimes, fever episodes present a regular “clockwork” periodicity, as in cyclic neutropenia and PFAPA syndrome.[5]

Box 1. Common infectious causes of fever between 1- 2 week duration

1) Bacterial: This group falls into three categories. a) Common seasonal or tropical infections b) other systemic infections c) Less common or unusual infections

   a) Enteric fever, leptospirosis and scrub typhus are the common bacterial tropical infections encountered. Frequency of individual diseases varies from region and different time period.

   b) Other systemic infections: Partially treated or complicated pneumonia, urinary tract infection, meningitis.

   c) Unusual or less common infections like tuberculosis, brucellosis, osteomyelitis or occult abscesses are included in this category. Though infective endocarditis has become rare, one should consider this also as a differential diagnosis.

2) Viral: Epstein-Barr (EBV) virus infection is the only viral infection to be considered in this category. In immunocompromised individuals, HIV and CMV infection have to be considered.

3) Parasitic: Malaria has become rarer, but has to be considered as a cause, in regions, where still prevalent.

4) Fungal: Only during the treatment of a child with chemotherapy or impaired immunity or on central venous access or total parenteral nutrition, fungal infections need to be considered. Otherwise they are not considered as a cause in common situations.

Box 2. Non-infectious causes for fever of 1-2 week duration

1. Neoplasms: Leukemia and lymphoma are important but rarer causes
2. Immune mediated disorders: Kawasaki disease and hemophagocytic lymphohistiocytosis (HLH) are the two most common disorders encountered in this category. Acute rheumatic fever, systemic lupus erythematosus (SLE), systemic juvenile idiopathic arthritis (SJIA) Crohn's disease, Behçet's disease, juvenile dermatomyositis (JDM) and vasculitis syndromes are other rare causes.
3. Autoinflammatory disorders: Periodic fever, aphthous stomatitis, pharyngitis, adenopathy (PFAPA) syndrome, familial Mediterranean fever (FMF), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), cryopyrin-associated periodic syndromes (CAPS), familial cold autoinflammatory syndrome (FCAS).
4. Hypersensitivity diseases: Hypersensitivity pneumonitis, drug fever.
5. Miscellaneous disorders: Congenital insensitivity to pain with anhidrosis, anhidrotic ectodermal dysplasia, diabetes insipidus, central nervous system abnormalities, infantile cortical hyperostosis (Caffey's disease) and factitious fever.

In some cases, hereditary auto inflammatory disorders (e.g. familial Mediterranean fever and hyper-IgD syndrome) or EBV infection may cause fever at regular intervals and a well elicited history, clinical examination as well as specific laboratory tests may be helpful in confirming these diseases.

Neoplasms are less common: Leukemia and lymphoma are the two main neoplasms that can present with recurrent fever at admission and the illness history, clinical findings with focused diagnostic tests are useful for the confirmation of diagnosis.[6]

Given in Box 3 are the clues from the history, signs and symptoms, suggestive of some specific conditions.

Viral infections

Prolonged febrile episodes have been reported to be caused by CMV, EBV and HIV infections. Fever associated with EBV infection lasts for 7-10 days on average and usually resolves within three weeks. Prolonged fever associated with arthralgia was attributed to persistent parvovirus B19 infection. Other accompanying symptoms included fatigue, night sweats, headache, abdominal pain, skin rash, hyperesthesia, swelling of the hands and feet, erythema nodosum, increased inflammatory markers and moderate anemia. Most of the diagnosis is based on serologic and PCR tests. HIV infection by itself is usually not responsible for prolonged fever, but febrile illnesses often occur in patients with acquired immunodeficiency syndrome (AIDS), as a result of opportunistic infections.

Box 3. Clues for diagnosis

History

- Fever provoked by cold exposure: Familial cold autoinflammatory syndrome
- Fever after immunizations: Hyper IgD with periodic fever syndrome
- Rat exposure: Rat bite fever
- Cattle or raw milk exposure / travel to endemic areas: Brucellosis, malaria, relapsing fever, visceral leishmaniasis, scrub typhus

Symptoms and signs

- Relative bradycardia: Brucellosis, salmonellosis
- Arrhythmias (tachycardia, bradycardia) due to a conduction defect: Acute rheumatic fever, infective endocarditis
- Oral ulcers: Crohn's disease, Behçet's disease, cyclic neutropenia, PFAPA syndrome, hyper Ig D with periodic fever, HSV, drug fever
- Arthritis/arthralgia: SJIA, hyper IgD with periodic fever syndrome, familial cold agglutinin syndrome, Behçet's disease, parvovirus B19, relapsing fever, trench fever, chronic meningococcemia, rat bite fever, brucellosis
- Lymphadenopathy: Cyclic neutropenia, PFAPA syndrome, systemic JIA, hyper IgD periodic fever syndrome, EBV
- Splenomegaly: SJIA, hyper IgD with periodic fever, familial Mediterranean fever, EBV, relapsing fever, chronic meningococcemia, brucellosis, malaria, visceral leishmaniasis
- Uveitis: Crohn's disease, Behçet's disease
- Weight loss: Crohn's disease, malignancy
- Abdominal pain: Crohn's disease, familial Mediterranean fever, hyper IgD with periodic fever, parvovirus B19, relapsing fever
- Serositis: Familial Mediterranean fever, systemic JIA, systemic lupus erythematosus
- Conjunctivitis: Familial cold agglutinin syndrome, trench fever
- Genital ulcers: Behçet's disease
- Transient rash during fevers : Systemic JIA
- Erythema nodosum: Crohn's disease, Behçet's disease, parvovirus B19
- Erysipelas-like erythema: Familial Mediterranean fever

Bacterial infections

Occult bacterial infection is a potential cause of prolonged fever. Infection may have a defined primary focus, as in urinary tract infections, salmonellosis, cholangitis, endocarditis, osteomyelitis or dental abscesses.[7] Endocarditis should always be suspected in the case of unexplained prolonged fever with a changing or new cardiac murmur in patients with congenital heart diseases, presence of chronic indwelling catheters.

Specific agents identified as a cause of prolonged febrile episodes are relapsing fever due to borreliae, *Bartonella quintana*, *Mycobacterium tuberculosis*, *Spirillum minus*, meningococci in the setting of chronic meningococcemia and *Yersinia enterocolitica.*

Relapsing fever

Relapsing fever is characterized by recurrent fever, headache, myalgia, arthralgia, rigors and nausea.[8] *Borrelia recurrentis* is transmitted by a louse vector, while the other relapsing fevers are transmitted by soft tick vectors.

After 3-10 days of incubation period, fever abruptly appears and resolves within 3-5 days and then rash over the trunk and shoulders may develop which disappears in

a couple of days. Systemic symptoms like abdominal pain, hepatosplenomegaly, jaundice, renal involvement, central nervous system manifestations, thrombocytopenia and bleeding manifestations have been described. Death may occur due to hepatic or cardiac failure, pneumonia, subarachnoid hemorrhage or splenic rupture. Diagnosis relies on microscopy performed on a thick blood smear obtained during febrile episodes, culture in specialized liquid media and molecular detection. In recent times it is being diagnosed by multiplex real-time PCR assay.

Brucellosis

Both *B.melitensis* and *B.suis species* cause prolonged fever and has a wide range of clinical manifestations. The signs and symptoms may include persistent fever and lethargy, osteoarticular complaints and epididymo-orchitis, hepatosplenomegaly, mild elevation of liver enzymes and lymphocytopenia.[9] History of exposure to cattle, goats, other animals or consumption of raw milk, approximately 1-4 weeks before clinical onset may be present. In brucellosis, the infection is indolent and causes nonspecific symptoms and signs and if untreated, does not resolve.

Enteric fever

Patients with enteric fever have prolonged fever with other protean systemic manifestations. The diagnosis can be ideally made with blood culture which should be repeated if initially negative and fever persists. Serologic testing is not recommended.[10]

Leptospirosis

The clinical features include nonspecific findings like fever, rigors, myalgia, conjunctival congestion, headache, cough, jaundice and AKI following exposure to soil or water contaminated with animal urine or infected animal tissues.[11]

Infective endocarditis

Infective endocarditis (IE) is not common, yet an important cause of prolonged fever in children. Viridans streptococci, enterococci and staphylococci (including *Staphylococcus aureus* and coagulase-negative staphylococci) are the organisms most commonly isolated. Blood cultures may be negative if patient has received a trial of empirical antibiotics, in right-sided cardiac involvement, or infection caused by unusual or fastidious organisms (e.g., *Brucella, Coxiella burnetii*, *Bartonella* spp, anaerobes, fungi).

Children with suspected IE as the cause of FUO should have several blood cultures (aerobic and anaerobic) over a 24-hour period before initiation of antimicrobial therapy. Echocardiography is frequently performed to assess damage to the heart valves and look for valvular vegetations. However, the absence of these findings does not exclude the diagnosis of IE.[12]

Complications of upper respiratory tract infection

Even the most frequent upper respiratory tract infections (URTI) and infections of related organs, such as mastoids or sinuses, present as FUO in children.[13] Mastoiditis, sinusitis, chronic or recurrent otitis media, chronic or recurrent pharyngitis, tonsillitis, peritonsillar abscess and nonspecific URTI are reported as causes of prolonged fever in children.

Tuberculosis

Tuberculosis is a known cause of prolonged fever with protean manifestation and is common in the Indian subcontinent. The duration of the febrile episodes ranges from a few hours to one week or even more. Chest X-ray is of limited utility because tuberculosis in children is often extra pulmonary. Computed tomography is of some help in detecting granulomas.

Intra-abdominal abscess

The intra-abdominal abscesses in various locations other than liver like subphrenic, perinephric and pelvic abscesses, can cause prolonged fever. Index of suspicion should be high if there is any prior abdominal complaint. Many children with liver abscess have hepatomegaly and right upper quadrant tenderness, whereas, some may have only fever.[14]

The common pathogens causing intra-abdominal abscess are gram negative organisms like *E.coli*, enterococcus and anaerobes. Usually ultrasonography or CT of abdomen demonstrates the infected collection. On strong suspicion if the usual imaging techniques show no clue, radioisotope or gallium scanning may be warranted.

Fungal diseases

Fungal infection is rarely a cause of prolonged fever, with histoplasmosis and coccidioidomycosisas as possible etiologies.[15,16] In recent years increase in prevalence of immunocompromised patients with autoimmune diseases on immunomodulatory treatment and increased duration of hospitalization of patients in intensive care units have led to increased incidence of coccidioidomycosis.

Parasitic infections

Malaria, with its typical fever patterns and visceral leishmaniasis are the important parasitic causes of recurrent febrile episodes. In both infections, residence in endemic areas should guide clinical suspicion. In congenital toxoplasma infection, recurrent episodes of fever occur at 1, 3 and 6-weeks of age associated with neurological and ocular abnormalities due to dysfunction of the hypothalamic thermoregulatory center.

Malaria: Malaria is caused by the intracellular plasmodium protozoa transmitted to humans by female anopheles mosquitoes; the species identified included *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium vivax* and *Plasmodium ovale*. Malaria is characterized by paroxysms of fever, chills, sweats, fatigue and splenomegaly.[17] Pallor is common due to anemia. The typical fever bouts are due to the rupture of schizonts, which occurs every 48 hours with *P.vivax and P.ovale* (tertian fever) and every 72 hours with *P.malariae* (quartan fever). Diagnosis is established by identification of organisms on peripheral blood smears and dual antigen detection.

Immune-mediated and granulomatous diseases

Among the common causes of prolonged fever, it is important to mention Crohn's disease, especially in adolescents.[18] In Crohn's disease, fever may precede the other typical manifestations of inflammatory bowel disease, such as abdominal discomfort or loose stools, by weeks or months. Microcytic hypochromic anemia and growth retardation are useful diagnostic clues.

Behcet's disease

It is a less common cause of prolonged recurrent fever, which should be included in the differential diagnosis with Crohn's disease due to common clinical features. Oral and genital ulcers, together with uveitis and skin lesions, are the main clinical manifestations of Behcet's disease, ulcerative lesions may develop in any part of the gastrointestinal tract. The age at onset in children is usually between 8 and 12 years.[19]

Systemic lupus erythematosus (SLE) and juvenile dermatomyositis (JDM)

SLE and JDM can cause prolonged fever; related signs and symptoms (e.g. characteristic skin involvement in JDM) and autoantibody testing (e.g. anti-dsDNA autoantibodies in SLE) strongly suggest the diagnosis. The onset of autoimmune diseases in early childhood is rarer than in late childhood and adolescence but nonetheless, it is possible. In autoimmune diseases, fever episodes generally have a long duration and during afebrile intervals, symptoms tend to persist, often worsening overtime. In SJIA, fever can be the initial isolated sign for few months. It is often associated with an evanescent salmon pink rash that transiently appears when the temperature increases. The patient typically exhibits a rapid return to baseline or below baseline body temperature. Initially, the typical fever pattern may be less evident, but it may be observed after treatment with non-steroidal anti-inflammatory drugs (NSAIDs). Usually, the onset of symptoms occurs before 10 years of age and fever is present for a period of weeks or even months. Fever is the most common clinical presentation of SJIA, followed by arthritis and rash. Other findings of SJIA are lymphadenopathy, hepatomegaly or splenomegaly and serositis. Appearance of an unremitting fever in SJIA should be a red flag suggesting the possible development of a macrophage activation syndrome (MAS).

Other causes of prolonged fever in the differential diagnosis are neoplasms, leukemia and lymphoma. The rare causes of prolonged fever include factitious fever, drug fever, diabetes insipidus, histiocytic disorders and central nervous system abnormalities, such as agenesis of the corpus callosum or hypothalamic dysfunction.

Hemophagocytic lymphohistiocytosis (HLH)

HLH is a non-malignant, severe life-threatening disorder which must be intervened early. Uncontrolled proliferation of activated lymphocytes and histiocytes leads to hemophagocytosis, dysregulation and hypersecretion of inflammatory cytokines. Commonly it is infection associated HLH, a reactive process triggered by infection, immunologic disorder.

Criteria for diagnosis include prolonged fever, with hepatosplenomegaly, hyperferritinemia and cytopenias.[20] Other findings include liver dysfunction, coagulopathy, hypertriglyceridemia, or hypofibrinogenemia.

Infantile cortical hyperostosis

Another not so uncommon disease in the clinic setting is infantile cortical hyperostosis (Caffey's disease) which is an inherited disease characterized by persistent fevers, sometimes as high as 40°C (104°F), sub periosteal bone hyperplasia and swelling of overlying tissues. Patients exhibit fever, tenderness over the affected regions and irritability. The clinical features, with radiologic changes of periosteal involvement of the site clinch the diagnosis.

Kawasaki disease

Kawasaki disease is a multisystem vasculitis of unknown origin which can be diagnosed early with a high index of suspicion. It is an important cause of prolonged fever in children. The other common associated findings are bulbar conjunctivitis, oral changes, rash, edema, erythema of hands and feet, unilateral cervical adenopathy and delayed periungual desquamation. Some of these manifestations may not appear until the second week of fever and some may have occurred and resolved by the time the patient is examined. The echo changes with aneurysm in coronary arteries are the common complications.

Kikuchi disease

Kikuchi disease (Kikuchi-Fujimoto disease, Kikuchi histiocytic necrotizing lymphadenitis), is an uncommon benign disorder characterized by fever and cervical lymphadenopathy that may last for one to four months.[21] Fatigue, hepatosplenomegaly, nausea, vomiting, diarrhea, joint pain, arthritis, and rash may occur. Kikuchi disease is more common in adolescent females; the pathogenesis is related to a T cell and histiocytic response to an infectious agent. Lymph node biopsy demonstrating paracortical foci with necrosis and histiocytic cellular infiltrate confirms the diagnosis.

Diabetes insipidus

A cause of prolonged fever in infants and young children can be either central or nephrogenic diabetes insipidus (DI).[22] It is difficult to identify the symptoms of polyuria, polydipsia, unexplained dehydration, hypernatremia in a young child until the evidence of weight loss, hypernatemia and decreased perfusion appear. The diagnosis is established by the following investigations - serum electrolytes, osmolality of serum and urine during normal hydration and water deprivation and confirmed by estimation of antidiuretic hormone by radioimmunoassay.

Drug fever

Drug fever can happen with any drug. A proper history of drug intake should be taken when dealing with prolonged fever. Most of the times, drug fever is due to hypersensitivity reaction. Rarely drugs can impair thermoregulatory mechanisms and cause fever. Discontinuation of the drug resolves the fever in 48 to 72 hours.

Points to Remember

- ***When investigating fever of 1-2 weeks, it is important to consider the age at onset, family history, travel history, exposure to animals, periodicity, associated symptoms and response to treatment.***
- ***A careful physical examination during and between febrile episodes may provide useful clues and guide laboratory investigations.***
- ***It is important to rule out the possibility of an infectious disease, the common ones being enteric fever, scrub typhus, malaria and leptospirosis.***
- ***After excluding an infectious etiology, neoplastic, immune-mediated and autoinflammatory causes should be taken into consideration.***
- ***Repeated clinical examinations are mandatory, as new signs and symptoms may appear over time which may give a clue to the likely diagnosis and help to choose the appropriate laboratory investigations.***

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CLIPPINGS

Timing of introduction to solid food, growth and nutrition risk in later childhood.

A longitudinal cohort study was conducted to evaluate the relationship between the timing of infant cereal introduction between 4 and 6 months of age and growth and dietary intake in later childhood. Healthy children 0 to 10 years of age participating in The Applied Research Group for Kids cohort study between June 2008 and August 2019 in Toronto, Canada were enrolled.

Of 8943 children included, the mean (SD) age of infant cereal introduction was 5.7 (2.1) months. In the primary analysis, children who were introduced to infant cereal at 4 vs. 6 months had 0.17 higher body mass-index z-score (zBMI) (95% CI: 0.06, 0.28; P = .002) and higher odds of obesity (OR 1.82; 95% CI: 1.18, 2.80; P=0.006) at 10 years of age. In the secondary analysis, children who were introduced to infant cereal at 4 vs. 6 months had 0.09 higher height for age z-score (zHeight) (95% CI: 0.04, 0.15; P=0.002) at 1 year of age, an association that was not observed at 5 or 10 years of age. Children who were introduced to infant cereal at 4 vs. 6 months had higher nutrition risk which was primarily determined by a less favorable eating behavior score at 18 months to 5 years of age (0.18 units higher; 95% CI: 0.07, 0.29; P=0.001).

The researchers concluded that introduction of infant cereal at 4 vs. 6 months was associated with higher zBMI, higher odds of obesity, similar zHeight and less favorable eating behavior. These findings support recommendations for introducing solid food around 6 months of age.

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FEVER

APPROACH TO A CHILD WITH FEVER BEYOND 2 WEEKS

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****Winsley Rose**

Abstract: *Prolonged fever of two weeks duration or more poses diagnostic challenges due to a wide variety of differential diagnoses including infections, malignancies, rheumatological conditions and other rare causes. It is important to have a structured approach to make a definitive diagnosis. A good history, meticulous physical examination supported by a step wise escalation of investigations to arrive at a definite diagnosis is the key to successful management of prolonged fever. Empirical steroids, anti-tuberculous and broad spectrum antibiotic therapy should be avoided till a definite diagnosis is established.*

Keywords: *Fever, Pyrexia of unknown origin, Approach, Algorithm.*

Fever is one of the commonest complaints for which parents seek health care.[1] Fever in children is usually caused by viral illnesses and usually resolves on its own. Some fevers are due to common bacterial infections that can be diagnosed by a thorough history and clinical examination; these children are treated with empirical antibiotics without laboratory investigations. Sometimes the diagnosis is not that straightforward and might require multiple investigations before one reaches a final conclusion.[2] This article provides an approach to such prolonged fever that last beyond 2 weeks, which could be due to infections, malignancies, rheumatological conditions and other rare etiologies.

Temperature homeostasis and fever

Body temperature is regulated by the thermoregulating centre of hypothalamus. The thermoregulatory centre balances heat production, derived predominantly from metabolic activity in the muscles and liver, with the dissipation of heat from the skin and lungs. The thermoregulation centre can maintain a stable body temperature when the environmental temperature is normal.[3] The upper limit of normal body temperature is 37.2°C (98.9°F) in the morning and 37.7°C (99.9°F) in the late afternoon/ early evening peak. The mean amplitude of variation is 0.5°C (0.9°F).[4] Fever is an abnormal increase in body temperature that occurs during a specific biological response that is mediated and controlled by the central nervous system. A rectal temperature above 100.4º F (38º C) is widely regarded as fever in infants and young children.[5,6] Axillary temperature is 0.3-0.6ºC lower than the rectal temperature.[7]

Fever of unknown origin (FUO)

The classical definition of "Fever of unknown origin (FUO)" was framed by Petersdorf and Beeson in 1961 who described it as a well-documented fever of at least 3 weeks duration without an apparent source after 1 week of inpatient investigation.[8] Durack, et al further classified FUO into 4 categories in the wake of the arrival of HIV, intensive care and immunomodulation. The 4 categories are: Classic FUO, neutropenic FUO, nosocomial FUO and HIV associated FUO.[9]

Etiological considerations of FUO

The causes of fever of unknown origin include infections, malignancies, connective tissue disorders, drug fevers and other inherited or acquired systemic disorders.[10] In a study done in south India among children with fever more than 8 days, the most common aetiology was infectious diseases (90.6%) followed by malignancy (4%) and collagen vascular disease (1.3%).[11] Similarly, a descriptive study from Mumbai evaluated 49 children with fever lasting for more than 7 days and infections were the cause in 34 (79%), collagen vascular diseases in 6 (14%) while 3 (7%) had other causes.[12] Some of the infective and non- infective causes of fever of unknown origin is listed in Table I.

FUO evaluation

The evaluation for prolonged fever starts with a detailed history and physical examination, followed by screening laboratory investigations and then targeted investigations to arrive at a diagnosis.

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Table I. FUO - Causes[13]

Infectious	Rheumatological	Malignancy	Miscellaneous
Bacterial Systemic Tuberculosis Salmonellosis Brucellosis Leptospirosis **Localised** Pyelonephritis Endocarditis Osteomyelitis Liver abscess Mastoiditis Sinusitis Subdiaphragmatic abscess	Juvenile idiopathic arthritis Systemic lupus erythematosus Kawasaki disease Polyarteritis nodosa	Leukemia Lymphoma Neuroblastoma	Drug fever Ectodermal dysplasia Periodic fever
Viral EBV, hepatitis A			
Rickettsial Scrub typhus			
Parasitic Malaria			

History

Age: The child's age can be a clue towards diagnosis in FUO. Young children are prone to get respiratory or genitourinary tract infection, localized infection (abscess, osteomyelitis), juvenile idiopathic arthritis (JIA) etc. In the adolescent age group, tuberculosis, inflammatory bowel disease, autoimmune processes and lymphoma are more common.[13]

Degree of fever (Table II)**:** High grade fever with chills and/ or rigor may suggest malaria infection, urinary tract infection, amoebic liver abscess, infective endocarditis, brucellosis or other loculated collection of pus.[14]

Pattern of fever: Continuous or sustained fever. Fever that does not fluctuate more than about 1°C (1.5 °F) during 24 hours, but at no time touches normal.[15] Continuous fevers are characteristics of lobar and gram-negative pneumonia, typhoid, acute bacterial meningitis, urinary tract infection, among others (Fig.1).

Continuous fever with stepladder pattern is seen in enteric fever (Fig.2). The fever progressively increases each day. The stepladder fever pattern that was once the hallmark of typhoid fever now occurs in as few as 12% of cases. Following effective therapy of typhoid fever, fever defervescence occurs gradually, by lysis.[15]

Table II. Normal and febrile body temperature ranges[16]

Body temperature	°C	°F
Normal	37–38	98.6–100.4
Mild/low grade fever	38.1–39	100.5–102.2
Moderate grade fever	39.1–40	102.3–104.0
High grade fever	40.1–41.1	104.1–106.0
Hyperpyrexia	>41.1	>106.0

Intermittent fever (Fig.3)**:** Intermittent fever, for instance due to malaria, will be present only for several hours during the day (Table III). Effective anti-malarial therapy leads to a rapid fever defervescence-by crisis (Fig.4). This pattern of fever can be seen in malaria, pyogenic infections, tuberculosis (TB), schistosomiasis, lymphomas, leptospira, borrelia, kala-azar, or septicemia.[15]

The Pel-Epstein's fever is an intermittent low-grade fever characterized by 3-10 days of fever with subsequent afebrile periods of 3-10 days (Fig.5). It is thought to be a typical but rare manifestation of Hodgkin's lymphoma.[16]

Remittent fever is characterized by daily fluctuations of temperature exceeding 2°C, but temperature at no time

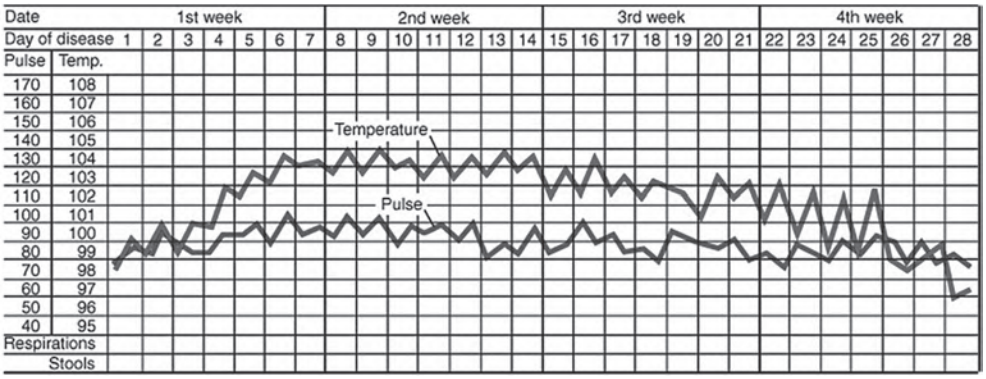

Fig.1. Continuous fever in typhoid. Note the relative brasdycardia[15]

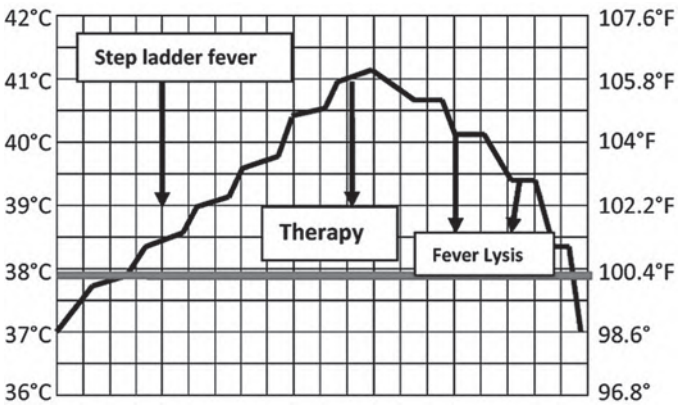

Fig.2. Continuous fever in typhoid - Step ladder pattern[15]

touches normal. Remittent fevers are often associated with infectious diseases such as infective endocarditis, rickettsial infections, brucellosis, among others.

Relapsing fever - Week-long fevers with week-long remissions which are seen in borreliosis (Fig.6).

Associated symptoms

Suffused eyes are associated with Kawasaki disease, leptospirosis, tuberculosis and infectious mononucleosis. Gastrointestinal complaints may suggest salmonellosis, leptospirosis, intra-abdominal abscess, or inflammatory bowel disease (IBD). Nasal discharge may suggest rhinosinusitis.[17] Recurrent pharyngitis with ulcerations may suggest periodic fever with aphthous stomatitis, pharyngitis and adenitis syndrome.[18] Limb or bone pain may suggest leukemia or lymphoma, osteomyelitis or septic arthritis, brucellosis, infantile cortical hyperostosis etc.[19,20] Sweating is an important history to ask. When child has excessive sweating and heat intolerance, it could be a symptom of hyperthyroidism.[21] History of heat intolerance

Table III. Pattern of fever in malaria

Type of fever in malaria	Organism	Periodicity of fever
Tertian fever	P. vivax and P. ovale.	48 hours
Quartan fever	P. malariae malaria	72 hours
Quotidian fever	P. falciparum malaria	24 hours

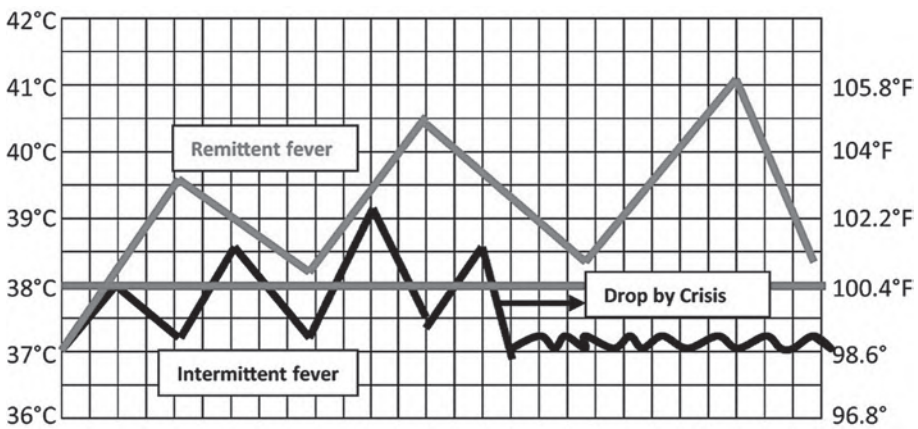

Fig.3. Intermittent fever[15]

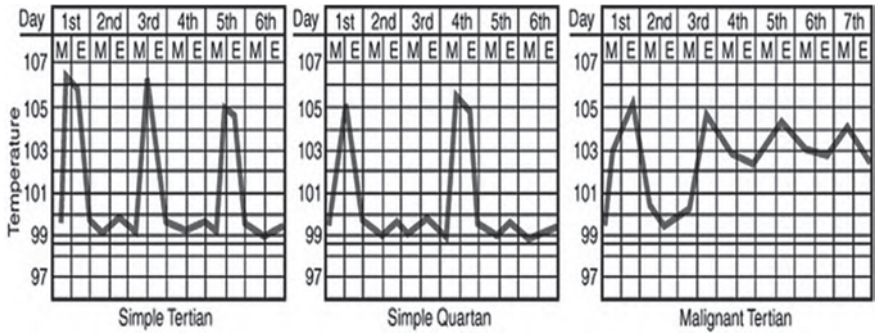

Fig.4. Periodicity of fever in malaria[15]

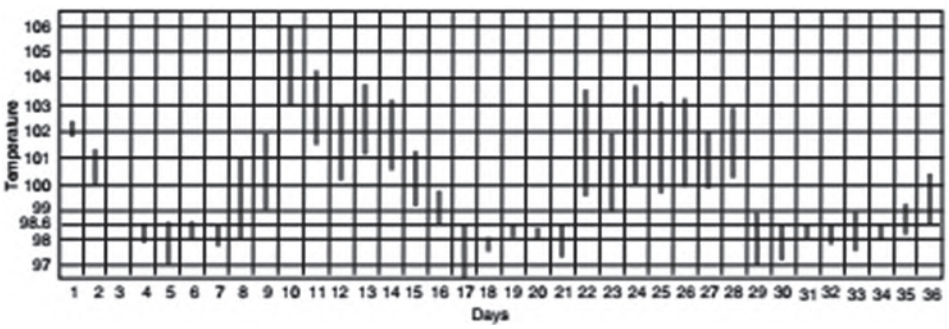

Fig.5. Pel-Ebstein fever[16]

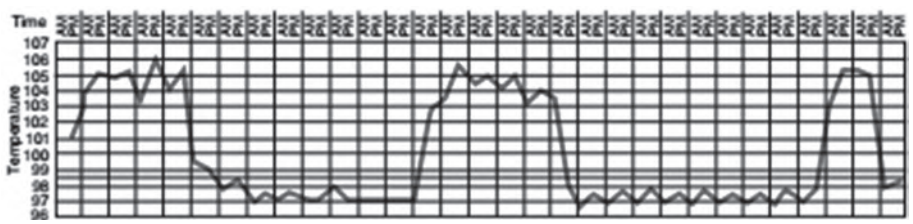

Fig.6. Relapsing fever[15]

without sweating is suggestive of ectodermal dysplasia.[22] Night sweats are seen in infections like TB, nocardia, brucellosis, liver or lung abscess and sub-acute infective endocarditis, as well as in non-infectious diseases such as polyarteritis nodosa and malignancies such as lymphomas.[23]

Exposures

Animal exposure: Ask for history of exposure to wild or domestic animals. Enquire about pets at home and any recent sickness or death of pets. A history of tick bite or travel to tick or mite infested area should be obtained as it may be important in many rickettsial infections. A history of exposure to cattle, goats or sheep or consumption of unpasteurized milk should be taken if brucellosis is suspected.[24] Any history of pica should be elicited. Eating of dirt is a particularly crucial evidence to infection with Toxocara (visceral larva migrans).[25]

Travel history: Detailed travel history, even in the past, taking into account the length of incubation period, is important to diagnose unusual infections. Endemic diseases should always be remembered at the time of the clinical investigation.

Contact history: A detailed history of fever in any of the family members or other contacts is important. History of contact with an adult with tuberculosis or within the last 2 years reinforces the suspicion of tuberculosis.[26]

Medical interventions

Patients with a history of abdominal surgery have an increased risk of intra-abdominal abscess.[27] The list of potential infectious pathogens may need to be expanded in children with tracheotomy tubes, gastric tubes, cochlear implants, or other implantable devices.[28]

Table VI. Medications causing fever of unknown origin[30]

Class of drug	Drugs
Antimicrobial agents	Carbapenems, cephalosporins, minocycline , nitrofurantoin, penicillins, rifampin, sulfonamides
Anticonvulsants	Barbiturates, carbamazepine, phenytoin
Antihistamines	
Cardiovascular drugs	Hydralazine, procainamide, quinidine
Histamine2 blockers	Cimetidine, ranitidine
Iodides	
Herbal remedies	
Nonsteroidal anti-inflammatory drugs	Ibuprofen, sulindac, phenothiazines, salicylates

Drug intake

The list of drugs consumed or applied topically should be elicited including over the counter preparations and native medicines. Phenothiazine and anticholinergic drugs inhibit sweating. Ephedrine and related compounds may affect thermoregulatory control mechanism. In drug fever, there is a lag time from the initiation of the drug to the onset of fever and there is an infrequent association with eosinophilia and rash (Table VI).[29]

Family history

Certain unusual causes of fever like nephrogenic diabetes insipidus, familial dysautonomia and periodic fever are inherited.[29]

Examination in a child with FUO

Temperature monitoring: The first step is to confirm fever by measuring temperature by medical personnel and to exclude factitious fever, especially in patients with good medical knowledge and apparently good health despite wide-swinging fever patterns.[31]

Appearance: The general appearance and activity should be observed. The presence of toxicity in older children with prolonged fever is helpful in some infections like typhoid and typhus fever.

Sweating during fever: The absence of sweat during fever could be suggestive of dehydration due to vomiting, diarrhea, or diabetes insipidus. It could also be rarely associated with anhidrotic ectodermal dysplasia, familial dysautonomia or atropine exposure.

Anthropometry: Weight loss is associated with infections like tuberculosis, HIV and malignancies. Short stature may be seen in inflammatory bowel disease, hypopituitarism or chronic disease.

Skin examination: The examination of skin for specific lesions and rashes must be done carefully and repeated if needed. Infective endocarditis has notable skin manifestations, namely purpura, Osler nodes, Janeway lesions and conjunctival hemorrhages.[32] Eschar is a characteristic finding in scrub typhus and in a study from south India, eschar was present in 40.8% of the cases.[33] A seborrheic rash may be a sign of histiocytosis.[34] Evanescent rash present during periods of rise of temperature is suggestive of JIA.[35]

Lymphadenopathy: Generalized lymphadenopathy may be present in infections like tuberculosis, atypical mycobacterial infections, infectious mononucleosis and HIV. Leukemias, lymphomas and other malignancies are characteristically associated with lymphadenopathy. The rare causes of prolonged fever with lymphadenopathy are Kikuchi disease, autoimmune lymphoproliferative syndrome, hemophagocytic lymphohistiocytosis and periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome.[36]

Oral cavity: Hyperemia of the pharynx suggests infectious mononucleosis, Kawasaki disease or leptospirosis.[17] Coated tongue is a common sign in typhoid fever.[37] Gingival hypertrophy is associated with leukemia and granulomatous diseases like sarcoidosis, Crohn's disease and Wegener's granulomatosis.[38] Recurrent oral candidiasis may be found in immunodeficient states such as HIV, malignancies and immunosuppressive therapy.[39]

Sinuses: Purulent or persistent nasal discharge may be a sign of sinusitis. Tenderness over the sinuses may be due to sinusitis.

Abdominal examination: To look for tenderness or rigidity in abscess, hepatitis and peritonitis. Rectal examination may reveal perirectal lymphadenopathy or tenderness, which suggests a deep pelvic abscess, iliac adenitis or pelvic osteomyelitis.

Musculoskeletal: Signs of arthritis may be present. The muscles and bones should be palpated carefully. Tenderness over a bone may suggest osteomyelitis or bone marrow invasion in neoplastic disease. Sub-diaphragmatic abscess may present as tenderness over the trapezius. Generalized muscle tenderness may be found in dermatomyositis, polyarteritis, Kawasaki disease, mycoplasma or arboviral infection.

Cardiovascular examination: New/changing cardiac murmurs may indicate endocarditis.

Eye examination: The following eye findings are useful in diagnosing fever of unknown origin (Box 1).

Investigations

Investigations should be tailored to the diagnostic possibilities in a child after a detailed history and examination. The need for inpatient evaluation and the pace of evaluation depends on the illness severity. Though ordering a battery of tests at once is not encouraged, certain first line investigations are done for every patient presenting with fever for more than two weeks.

Common investigations to aid in diagnosis

- Complete blood count / differential count and peripheral smear
- C-reactive protein, ESR
- Blood culture and sensitivity (if infective endocarditis is considered, three sets of blood cultures collected from different venipuncture sites, with at least 1 hour between the first and last draw is essential. Yield of blood cultures is directly related to the volume of blood collected)
- Urine: Routine and microscopy examination with culture
- Chest X-Ray/Ultrasonogram abdomen
- ANA, ASO (if arthritis present)
- CSF, lymph node aspiration/biopsy etc. (as required)
- Bone marrow culture(bacterial, mycobacterial and fungal) and biopsy for histopathology

Box 1. FUO - Clues in eyes

- Bulbar conjunctivitis - Kawasaki's disease, leptospirosis.
- Palpebral or bulbar injection - Systemic lupus erythematosus.
- Punctate conjunctival hemorrhages, Roth spots- Bacterial endocarditis
- No pupillary constrictor response - Familial dysautonomia.[40]
- Uveitis-Juvenile idiopathic arthritis, tuberculosis.
- Choroidal tubercles - tuberculosis.

Complete blood counts

Complete blood cell count with differential WBC count are done as initial investigations. An absolute neutrophil count less than 5,000/µl may suggest typhoid fever. A polymorphonuclear neutrophil count more than 10,000/ml is highly suggestive of bacterial infection.[41]

Peripheral smear

Blood smear may show presence of malarial parasites. Presence of blasts more than 20% or certain morphological features in the blasts irrespective of the blast percentage is suggestive of acute leukemia.[42]

Inflammatory markers

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are nonspecific acute-phase reactants. An extremely elevated ESR (100 mm per hour or greater) suggests etiologies such as abdominal or pelvic abscess, osteomyelitis and endocarditis. However, ESR does not help discriminate between active autoimmune disease and infection. Also malignancies and noninfectious inflammatory diseases can cause an elevated ESR and CRP level. In one review, an ESR of 100 mm per hour or greater had a high specificity for malignancy (96%) and infection (97%) and its positive predictive value was 90%.[43] Elevated CRP level is a sensitive marker for infection and inflammation, but it is not sensitive enough to discriminate between disease processes.[44]

Organ involvement

Liver function tests and renal function tests should be done for evaluation of organ dysfunction.

Cultures

Blood cultures for aerobic and anaerobic pathogens are essential in the evaluation of fever of unknown origin.

Roadmap to FUO:

Step 1: Detailed history

i. Onset, duration and pattern of fever
ii. Associated symptoms/ loss of weight
iii. Previous history s/o immunodeficiency
iv. Exposure history- contacts/ ingestion/ animals/ ticks/ travel/ invasive procedures
v. Immunization history
vi. Drug history (for drug fever)

Step 2: Clinical examination

Detailed physical examination including:

i. Skin examination
ii. Lymphadenopathy
iii. Sinus tenderness
iv. Mastoid tenderness
v. Oral cavity
vi. Musculoskeletal examination

Step 3: Baseline investigations

- Stop non-essential medications.
- Complete blood count / differential count / blood picture
- Biochemical profile- LFT, creatinine.
- Blood culture and sensitivity
- Urine: routine and microscopy examination with culture
- Chest X-Ray/USG scan
- Malarial parasites*, Scrub IgM*
- Leptospira Ig M*
- Start empiric antimicrobial therapy*
- Observation and serial examination

*based on local epiemiology

Second line investigations, if fever persistent

Infectious	Rheumatological	Oncologic	Immunodeficiency
1. 3 sets of blood cultures 2. Tuberculosis workup - Mantoux, Gastric Juice / Induced Sputum for CBNAAT, MGIT 3. Echocardiography - to look for vegetations. 4. C-reactive protein, ESR (if suspected osteomyelitis, abscess, endocarditis)	1. ANA 2. Rheumatoid factor 3. C3, C4, CH50 4. Ferritin (as a screening test for HLH)	1. Tumor lysis workup (LDH, uric acid, Na, K, Ca, P) 2. Withhold steroids	1. HIV 2. Immunoglobulins 3. Lymphocyte subsets 4. Consider antibody titers to vaccination

Third line investigations (to be evaluated in a referral centre)

1. Chest-abdomen-pelvis computerized tomography
2. Paranasal sinuses radiography or tomography
3. PET scan
4. Bone scan (if suspecting osteomyelitis)
5. Bone marrow aspirate and biopsy
6. Lymph node/ organ biopsy if indicated
7. Angiotensin converting enzyme levels in suspected sarcoidosis
8. Thyroid function tests
9. Genetic testing for periodic fever syndromes

It is essential for diagnosis of typhoid fever, brucellosis, septicemia and infective endocarditis.[10]

Tuberculosis workup

Chest X-ray is the first investigation if tuberculosis is suspected. Sputum or fasting-morning gastric aspirates after fasting, for acid fast bacilli smear, mycobacterial culture (MGIT) and cartridge based nucleic acid amplification tests (CB-NAAT) should be obtained to diagnose pulmonary tuberculosis. Extrapulmonary tuberculosis will need a more detailed evaluation. Palpable lymph nodes can be subjected to biopsy. CECT might be required to look for lymph nodes in the thorax and abdomen.[26]

Rheumatological workup

In addition to inflammatory markers like ESR, CRP and ferritin, antinuclear antibody (ANA), complement levels and rheumatoid factor can be done if a collagen vascular disease is suspected.[2]

Serology

Serological tests can assist in the diagnosis of infectious mononucleosis (EBV VCA IgM), CMV infections, toxoplasmosis, salmonellosis, brucellosis, leptospirosis, rickettsial diseases and many other conditions.

Diagnostic imaging

Diagnostic imaging is useful in determining etiology of FUO. Chest radiograph should be obtained in all the cases of FUO. Radiographic examination of the sinuses and mastoids may be considered if infection at these sites suspected. Ultrasonography is a useful tool in diagnosing certain conditions such as intra-abdominal abscesses of the liver, subphrenic space, pelvis, or spleen.

CT or MRI scans permit detection of neoplasms and pyogenic collections without surgical intervention. Lesions of abdomen, chest, head, neck, retroperitoneal spaces and mediastinum may be evaluated with the help of CT and MRI scan. For a child with suspected inflammatory bowel disease, faecal calprotectin is a useful test which is a functional quantitative measure of intestinal inflammation. CT scan has greater resolution and can show extramural disease, while MRI is suitable when soft tissue characterization is required like perianal Crohn's disease.[45] Magnetic resonance imaging is the imaging modality of choice for establishing the diagnosis of osteomyelitis and arthritis or to delineate the location and extent of bone and soft-tissue involvement.[46] Positron emission tomography/ Computerized tomography (PET/CT) is a technique with high sensitivity for detecting neoplasms, infections and inflammations. This makes it an ideal diagnostic tool for the investigation of FUO.[47]

Echocardiography should be considered if endocarditis is suspected. Transesophageal echocardiography is more sensitive than transthoracic echocardiography to evaluate infective endocarditis.

Invasive testing

- Invasive procedures include lumbar puncture for those with headache, skin biopsy for rash, lymph node aspiration or biopsy for lymphadenopathy and bone marrow aspiration and biopsy. Bone marrow aspiration and biopsy is useful in diagnosing leukemia, metastasis, mycobacterial, fungal or parasitic diseases. Hence, sample should be sent for bacterial, fungal and mycobacterial cultures. Other indications for a bone marrow biopsy include histiocytosis, hemophagocytosis or storage diseases.[48]
- Biopsy of abnormal tissue based on diagnostic imaging is helpful in establishing a diagnosis of FUO. Computed tomography or ultrasound-guided aspiration or biopsy has reduced the need for an exploratory laparotomy or thoracotomy. Bronchoscopy, laparoscopy and GI endoscopy may provide direct visualization and biopsy material when organ-specific manifestations are present.

Management

The management of prolonged fever should be supportive until the definite etiology is determined. Antipyretics can be given to control the fever. The definitive management of prolonged fever depends on the final diagnosis obtained. However, it is prudent to start narrow spectrum empirical antibiotics after obtaining adequate blood cultures based on the local epidemiological pattern till a confirmed diagnosis is reached. Therapeutic trial of empiric broad spectrum antibiotics, antimalarials and antituberculous therapy should be avoided as it can delay definite diagnosis. Empiric steroid therapy should also be avoided as it can obscure the symptoms and signs of the underlying malignancy.

Conclusion

A detailed history, thorough physical examination and baseline investigations that are focused on the local epidemiology are important first steps in making a diagnosis in a child with prolonged fever. Use of non-invasive tests should be considered before evaluation with invasive and expensive investigations in the management of a child with prolonged fever.

A step wise approach to the management with empirical treatment for tropical fevers based on local epidemiology is useful. One should avoid empirical steroid therapy, anti-tuberculous therapy and broad spectrum antibiotic therapy till a definite diagnosis is established.

Points to Remember

- **A *detailed history and thorough examination are the cornerstone for diagnosis in a child with prolonged fever.***
- ***Epidemiological data, contact history, previous medical history, fever pattern, focused physical examination and screening tests often provide adequate information to establish a diagnosis.***
- ***Non-invasive tests are performed first before taking up the child for invasive and expensive investigations in a step wise manner based on the clinical details.***
- ***Management includes supportive treatment as well as targeted therapy after the diagnosis is obtained. empirical broad spectrum antimicrobials, anti-malarials, anti tuberculous therapy and steroids should be avoided.***

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NEWS AND NOTES

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Neonatology Association of Tamil Nadu

(TN DIGI NEOCON 2021)

Virtual Conference

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FEVER

PERIODIC FEVER

Karamath S. Pyarejan

Abstract: *Periodic fevers are often poorly understood due to the lack of understanding and many a times are missed. Even though these are rare, the children who have these conditions are subjected to multiple unnecessary investigations and treatments. Understanding the concept of auto-inflammation can be helpful in the approach to many chronic diseases and their treatment.*

Keywords: *Periodic fever, Autoinflammatory syndromes, Recurrent fever.*

Fever is the most common presenting complaint in children. In most of the cases it is of short duration due to common childhood infections. Rarely fever may recur.

Whenever fever becomes a recurrent complaint it can be approached as shown in Fig.1. Periodic fever is one of the causes for recurrent fever (Box 1).

Periodic fever

The periodic fever syndromes are autoinflammatory diseases characterized by unprovoked inflammation. They are distinguished from autoimmune disorders by the absence of significant levels of autoantibodies or autoreactive T cells. These are due to defects in proteins involved in the innate immune system and single gene mutations in some.[1,2]

Box.1. Recurrent fever

1. Single illness where symptoms wax and wane
2. Multiple unrelated illnesses of same organ system
3. Multiple unrelated illnesses of different organ systems
4. Periodic fevers: Recurrent episodes of illness where fever is the predominant feature and other features are usually similar in each episode with afebrile intervals.

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Characteristics of periodic fever are as follows

A. Three or more episodes of unexplained fever in a 6 month period occurring at least 7 days apart.
B. Episodes rarely last for more than 7 days, on an average 4 days.
C. They do not have an infectious etiology
D. Usually well between the episodes
E. Many have a genetic background and or hereditary.
F. Usually associated with inflammation in different parts of the body.

Pathogenesis

Periodic fevers belong to the class of auto inflammatory syndromes - A recently explained group of disorders which are related to but are distinct from autoimune diseases.

The cornerstone of immune system is the ability to differentiate self from non-self. This traditional concept explains the response against infections but cannot explain tumors or presence of auto reactive lymphocytes. The current concept is danger signal theory i.e. Immune system mounts an immune response to danger signals whether they are from exogenous pathogens or endogenous damaged tissue. Failure of this mechanism results in self-directed inflammation and the autoimmune diseases are classic examples for this.

Autoinflammatory syndromes are also diseases in which there is self-directed inflammation but unlike autoimmunity, here there is no B or T cell response but activation of innate immune cells (macrophages and neutrophils).[4] In essence a seemingly unprovoked inflammation without autoantibodies or antigen specific T lymphocytes.[1] Autoimmune diseases and auto inflammatory diseases may be considered as part of an 'immunological disease continuum' as how unregulated disorders of immune system can range from pure autoimmune to pure auto inflammatory end of the spectrum given in the Fig.2.

Since the innate immune responses are involved in the pathogenesis, treatment approaches also target cytokine cascade like etanercept, anakinra, colchicine or infliximab.[5]

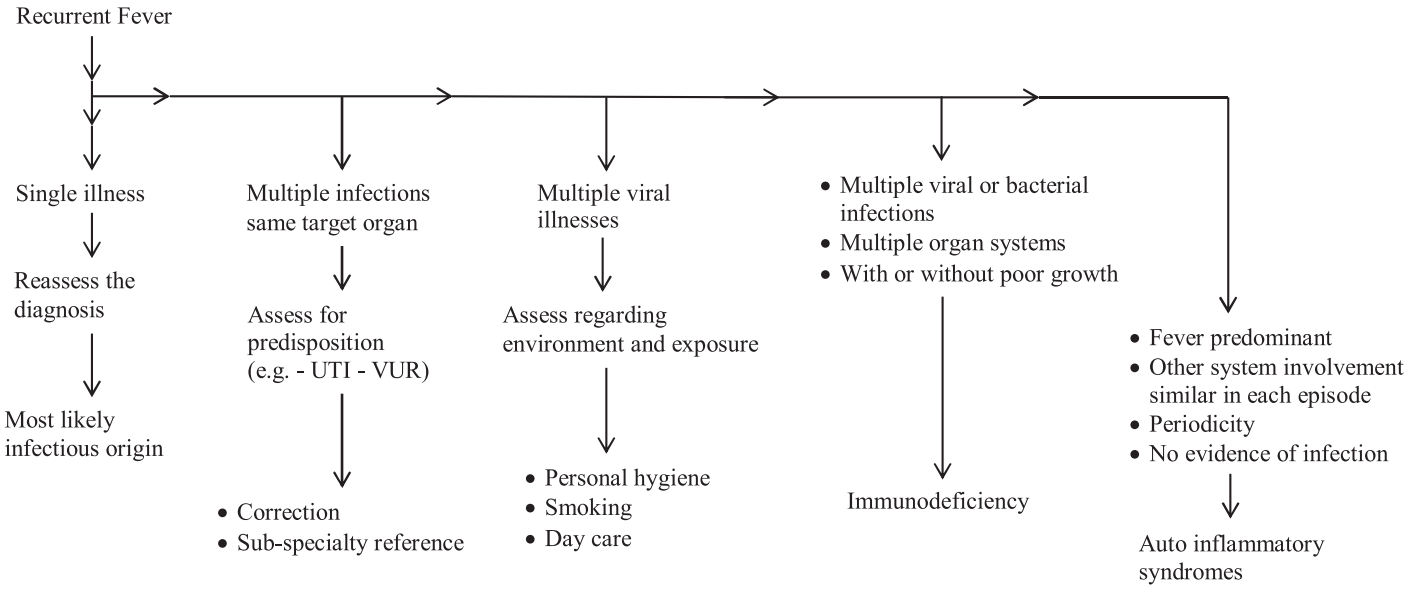

Fig.1. A proposed approach to recurrent fever in children[3]

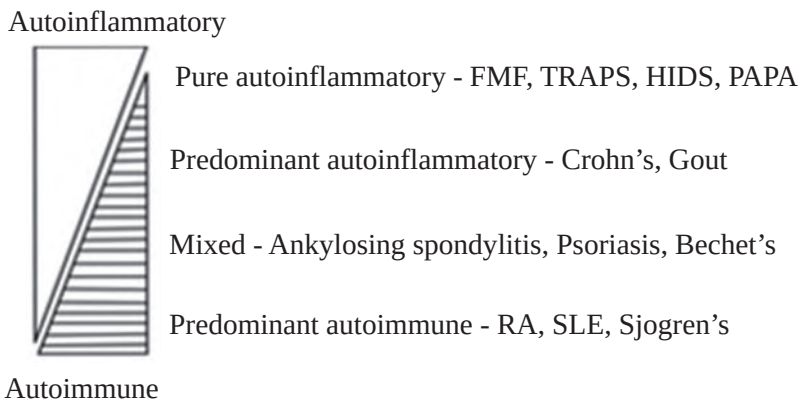

Fig.2.The immunological disease continuum[4]

FMF-Familial mediterraneanfever, TRAPS-Tumournecrosis factor receptor associated periodic syndromes, HIDS-Hyper immunoglobulin D syndrome, PAPA Syndrome-Pyogenic arthritis, pyodermagangrenosum and acne, FCAS-Familial cold autoinflammatory syndrome, MWS-Muckle Wells Syndrome, NOMID/CINCA-Neonatal onset multi-system inflammatory disease or chronic inflammatory neurological cutaneous articular syndromes, DIRA-Deficiency of IL 1 receptor antagonist

Types of periodic fever

The most common heritable periodic fever disorders in children are Familial Mediterranean fever (FMF) and HIDS. FMF is an autosomal recessive disease found in people of Mediterranean descent. Periodic fevers based on the inheritance pattern can be classified as follows.

Autosomal dominant

1. Tumour necrosis factor receptor associated periodic syndromes (TRAPS)
2. Familial cold autoinflammatory syndrome (FCAS)
3. Muckle Wells Syndrome (MWS)
4. Neonatal onset multi-system inflammatory disease or chronic inflammatory neurological cutaneous articular syndromes (NOMID/CINCA)
5. Pyogenic arthritis, pyoderma gangrenosum and acne(PAPA Syndrome)

Autosomal recessive

1. Familial Mediterranean Fever (FMF)
2. Hyper Immunoglobulin D syndrome (HIDS)
3. Deficiency of IL 1 receptor antagonist (DIRA)

Familial Mediterranean fever (FMF)

- Most common periodic fever in people of Mediterranean descent.
- Recurrent fever with abdominal, chest and joint pain.
- Gene defect in MEFV gene - which codes for 'pyrin' - a protein with a role in natural control of inflammation.
- Episodes lasting for 1 to 4 days and resolve without treatment.
- Starts before the age of 20 years.
- Inflammatory markers like ESR may be elevated during the episode.
- Colchicine is effective and colchicine response may help in diagnosis.
- Like many other autoinflammatory syndromes can lead to amyloidosis.
- Lifelong colchicine therapy completely prevents the risk of amyloidosis.[6]

Tumour necrosis factor receptor associated periodic syndromes (TRAPS)

- Fever with abdominal pain, diarrhea, skin rashes, muscle pain and characteristic swelling around the eye.
- Genetic defect in TNF receptor associated protein leading to over action of TNF. Hence therapy is directed towards anti-TNF.
- Onset in late childhood.
- No response to colchicine.
- Severe amyloidosis is a late complication.
- Steroids, etanercept or anakinra are tried.

Hyperimmunoglobulin D syndrome (HIDS)

- As the name suggests increased IgD with fever, skin rash, cervical adenopathy and abdominal symptoms.
- Episode lasting 3 to 7 days, recurring every 2 to 12 weeks.
- Starts in early infancy.
- Genetic defect in mevalonate kinase. How this leads to auto inflammation is not yet clear.
- NSAIDs during episodes or anakinra or etanarcept may be of help.
- Usually episodes become milder over time.

Neonatal onset multi-system inflammatory disease or chronic inflammatory neurological cutaneous articular syndromes (NOMID/CINCA)

- Starts at birth or within the first weeks of life.
- Skin rash, fever, chronic meningitis with hearing and visual loss.
- Less severe variants which present later in life are Muckle Wells Syndrome (MWS) and Familial old Auto inflammatory Syndrome (FCAS).
- All of these - NOMID, MWS, FCAS - together are grouped together as Cryopyrin associated auto inflammatory syndromes (CAPS).[7]
- FCAS - Exposure to cold (such as even exposure to AC) can trigger a episode. Short duration - <24 hours fever, rash and arthralgia.
- Prognosis for CAPS is generally poor with severe joint deformities and sequlae due to neurological damage.

Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome

- Recurrent episodes of sterile erosive arthritis.
- Recurrent debilitating aggressive ulcerative skin lesions in lower extremities.
- Onset in early childhood.
- Mutations in PSTPIP1 protein.
- Anakinra, etanercept and infliximab are used.

Deficiency of IL 1 receptor antagonist (DIRA)

- Bone pain with pustules in the skin.
- Multifocal sterile osteolytic lesions in X-ray.
- Onset - Within 2 weeks of birth.
- Anakinra used as treatment.

Periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA)

- Genetic basis yet to be elucidated.
- Abrupt onset attacks with each lasting for 3 to 7 days.
- Usually decreasing frequency by age, resolves by 10 years of age.
- Dramatic response to steroids even a single dose, but may shorten the interval before the next episode.
- Fever does not respond to paracetamol.
- Cimetidine and tonsillectomy are tried as treatment.

Diagnosis

Approach essentially involves ruling out common infectious causes of fever. Other causes of recurrent/ prolonged fever such as brucellosis, malaria or infectious mononucleosis need to be ruled out. Infants with UTI may present like periodic fever. Bone Marrow examination to rule out leukemia is necessary before trial with therapy.

Appropriate first line investigations in a child with periodic fever would be[8,9]

- CBC, CRP and ESR in all patients
- Chest X-ray
- USG abdomen
- EBV serology
- Peripheral smear study
- Blood/ urine/throat culture
- Bone marrow aspiration.

Treatment

Since innate immune system is involved, steroids or other immunosuppressive therapies generally are not helpful in auto-inflammatory syndromes. Cytokine pathway blockade is the usual approach for treatment.

Etanercept

- TNF inhibitor useful in TRAPS, PAPA and HIDS.
- Also used in mixed autoimmune/auto-inflammatory diseases like JIA/RA, AS and psoriasis.

Anakinra

- IL 1 receptor antagonist used in CAPS, DIRA, PAPA and FMF.

Colchicine

- Though initially used only in gout and thought to work by inhibiting uric acid crystal formation, this drug appears to inhibit multiple proinflammatory mechanisms, while enabling increased levels of anti-inflammatory mediators.
- Used extensively in FMF, also in gout and Behcet's disease.

Points to Remember

- ***Fever need not always be due to infections.***
- ***Autoimmunity and auto-inflammation are both self directed inflammation processes.***
- ***Periodic fevers must be thought of in a well child with episodic / recurrent fever.***
- ***Steroids/ immunosuppressants should always be started after a proper diagnosis.***

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FEVER

FEVER IN THE IMMUNOCOMPROMISED CHILD

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Abstract: *Fever in the immunocompromised child is a medical emergency, which if left untreated can lead to serious morbidity and mortality. High degree of suspicion, prompt evaluation and management are essential for a successful outcome in children with febrile neutropenia. Although majority of them may not have localizing symptoms or signs, a detailed history and frequent physical examination specifically of the perianal region, central line sites, ear and oral cavity are mandatory to identify source of infection. Blood cultures (adequate volume) are essential in identifying the bug especially when there is no identifiable focus. Risk stratification based on underlying disease, severity of neutropenia and presence of other comorbidities is essential in categorizing the severity and guiding decision on admission or outpatient therapy. Initial stabilization, prompt initiation of appropriate antibiotics (with anti-pseudomonas cover) and adequate supportive care are the cornerstones of treatment. Delay in administering the first dose of antibiotic significantly worsens the outcome. Education of the family as well as the primary pediatrician is important in this regard. Diagnosis and management of such fevers in the ER and the pediatric ward are reviewed along with institutional practices which are of special relevance to the primary pediatrician.*

Keywords: *Neutropenia, Immunocompromised, Malignancy, Hematopoietic stem cell transplant, Culture, Anti-pseudomonas cover.*

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Fever in the immunocompromised is a medical emergency and requires urgent evaluation and prompt empirical antimicrobial therapy. In this vulnerable population, rapidly progressive infections can be life-threatening if untreated and hence a heightened index of suspicion for infection is essential. Febrile neutropenia is one of the clinical conditions associated with a risk of life-threatening infections.

Why are infections dangerous in immunocompromised patients?

Fever is a natural response to any infection, but children with neutropenia have a blunted inflammatory response. The usual symptoms may be absent and they may not manifest the classic signs of infection such as redness and swelling at the infection site.[1] The infection may rapidly progress to sepsis and death. For this reason, immunocompromised patients with neutropenia and fever need to seek immediate medical attention.[1] These patients may have difficutly in clearing infections, including viral. Moreover if empirical antibiotics have already been given, it makes it harder to determine the causative organisms. Immunocompromised patients are vulnerable to even the unusual opportunistic infections and infestations.

The severity of the infection depends upon a)host factors : primary illness, degree of neutropenia and b)etiological factors: cause of fever - infectious or non-infectious, the virulence and antibiotic susceptibility of microbiological organisms and c) contributing factors : poor nutrition, breaches in oral, gut and perianal mucosa - due to chemotherapy / radiotherapy / invasive procedures, poor seroconversion after routine immunization, presence of an indwelling intravenous access device and functional neutropenia as in hematologic malignancies that impair phagocytosis and killing of pathogens, even if the absolute neutrophil count is normal.

Primary immunodeficiency

Defects in different components of immunity correlate with increased risk for particular infection. Table I shows specific etiological organisms to be considered in specific immune defects.[2]

Table I. Immunological defects and susceptibility to specific infections

Immunological defect	Disease	Organisms causing infection
Neutrophil oxidase burst defect	Chronic granulomatous disease	Catalase positive bacteria (*S.aureus*), Enterobacteriaceae (*E.coli, K.pneumonia*), aspergillus, candida
Asplenia	Sickle cell anemia	Encapsulated bacteria - *S.pneumonia*, *N.meningitidis*, *H.influenzae*.salmonella
B cell dysfunction	X-Linked agammaglobulinemia	Bacterial infections, overwhelming EBV infection
T cell defects	HIV, DiGeorge syndrome	Viruses – HSV, EBV, CMV,VZV*, adenovirus Fungi-aspergillus, candida, PCP Bacteria-TB
Terminal complement deficiency	C5-C9 Deficiency	*N. meningitidis*

* HSV - Herpes simplex virus, EBV - Epstein- Barr virus, CMV - Cytomegalovirus, VZV - Varicella zoster virus, PCP - Pneumocytis carinii pneumonia

Acquired immunodeficiencies

This includes those on long term steroid therapy, hemato-lymphoid malignancies, solid tumors with bone marrow infiltration, chemotherapy, post-splenectomy, post-transplant immune suppressive therapy and acquired immunodeficiency syndrome (AIDS).

In both primary and secondary immunodeficiency, serious infection must be promptly considered and treated when children are i) febrile and neutropenic, ii) febrile and not neutropenic and iii) afebrile and neutropenic with signs of infection or clinical deterioration (e.g. hypothermia, hypotension, listlessness, confusion).

Neutropenia is defined as absolute neutrophil count < 1500 cells / microlitre. The degree of neutropenia (ANC in cells/microlitre) is classified as in Box 1.[3]

Febrile neutropenia (FN)

A single axillary temperature above 37.7°C or 37.4°C for more than one hour or a single oral temperature ≥38.3°C (101°F), a temperature ≥38°C (100.4°F) for longer than one hour or two elevations >38°C (100.4°F) during a 12-hour period for more than one hour in an immunocompromised child with neutropenia (absolute neutrophil count (ANC) <500 cells/microlitre or an ANC that is expected to decrease to <500 cells/microlitre during the next 48 hours) is febrile neutropenia.[4] Measuring temperature by rectal route is avoided in FN as there is possibility of introducing infection through mucosal trauma.

Prolonged FN is neutropenia with co-existent fever lasting for more than five days**,** which increases the risk of invasive fungal infections.[5]

Box 1. Degree of neutropenia

- Mild: ANC-1000-1500 cells / microlitre
- Moderate: ANC- 500-1000 cells / microlitre
- Severe: ANC < 500 cells / microlitre
- Profound: ANC <100 cells / microlitre

Table II. Risk groups for febrile neutropenia

High risk	Low risk
ANC <500 expected to last > 7 days or ANC <100	ANC expected to resolve in 7 days
Hepatic / renal dysfunction / new onset mental changes	No active co morbidities
Hemodynamic instability New onset hypoxia / pulmonary infiltrates	
Diseases - relapsed ALL, infant ALL, AML, B-NHL, following HSCT within hundred (100) days of transplant, high risk neuroblastoma, relapsed solid tumour.	

Box 2. Salient history to be elicited in febrile neutropenia

- Duration of fever.
- Primary diagnosis, e.g. haplo identical HSCT (more incidence of viral reactivation).
- Current medications including glucocorticoids, chemotherapy.
- Current antibiotic prophylaxis (to help in empiric antibiotic choice).
- Exposure to infection in the family.
- Symptoms to suggest focus of fever - respiratory, GIT, urinary.
- Presence and duration of central venous catheters.
- Post bone marrow transplant (duration post-transplant will help in suspecting the etiology).
- Check for previous microbiologically-confirmed diagnoses and pattern of resistance seen if culture results are available.
- Concomitant noninfectious cause of fever (e.g. blood products) to be checked for.

Clinical evaluation: Febrile neutropenic patients can be divided into high and low (or standard) risk groups according to criteria given in Table II.[4,6,7] Salient points in history is given in Box 2.[8]

Non-infectious causes of fever in immunosuppressed children have to be kept in mind and considered after ruling out infectious causes. They include drug fever, malignancy related fever, deep vein thrombosis, pulmonary embolus, transfusion reactions, dysautonomia (in children with central nervous system disease) and hemophagocytic lymphohistiocytosis (HLH).

Clinical examination

Impaired immunity leads to under development of clear signs of infection. Therefore a thorough physical examination is crucial with regular repeated review to pick up subtle signs of infection (Box 3). One point to note is that neutropenic patients will not develop an abscess.

Laboratory evaluation

First line investigations include -complete blood count, peripheral smear, CRP/procalcitonin, two sets of blood culture, urine routine and culture, liver and renal function.[4,5] It is important to take blood cultures from central and peripheral lines and age appropriate adequate volumes to avoid negative yield in cultures. Repeat blood culture is important if child remains sick. CRP is unreliable in severe neutropenia/ liver disease. Procalcitonin is useful to decide on cessation of therapy, has slightly better predictive value than CRP, rises within 3-4 hours in response to an infection as opposed to 24-48 hours in CRP, but not reliable post HSCT.[9] Other investigations based on the symptoms and signs are given in Table III.

Box 3. Assessment in a febrile immunocompromised child

- Vital signs and assessment of hemodynamic instability (septic shock).
- Review of focus[8]
  - Central line, port site to be assessed daily.
  - Oral cavity for mucositis/candida/dental infections.
  - ENT examination - ear discharge (otitis media / sinusitis).
  - Perianal pain, swelling.
  - Skin infections or lesions suggestive of fungi.
  - Examine abdomen for signs of neutropenic colitis/ pancreatitis / *C.difficile* colitis.
  - Check for new hepatosplenomegaly.
  - Lungs-look for tachypnea, desaturation (hypoxia with minimal chest findings is suggestive of pneumocystis or viral pneumonia).

Do not forget to examine the oral mucosa, genitalia and perineum.

Management

High risk patients are to be hospitalized and administered broad spectrum IV antibiotics. Knowledge of locally prevailing bacteriological profile and antimicrobial susceptibility data helps in guiding empiric therapy. First dose of antibiotic is administered without any delay preferably within 60 minutes, as delay increases the morbidity and mortality.

Other factors determining the plan of therapy are a) type of malignancy: hematolymphoid malignancy versus solid tumor, b) disease status: active disease versus in remission and c) phase of treatment: on intensive chemotherapy versus maintenance.

Table III. Investigations based on etiology/site involved

Etiology / Site involved	Investigations
Bacterial (Gram negative organisms are the most common cause in India)	Blood cultures Swab culture- relevant site
	CRP
	Procalcitonin
Viral (CMV/ Varicella / Adenovirus HSV/EBV)	Viral serology/PCR (blood, bodily fluid, respiratory secretions). Baseline blood PCR for CMV, especially post-transplant
Respiratory involvement	CXR, CT chest Nasopharyngeal aspirate for viral PCR (PCP / fungal features - to look for in imaging)
Gut	*C.difficile* toxin/PCR (For fever with acute diarrhoea and vomiting especially if received antibiotics, neutropenic colitis in patients with abdominal distension and diarrhoea) Abdominal USG (for hepatosplenomegaly in candidiasis)
CNS - Altered mental Status	CT Brain Lumbar puncture (ensure adequate platelet count before LP)
Others	Echo (to rule out valvular vegetations) Serum Ferritin (HLH diagnosis, differentiate engraftment fever from infection in post HSCT; trends better than single value)

Management of low risk patients

Low risk children can be considered for outpatient treatment. They must have increasing neutrophil counts or duration of neutropenia not expected to last more than seven days with stable renal and hepatic function and no significant comorbidities. They should have adequate gastrointestinal absorption. The family should also be readily accessible and live within close proximity to a medical centre (in case of deterioration) and be available for daily review.[10] In developing countries, gram negative organisms still account for the majority of infections in children with FN. Empiric antibiotic chosen should have antipseudomonas cover. The most common empiric regimen for outpatient management is oral ciprofloxacin/ levofloxacin or 4th generation cephalosporins.[10]

Management of high risk patients

Though FN can be caused by any community-acquired pathogen, opportunistic infections must also be considered. While bacteria are the most common causative agents, viral infections may also occur in children especially post-transplant. Fungal infections should be remembered in prolonged FN. The first dose of antibiotic therapy should be administered within one hour of initial presentation.[11]

In high-risk category, empirical antibiotic coverage is as follows:

Broad spectrum coverage- monotherapy or combination? Monotherapy: An anti-pseudomonas betalactam is the current recommendation except for centres with high rates of resistance or if the patient is hemodynamically unstable.[4,5,10] Piperacillin-tazobactam, cefoperazone-sulbactam or 4th generation cephalosporin (cefepime) is the first recommendation. Carbapenems can be reserved as second line antibiotics to prevent the emergence of drug resistant organisms. Colistin/polymyxin is reserved as third line drug.[12]

Combinations: Aminoglycosides are now rarely used because of oto and nephrotoxic effects since monotherapy with piperacillin-tazobactum/meropenem is equally efficacious.[13] In case of penicillin allergy, where cephalosporins and meropenem cannot be used, quinolones and glycopeptide combination can be tried.

Specific scenarios

Line infections: Most children with malignancy have an indwelling central venous catheter. If there is doubt about whether an infection is a line infection or a true bacteremia, cultures from the central venous line in addition to peripheral blood cultures are taken.

CLABSI [(Central line associated blood stream infection (BSI)]: If there is no growth in peripheral culture, it is only a colonizer.

CRBSI (Central line related blood stream infection): Both peripheral and central cultures grow the same organism with differential time to positivity of 2 hours indicating that there is BSI and the central line is the source.[14]

Consider urgent line removal in:[4]

1. Child with sepsis syndrome not responding to antibiotics and adequate supportive care.
2. S. aureus, candida or multidrug resistant organism in blood cultures.
3. Child develops fever or rigors after the line is accessed.
4. Child with septic thrombophlebitis, endocarditis, sepsis with hemodynamic instability.

- Use meropenem if meningitis is suspected or the child presents with shock.
- Consider PCP in a child with tachypnea, desaturation and typical CXR findings, especially in those who have missed cotrimoxazole prophylaxis.
- Patients at risk of renal impairment- care must be exercised when using nephrotoxic antibiotics. This includes patients receiving cisplatin and those with a single kidney (e.g. Wilm's tumor, post nephrectomy).
- Suspected *C. difficile* (toxin / PCR positive or significant diarrhea present). Non severe initial episode - add metronidazole or oral vancomycin. Severe initial episode or recurrent episode - add oral vancomycin[15]
- Perianal infection- redness, pain in perianal region is strongly suggestive of Gram-negative infection like *E.coli*, Klebsiella, Pseudomonas especially multidrug resistant organisms.

Specific Gram-positive cover is added only if patient has evidence of any of the following:[4]

- hemodynamic instability
- severe sepsis
- radiographically confirmed pneumonia
- clinically suspected catheter related infection
- skin or soft tissue infection
- known colonization with MRSA, vancomycin resistant enterococcus (VRE), penicillin resistant streptococcus
- severe mucositis

Indications for empiric fungal therapy[4]

- Non responsiveness to first line antibiotic therapy after 4-5 days.
- Evidence of fungal infection on imaging, recurrence of fever after apparent recovery from febrile neutropenia, fever after prolonged antibiotic therapy.

The two infections most often seen are candidiasis and aspergillosis.[4] Patients at risk of systemic fungal infection are those with prolonged severe neutropenia and who have probably received more than one course of intravenous antibiotics. The diagnosis of systemic fungal infection is notoriously difficult to confirm as blood cultures are nearly always negative. Therefore, empirical antifungal therapy is essential in patients in whom there is strong clinical suspicion of infection. In such patients CT scans of head/chest and ultrasound/CT of abdomen must be considered.

Candida may cause skin and/or mucosal infections, severe esophagitis or systemic disease with fever, jaundice and pulmonary infiltrates. A well-recognised syndrome is the hepatosplenic syndrome with fever, mild jaundice, increasing splenomegaly and sometimes hepatomegaly, which may occur following recovery of counts. Investigations to be obtained include cultures and Beta D Glucan (BDG).

Aspergillus usually presents with pulmonary infiltration, rhino-sinusitis and occasionally focal CNS signs. Investigations to be done are cultures, BDG and serum galactomannan.

Antifungal therapy[16]

Liposomal amphotericin- especially indicated for CNS fungal infections and mucormycosis. This can be given to children with established renal dysfunction as well. Possible side effects to be monitored for are hypokalemia, hypomagnesemia and renal dysfunction.

Echinocandins - if patient was on fluconazole prophylaxis and there is no CNS involvement, also in hemodynamically unstable.

Amphotericin- IV use indicated in severe rhinosinusitis due to aspergillosis or mucormycosis (immediate surgical debridement also important in the latter).

Follow up - Oral voriconazole may be of value as continuing therapy following systemic aspergillus infection, likewise fluconazole following systemic candida infection.

Antiviral therapy: The risk of non-bacterial infection is directly related to the degree of immunosuppression. Hematopoietic stem cell transplant recipients are profoundly immunosuppressed after total body irradiation and high dose chemotherapy. The most important viral infections to remember are varicella zoster, adenovirus and cytomegalovirus (CMV).[8]

Varicella

Search for target organ damage as a consequence of disseminated varicella infection. IV acyclovir is to be started as early as possible in case of suspected / frank varicella infection.[4] Varicella zoster immunoglobulin / IVIG is given in case of associated / predicted neutropenia. Strict barrier nursing should be practiced. Immunize the child with varicella vaccine after induction and during remission phase of disease. Therapy for other associated viral infections like H1N1 or dengue to be considered.

CMV

Children may present with fever, pancytopenia, hepatosplenomegaly and atypical mononuclear cells in the blood. Rarer manifestations include retinitis and pneumonitis. After transplant, CMV tends to be more aggressive and is an important cause of pneumonia, bone marrow suppression and encephalitis.

Diagnosis: Virus detection in urine, blood for PCR, nasopharyngeal aspirate, bronchial lavage.

Treatment: IV ganciclovir (cidofovir, foscarnet, if resistant).

Pneumocystis pneumonia-clues are cough, fever, tachypnea, lymphopenia, absence of chest signs on auscultation and bilateral infiltrates on chest X-ray. Very unlikely in patients on prophylactic cotrimoxazole. It is important to start immediate treatment with high dose cotrimoxazole at the first suspicion of PCP. If hypoxia is present, steroids should be added.

Other specific infective syndromes

Encephalitis - Herpes simplex, mumps, adenovirus, progressive multifocal leuco-encephalopathy, HSV6, JC/BK polyoma virus reactivation, post-measles, EBV, CMV, mycoplasma.

Hepatitis- CMV, hepatitis viruses, fungal infection (usually more acute) EBV, adenovirus.

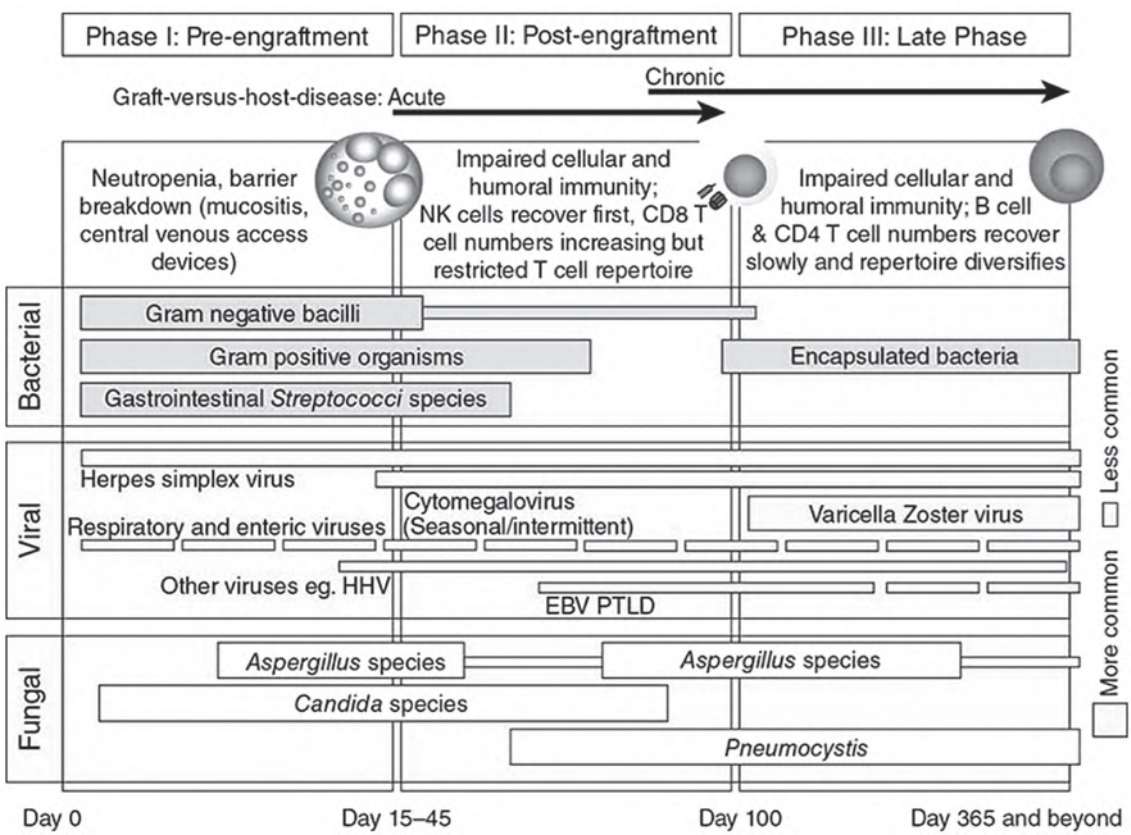

Fig.1. Timeline from transplant and infections to be suspected[17]

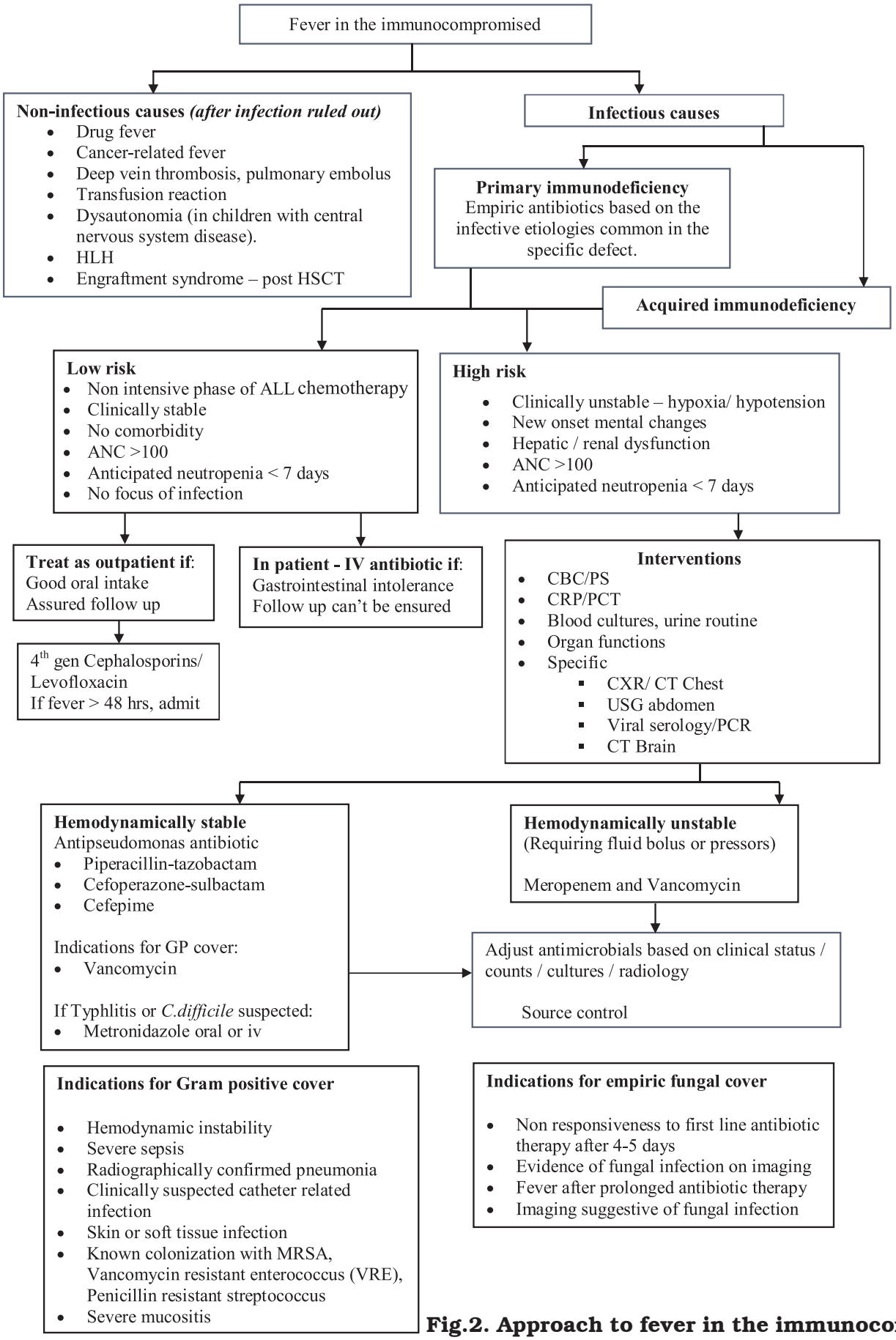

Fig.2. Approach to fever in the immunocompromised

Interstitial pneumonia-The various etiological organisms include *Pneumocystis jirovecii*, cytomegalovirus, measles, varicella-zoster (rare), fungal, mycoplasma, legionella. Common respiratory viruses include influenza, parainfluenza, adenovirus and RSV.

Hemorrhagic cystitis - BK virus

Various treatment options are ganciclovir for CMV, cidofovir for adenovirus, rituximab (use with caution) for EBV. Consider lung biopsy to prove etiology when the diagnostic tests and empiric treatment do not result in improvement.

All infectious causes have already been discussed in detail. For post stem cell transplant patients, the timeline from the date of transplant is an important clue that will guide us to suspect specific infections based on the time frame post-transplant. The various infections possible in different time frames have been outlined in Fig.1.[17]

Duration of antibiotic therapy in FN[4,5]

- Gram positive organisms - 7 to 10 days of therapy with recovery of ANC.
- Gram negative organisms - 14 days of therapy with recovery of ANC.
- Deep seated *S. aureus* infection - 6 to 8 weeks, need to look for complications (ultrasound abdomen, Echo).
- Fungal infection (stomatitis, superficial skin) - 7 to 10 days.
- Deep seated aspergillosis / mucormycosis - amphotericin B - 8 to 12 weeks.
- Resistant fungal infections - voriconazole /caspofungin - 6 to 8 weeks:

Role of antibiotic and fungal prophylaxis

- Routine antibiotic prophylaxis is not practiced in our country to avoid development of multidrug resistant organisms.[18]
- Routine PCP / fungal prophylaxis is considered in children following HSCT and with relapse on chemotherapy in children with leukemia.
- Pneumocystis carinii prophylaxis - cotrimoxazole 6 mg/kg on 2 days of the week.
- Candida prophylaxis - fluconazole, voriconazole - up to day 100 if no graft versus host disease (GVHD) in transplant patients and till duration of chemotherapy in children with leukemia.
- Antiviral prophylaxis with acyclovir 10 mg/kg/dose q8H for all patients in the first year post HSCT.

Supportive care during febrile neutropenia

- Granulocyte transfusion in severe sepsis, septic shock, especially in high risk patients (>7 days, ANC <100) where infection is not getting controlled despite adequate antimicrobial therapy.[19,20]
- Nutritional, psychological, financial support

Reverse barrier nursing and general instructions

- Hand washing and wearing protective gear are important components of reverse barrier nursing
- May necessitate separate room for mother and child
- Eating freshly cooked food
- Drinking boiled water
- Eating only fruits with peels which should be removed before consumption
- Avoiding contact with obviously infected patients
- Avoiding all live and pulse polio oral vaccines during therapy

A key element in the effective care of immunocompromised patients with fever and infection is hypervigilance. Not only these patients are at increased risk from a diverse range of microorganisms, but their resulting infections can present with subtle/ atypical symptoms and can rapidly progress to difficult-to-treat chronic disease states or to acute life-threatening clinical decompensation.

An aggressive approach and frequent re-evaluation of an immunocompromised patient's course and care is the key to successful outcome.

Fig.2 summarises the approach to fever in immunocompromised.

Points to Remember

- ***High index of suspicion, prompt diagnosis and management are essential in cases of fever in the immunocompromised which is a medical emergency and can present with only fever and subtle or atypical or no clinical signs.***
- ***Risk stratification based on underlying disease, degree of neutropenia, expected fall in ANC and underlying medical comorbidities helps in deciding on the need for admission and appropriate antibiotic.***

- ***Meticulous physical examination - especially the perianal region, ENT, central line site, to look for focus of infection.***
- ***Adequate volume of blood cultures (both via central and peripheral lines) is crucial in identifying the organism, especially in cases where the focus of infection is not identifiable.***
- ***Appropriate antibiotic having anti pseudomonas cover, should be administered within the first hour, as delay in giving the first dose of antibiotic increases the morbidity and mortality.***
- ***Addition of Gram-positive coverage / empiric antifungal coverage is needed wherever essential***
- ***CMV, adenovirus, varicella are common viral infections in post haplo-hematopoietic stem cell transplant setting.***
- ***Good supportive care and strict aseptic precautions are important components to ensure successful outcomes.***

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CLIPPINGS

Effect of Whole-Genome Sequencing on the Clinical Management of Acutely Ill Infants With Suspected Genetic Disease - A Randomized Clinical Trial.

Whole-genome sequencing (WGS) shows promise as a first-line genetic test for acutely ill infants, but widespread adoption and implementation requires evidence of an effect on clinical management.

A study was conducted at 5 US academic medical centers and affiliated children's hospitals to determine the effect of WGS on clinical management in a racially and ethnically diverse and geographically distributed population of acutely ill infants in the US. This randomized, time-delayed clinical trial enrolled participants from September 11, 2017 to April 30, 2019, with an observation period extending to July 2, 2019. Participants included infants aged between 0 and 120 days who were admitted to an intensive care unit with a suspected genetic disease. Data were analyzed from January 14 to August 20, 2020.

Patients were randomized to receive clinical WGS results 15 days (early) or 60 days (delayed) after enrollment, with the observation period extending to 90 days. Usual care was continued throughout the study. The main outcome was the difference in the proportion of infants in the early and delayed groups who received a change of management (COM) 60 days after enrollment. Additional outcome measures included WGS diagnostic efficacy, within-group COM at 90 days, length of hospital stay, and mortality.

A total of 354 infants were randomized to the early (n=176) or delayed (n=178) arms. The mean participant age was 15 days ; 201 participants (56.8%) were boys; 19 (5.4%) were Asian; 47 (13.3%) were Black; 250 (70.6%) were White; and 38 (10.7%) were of other race. At 60 days, twice as many infants in the early group vs the delayed group received a COM (34 of 161 [21.1%] vs 17 of 165 [10.3%]; *P*=.009) and a molecular diagnosis (55 of 176 [31.0%] vs 27 of 178 [15.0%]; *P*<.001). At 90 days, the delayed group showed a doubling of COM (to 45 of 161 [28.0%]) and diagnostic efficacy (to 56 of 178 [31.0%]). The most frequent COMs across the observation window were subspecialty referrals (39 of 354; 11%), surgery or other invasive procedures (17 of 354; 4%), condition-specific medications (9 of 354; 2%), or other supportive alterations in medication (12 of 354; 3%). No differences in length of stay or survival were observed.

In this randomized clinical trial, for acutely ill infants in an intensive care unit, introduction of WGS was associated with a significant increase in focused clinical management compared with usual care. Access to first-line WGS may reduce health care disparities by enabling diagnostic equity. These data support WGS adoption and implementation in this population.

The NICUSeq Study Group. Krantz ID, Medne L, Weatherly JM, Wild KT, Biswas S, Devkota B, et al. Effect of Whole-Genome Sequencing on the Clinical Management of Acutely Ill Infants With Suspected Genetic Disease - A Randomized Clinical Trial. JAMA Pediatr. Published online September 27, 2021. doi:10.1001/jamapediatrics.2021.3496.

FEVER

SYMPTOMATIC MANAGEMENT OF FEVER

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Abstract: *Fever is a normal response in many conditions, the most common of which is infection. Treatment of fever may be helpful if the child is uncomfortable and includes both pharmacological and non-pharmacological therapy. Recommended antipyretic is paracetamol according to the child's age and weight. Simultaneously the cause of the fever should be evaluated and treated accordingly.*

Keywords: *Fever, Antipyretics, Treatment, Children, Paracetamol.*

Fever is a normal protective, immune response to a variety of conditions, the most common of which is infection. Fever occurs when the temperature of the body is elevated as a result of the body's thermostat being reset to a higher than usual temperature. Normal body temperature (axillary temperature widely used) is around 37°C (98.6°F), plus or minus about 0.6°.[1] When any infection or inflammation sets in, the hypothalamus in brain responds by raising the body temperature to fight the condition. So, fever is infact body's defence mechanism against various types of insult.

The raised temperature can also help in controlling the disease process, but at the same time it makes the child uncomfortable and increases the metabolic needs of the body.

So, fever itself is neither a friend nor a foe; rather, it is a messenger that brings notification whenever the body is responding to an insult. It is a symptom and not a disease by itself. Nearly every child can develop a fever at some point in life. The severity of illness is not decided by fever alone, it is decided by the associated signs like presence of shock, altered mental status, respiratory distress, presence of skin rashes or bleeding and whether the child is immunocompetent or immunocompromised. The challenge is to know when to be concerned and start evaluating the child.

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When to treat

Fever by itself not dangerous in most cases. The decision to evaluate and /or treat a febrile child does not depend on the height of temperature but on the appearance and behaviour of the febrile child. Treatment of fever is recommended if the child feels uncomfortable and has an underlying problem including diseases of the heart, lung, central nervous system and in immunocompromised states. Treatment of fever has not been shown to prevent seizures in all children who had febrile seizures in the past.[3] Fever situation needing urgent attention and intervention is given in Box 1.

Treatment[2,3]

Management includes pharmacological and non-pharmacological methods.

Pharmacological management

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 or ibuprofen, according to the child's age and weight. Fixed drug combinations are not rational and should not be used.

Paracetamol: Oral paracetamol is traditionally considered to be safe based on clinical experience. It has a wide therapeutic window, short duration of action and hence

Box 1. Conditions necessitating intervention

Fever in a neonate

Fever in an infants less than 3 months

Fever in an immunocompromised child

New episode of fever in a child in ICU

Fever during outbreak situation

Any chronic illness

has to be repeated every 4-6 hours. Ideally a drug used merely for symptomatic relief should be short acting so that it can be repeated frequently as per the need. Hence, it can be used even in neonates. It is considered to be safe in the right dose even in liver diseases.

Rectal route has good tolerability, but dose needs to be double that of the oral dose. There is no advantage of rectal route over oral route as far as its antipyretic efficacy is concerned. On the contrary, rectal absorption is erratic. It is more suitable for febrile cases with vomiting. IV preparation of paracetamol is available but its use should not be encouraged except in ICU setting, because of the cost and complexity in administration as IV infusion, compared to oral or rectal. It is well tolerated with complications same as via oral route.

Ibuprofen: Ibuprofen is considered safe in children though it may lead to dyspepsia, nausea, vomiting and at times gastrointestinal bleeding. It can be repeated every 6-8 hourly and not 4-6 hourly as in case of paracetamol. It can be considered as an alternative to paracetamol as a last resort like allergy or no response to paracetamol. Minimum age for ibuprofen administration for fever is 3 months. Table I depicts the drugs used in treatment of fever, with their doses.

The use of antipyretics does not prevent either febrile convulsions or reactions to vaccines. Caution is recommended using antipyretics in chronic diseases such as pre-existing hepatic and renal impairment or in cases of diabetes, cardiac disease and severe malnutrition. Giving combinations of paracetamol and ibuprofen or alternating them during illness does not improve the outcome. It unnecessarily increases the chance of toxicity and is not recommended.

In asthmatic children with fever, paracetamol does not seem to worsen asthma symptoms. NSAIDs like mefenamic acid, nimesulide, diclofenac etc are not recommended in children owing to its serious side effects and very narrow safety window. They also supress evolving diseases and confuses clinical picture resulting in delayed diagnosis. Aspirin need not be used for relief of fever in children due to fear of Reye's syndrome, besides the risk of metabolic acidosis and coma. Aspirin is to be reserved for rheumatological conditions and vasculitis syndrome like Kawasaki disease.

Non pharmacological management

Sponging and baths: Sponging is not as effective as medications for fever. Its role is controversial and hence generally not recommended. Tepid sponging with water at 28-30^{o}C can be done after using appropriate medication, to reduce the temperature faster, especially in cases of heat stroke and hyperthermia. Use of ice cold water is not recommended. Alcohol should not be used for sponging because of the risk of toxicity as it can be absorbed through the skin. Child can also be given bath with tepid water but one needs to becareful to avoid hypothermia especially in young infants.

Hydration: Fever can lead to dehydration because of multiple factors like vomiting, excessive sweating and reduced intake. To reduce this risk, parents should encourage their child to drink an adequate amount of fluids. Fluids such as milk (breast milk or top milk), water, soup, fruit juice, coconut water, lassi or some ready to use drinks should be offered to children depending on their age and liking. If the child is unwilling or unable to drink fluids for more than a few hours, the parent should consult their doctor.

Table I. Drugs indicated in treatment of fever

Drug	Dose (mg/kg/dose)	Interval	Maximum dose mg/kg/day	Side effects
Paracetamol (para-aminophenol derivative)	10-15 (PO) IV - 15mg	4-6 hours (PO) IV - 6 hours	60-90 (PO) IV- 75	Rashes, blood disorder. In case of overdose - liver and renal toxicity
Ibuprofen* (propionic acid derivative)	10	6-8 hours	40	G I discomfort, nausea, diarrhoea and occasionally bleeding and ulceration. Headache, fluid retention, hypersensitivity reaction

*Though certified as safer as per western data, it is not routinely used as antipyretic due to its potential to cause serious side effects in certain tropical diseases like dengue.

Table II. Management of fever- Do's & Don'ts

Do's	Don'ts
- Always document the fever - Give paracetamol only to comfort the child - Give enough rest - Plenty of fluids - Offer adequate nutritious food	- Don't chase thermometer reading. - Don't over cloth the child. - Don't use ice water for sponging. - Don't use paracetamol for more than 4-6 times a day and not exceeding 15 mg/kg/dose. - Don't use IV Paracetamol routinely as it is not superior to oral or rectal route. Indicates only when both these routes cannot be used as in a post operative state. - Don't use mefenamic acid, aspirin or nimesulide as antipyretics. - Don't continue to treat child at home if any warning signs is observed but has to consult doctor.

Rest: Fever causes most children to feel tired with bodyaches. During this time, parents should encourage their child to rest as much as the child wants. It is not necessary to force the child to sleep or rest if he or she feel better. However strenuous physical activities should be avoided.

Heat stroke: It should be differentiated from hyperpyrexia. It is fever >41°C (105.8°F) where setting in thermoregulatory center is unchanged but heat production exceeds capacity to loose heat. It is usually not due to infection. It is either exogenous heat exposure or excessive endogenous heat production. Skin is usually hot and dry. It can cause hepatic and renal failure, disseminated intravascular coagulation (DIC) and multi organ dysfunction syndrome (MODS). Antipyretics are of no use in heatstroke. The child has to be shifted from hot to cool environment. Use of cold water spreads, cool packs and fanning needs to be done. Plenty of liquids should be given and if unable to take orally, IV fluids needs to be given.

Box 2. Red flag signs[2]

- Disproportionate heart rate and respiratory rate.
- Differential body temperature (warm body with cold extremities)
- Impaired circulation characterized by poor capillary refill, mottled ashen coloured skin
- Chest retraction
- Faucial membrane
- Purpuric spots
- Meningeal signs
- Tense distended abdomen

Table II. Depicts Dos and Don'ts in management of fever.

Red flag signs

Indicate that child is not well and needs urgent interventions. When any of the red flag sign is encountered, one needs to act immediately (Box 2).

Fever phobia : Parents have a fear over fever. This may be the reason for many emergency visits or phone calls in the middle of night. This should be tackled by good education and proper counselling. Pediatricians need to spend some time with parents to reassure them.[4]

Conclusion

Fever is a symptom and not a disease by itself. Goal of the therapy is not treating a number, but rather a child's discomfort. Paracetamol and ibuprofen are the agents of choice for relieving symptomatic discomfort in children. Non pharmacological measures like sponging, increased fluid intake, sufficient rest add to the comfort of child and can be used in addition to antipyretics. Parents should be counselled on proper dose of antipyretics. Simultaneously the cause of the fever should be evaluated and treated accordingly.

Points to Remember

- ***Fever is just symptom and not a disease.***
- ***Antipyretics are used to reduce the discomfort associated with fever.***
- ***Paracetamol and ibuprofen are the antipyretics of the choice.***
- ***Counsel parents to on the proper dose of the antipyretics and to avoid fever phobia.***

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CLIPPINGS

Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce.

In December 2020, the University of California San Diego Health (UCSDH) workforce experienced a dramatic increase in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Vaccination with mRNA vaccines began in mid-December 2020; by March, 76% of the workforce had been fully vaccinated, and by July, the percentage had risen to 87%. Infections had decreased dramatically by early February 2021. Between March and June, fewer than 30 health care workers tested positive each month. However, after the end of California's mask mandate on June 15 and the rapid dominance of the B.1.617.2 (delta) variant that first emerged in mid-April and accounted for over 95% of UCSDH isolates by the end of July, infections increased rapidly. This included cases among fully vaccinated persons.

From March 1 to July 31, 2021, a total of 227 UCSDH health care workers tested positive for SARS-CoV-2 RT-PCR assay of nasal swabs; 130 of the 227 workers (57.3%) were fully vaccinated. Symptoms were present in 109 of the 130 fully vaccinated workers (83.8%) and in 80 of the 90 unvaccinated workers (88.9%). (The remaining 7 workers were only partially vaccinated.) No deaths were reported in either group; one unvaccinated person was hospitalized for SARS-CoV-2–related symptoms.

Vaccine effectiveness was calculated for each month from March through July; the case definition was a positive PCR test and one or more symptoms among persons with no previous Covid-19 infection. Vaccine effectiveness exceeded 90% from March through June but fell to 65.5% in July. July case rates were analyzed according to the month in which workers with Covid-19 completed the vaccination series; in workers completing vaccination in January or February, the attack rate was 6.7 per 1000 persons, whereas the attack rate was 3.7 per 1000 persons among those who completed vaccination during the period from March through May. Among unvaccinated persons, the July attack rate was 16.4 per 1000 persons.

The SARS CoV-2 mRNA vaccines, BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna), have previously shown efficacy rates of 95% and 94.1%, respectively, in their initial clinical trials, and for the BNT162b2 vaccine, sustained, albeit slightly decreased effectiveness (84%) 4 months after the second dose. In England, where an extended dosing interval of up to 12 weeks was used, Lopez Bernal et al. reported a preserved vaccine effectiveness of 88% against symptomatic disease associated with the delta variant. As observed by others in populations that received mRNA vaccines, this study data suggests that vaccine effectiveness against any symptomatic disease is considerably lower against the delta variant and may wane over time since vaccination.

The dramatic change in vaccine effectiveness from June to July is likely to be due to both the emergence of the delta variant and waning immunity over time, compounded by the end of masking requirements in California and the resulting greater risk of exposure in the community. Findings of this study underline the importance of rapidly reinstating nonpharmaceutical interventions, such as indoor masking and intensive testing strategies, in addition to continued efforts to increase vaccinations, as strategies to prevent avoidable illness and deaths and to avoid mass disruptions to society during the spread of this formidable variant. Furthermore, if our findings on waning immunity are verified in other settings, booster doses may be indicated.

Keehner J, Horton LE, Binkin NJ, Laurent LC, Pride D, Longhurst CA, et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. N Engl J Med 2021; Sep 30; 385:1330-1332 DOI: 10.1056/NEJMc2112981.

FEVER

ANTIMICROBIAL CHOICE IN TROPICAL INFECTIONS

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Abstract: *Febrile infections that are prevalent and unique to tropical and subtropical regions are collectively known as tropical infections. Enteric fever, leptospirosis, scrub typhus and malaria are the most commonly encountered tropical infections in our country. Epidemiology, disease pattern, morbidity and mortality varies from region to region. It is important to treat them early as delay in institution of specific therapy may lead to increased morbidity and mortality. Early diagnosis and prompt management by choosing appropriate antimicrobial agents is very crucial for favorable outcome. Blood culture is the gold standard for the diagnosis of enteric fever. Third generation cephalosporins are considered as the first choice for treatment. Azithromycin is reserved for relapses and should ideally be used for extensively drug resistant typhoid. Diagnosis of leptospirosis and scrub typhus mainly depend upon relevant epidemiological factors with typical clinical features. Drug of choice for leptospirosis is penicillin while doxycycline is the drug of choice for scrub typhus. For uncomplicated P.vivax chloroquine is the drug of choice. Artemesinin combination therapy is recommended for falciparum malaria. All severe and complicated malaria should be treated as falciparum malaria. Primaquine is needed for prevention of relapses in malaria.*

Keywords: *Tropical infections, Antimicrobial, Enteric fever, Scrub typhus, Leptospirosis, Malaria, Children.*

Each year, different parts of India witness a rise in seasonal infections, especially during the monsoon and post monsoon period. These include enteric fever, leptospirosis, scrub typhus, malaria, dengue and other infections leading to very high morbidity and mortality. Appropriate antimicrobial therapy along with early stabilization of sick children are of paramount importance for favorable outcome.

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Enteric fever

The term, enteric fever, includes typhoid and paratyphoid fever caused by bacteria of the genus Salmonella which comprises *Salmonella typhi*, *S paratyphi A*, *S paratyphi B* and *S paratyphi C*. India carries a high disease burden of having 7 to 9 million cases per year with 500-700 cases per 1 lakh population/ year.[1] Recently, there have been concerns and challenges in terms of increasing proportion of infections in very young children, rising paratyphoid infections and emerging drug resistance.[2,3]

Management

Most cases can be safely treated on a domiciliary basis. Patients who have persistent vomiting, severe diarrhea, abdominal distension, toxemia and complicated typhoid would need hospitalization. The main stay of treatment of typhoid is specific antibiotic therapy along with meticulous general supportive measures like maintaining proper hydration, good nutrition, antipyretics and other symptomatic treatment when indicated. Contrary to popular belief, there is no need to restrict any type of diet in cases of typhoid.

Antimicrobial therapy and its resistance in typhoid

Multiple drug resistant (MDR) typhoid fever was reported in India in early 1980's, hence chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole are no longer used as first line drugs. After that, fluoroquinolones became the mainstay of treatment.[4] Ciprofloxacin resistance developed in the late 1990s. Since then, cefixime and azithromycin are the available choices for uncomplicated cases and ceftriaxone as intravenous therapy for serious and complicated cases as per the national treatment guidelines for antimicrobial use in infectious diseases released by the National Centre for Disease Control.[5]

Ceftriaxone resistance is not an issue in India as per current resistance pattern.[6] With the lesser use of quinolones

and conventional drugs, there has been a reversal of sensitivity to drugs like chloramphenicol, co-trimoxazole, amoxycillin and ampicillin.[7]

IAP recommendations for Enteric fever 2019[6]

First line drugs

Currently, third generation cephalosporins (oral or IV) are the treatment of choice for typhoid fever.

For domiciliary treatment: Since typhoid bacilli are intracellular, higher doses of cefixime (15-20 mg/kg - maximum 1200 mg) for minimum of 2 weeks is needed. Mean time for defervesence is 6-8 days. Cefixime has shown superior efficacy over quinolones and has similar efficacy to parenteral ceftriaxone. It is a very good, safe and non toxic alternative and can be used as an oral switch following use of ceftriaxone. Randomized control trials (RCTs) of third-generation cephalosporins, primarily ceftriaxone/cefixime, in treating typhoid fever have reported an average fever clearance of 7 days, with a treatment failure rate between 5 and 10%, relapse rates of 3-6% and fecal carriage of less than 3%.[8] Cefpodoxime (10mg/kg/day) given twice daily has also been shown to be as effective as cefixime in view of similar Gram-negative activity, but has not been widely studied. In the absence of good efficacy data and lack of standardized dose for typhoid fever, it is not recommended.[8]

For hospitalized patients: Third generation injectable cephalosporin - ceftriaxone (75-100 mg/kg/day) given once or twice daily is the first line therapy. Maximum dose is 4g/day.[6] Mean time for defervesence is 6-8 days. Oral switch to cefixime as soon as possible will reduce the length of hospitalization and drug induced phlebitis. Biliary sludging can occur with its use and if symptomatic, cefotaxime in a dose of 150-200 mg/kg/day in 3 divided doses can also be used.[6]

Second line drugs

Macrolides: Azithromycin 10-20 mg/kg/day orally once per day (maximum 1000 mg per day) - has shown promising results in uncomplicated typhoid and quinolone resistant strains. Since Salmonella are intracellular organisms, azithromycin has good efficacy in cases of enteric fever. Mean time for defervescence is 4.4 days with a low relapse rate of 0-3%. It is not recommended as a primary choice but must be reserved for XDR typhoid and at times during relapse. Prolongation of QT interval is an important side effect and should be kept in mind.

Monobactams: Aztreonam belongs to this group of antibiotics and has a Gram negative action. It is effective in a dose of 50-100 mg/kg/day in three divided doses for 7-14 days. Mean time for defervescence is longer than cephalosporins. It is a second choice mainly in MDR cases allergic to the cephalosporins. In complicated MDR typhoid, when there is no response to parenteral third generation cephalosporin, aztreonam is a good option.

Fluoroquinolones (oral/IV): In the era of quinolone susceptibility, quinolones were considered the most important drug and known for their dramatic response with a short mean time for defervescence of just 4 days without almost any relapse. The dose of ciprofloxacin used was 15-20 mg/kg/day and ofloxacin, 10-20 mg/kg/day. However, with increasing MIC of quinolones and very high incidence of quinolones resistance they are not used currently.

Response to therapy and duration of antibiotic treatment: The usual duration for defervescence in enteric fever is 5 to 6 days in optimally treated cases. Most of the children become afebrile within 7 days of treatment, but therapy should be continued for at least 14 days in uncomplicated cases or for 7 days after defervescence.

Some children continue to have fever even at the end of one week (delayed response) but are otherwise well. In such cases, there is decreased toxemia and reduced spikes and intensity of fever. Such situations do not warrant change or addition of antibiotic. They just need counseling and reassurance.

In 5-10% cases, in spite of using in vitro susceptible drug in correct dose, child continues to have fever with toxemia beyond one week (clinical failure). This can be managed by switching to alternative sensitive drug like azithromycin or quinolones. Available data do not support the use of combination of more than one antibiotic.

It is also important to consider other causes of fever beyond one week like drug fever, thrombophlebitis, co-infection (very rare) and complications like hemophagocytic lymphohistiocytosis (HLH).

Table I describes currently recommended antibiotics of choice for enteric fever.

Adjuvant steroid therapy

Use of steroids for defervescence is to be avoided as it increases the relapse rate and the risk of enteric perforation. High dose corticosteroids (dexamethasone, 3 mg/kg initially followed by 1mg/kg 6 hourly for 48 hours) have earlier been recommended for treatment of patients with severe typhoid fever with complications like shock, CNS involvement and DIC. However, there is no recent data to support use of steroids in enteric fever.[6]

Table I. Antibiotic choice in enteric fever

Drug	Dosage	Remarks
Cefixime (First line oral)	15-20 mg/kg for 14 days or 7 days after defervescence whichever is longer	Delayed defervescence and high relapse rate
Azithromycin (Second line oral)	15-20 mg/kg for 7 days	Good for intracellular organism, needs to be reserved for other conditions including XDR typhoid Because of single daily oral dose and short duration of treatment, there is potential for misuse and overuse
Ceftriaxone (First line parenteral)	75-100 mg/kg	For inpatient, switch to oral cefixime as soon as possible
Aztreonem (Second line parenteral)	50-100 mg/kg/day in 3 divided doses	Restricted use only in cases of allergy to cephalosporins In complicated cases as a second line
Quinolones (for >8 years only)	10-20 mg/kg	Rising MICs, high resistance rates;not recommended now. Reserved for selected cases especially relapse and therapeutic failures after nalidixic acid sensitivity report; switch to oral from IV is possible.

Therapy for relapses

Cultures should be obtained and standard treatment should be administered. They respond well and quickly to the same drug as used for primary therapy but in proper doses and right duration. Quinolones, if not used earlier and azithromycin are also good alternatives.

Therapy of carriers

It is uncommon in children. When chronic carriage is demonstrated, treatment is with amoxicillin100 mg/kg/day with probenecid 30mg/kg/day or cotrimoxazole 10 mg/kg/day of TMP for 6-12 weeks. Alternatively, quinolones can be given for 28 days in dose of 10 mg/kg per day.

Leptospirosis

Leptospirosis is a worldwide underdiagnosed zoonosis, caused by Gram negative spirochetes called Leptospires.[8] Approximately half of all pathogenic serovars are classified in *Leptospira interrogans* or *Leptospira borgpetersenii*. Major outbreaks reported in South-East Asia include Jakarta (2003), Mumbai (2005), Surat and Srilanka (2008).[9] Most cases occur in the monsoons and during flooding as leptospires survive in fresh water and damp soil and increased infection is seen with floods and water stagnation.

Treatment[10,11]

Treatment of leptospirosis consists of antibiotics with supportive care and close monitoring of renal, hepatic and circulatory function. Early antibiotic treatment aids in faster recovery and prevents progression of the disease. Appropriate antibiotics, when started early are found to be more efficacious. After 10 days of illness, their efficacy is reduced. Still, antibiotic therapy should not be denied even if patient presents late. One should not wait for the laboratory reports as serology turns out to be positive only by the end of the first week and by that time patient becomes more seriously ill.

Mild cases: Drug of choice is oral doxycycline in a dose of 2mg/kg/day (maximum 100 mg twice daily) in two divided doses.[12] It can be used safely even in children below 8 years. Other alternatives include oral amoxicillin 50mg/kg in 3 divided doses, ampicillin 100mg/kg/day in 4 divided doses. In children with allergy to penicillin, azithromycin 10 mg/kg on day 1 followed by 5 mg/kg on subsequent 4 days can be used.

Severe cases: Severe infections should be managed by intravenous benzyl penicillin for 7 days in a dose of 6-8 million units/m^2/day divided every 4^{th} hourly.[12] As an alternative, third generation cephalosporins, ceftriaxone - 80-100 mg/kg (maximum 4 gm) in 2 divided doses or cefotaxime, 100-150 mg/kg in 3 divided doses can be given.

Jarisch-Herxheimer reaction is characterized by high fever, rigors, hypotension following initiation of antimicrobial therapy and is due to an acute response to rapid clearance of spirochetes from the circulation. Role of steroids has not been clearly established. It should be used on a case to case basis. There have been some

reports of use of high dose pulse steroids (methyl prednisolone - 30 mg/kg/day) for treatment of immune complex mediated renal failure. High dose pulse steroids has also been tried in children with acute respiratory distress and pulmonary involvement but its beneficial role is not fully established.

Aggressive supportive care with strict attention to fluid and electrolyte balance is very essential and appropriate IV fluids, inotropic agents, diuretics, dialysis, use of blood products, mechanical ventilation, etc. should be provided as per the individual case.

Scrub typhus

Indian tick typhus and scrub typhus are commonly seen rickettsial diseases in our country and are caused by rickettsiae which are obligate intracellular proteobacteria spread by eukaryotic vectors like ticks, mites, fleas and lice. These infections have been reported from various states and union territories.[12-14]

Treatment

Treatment must be initiated empirically in suspected cases as soon as possible without awaiting laboratory confirmation, as morbidity and mortality escalate rapidly with every day of treatment delay. Also treatment should not be discontinued solely on the basis of a negative test result.[15] While awaiting laboratory results, concomitant empiric treatment may need to be given for other conditions which are life threatening and cannot be reliably ruled out (e.g. meningococcemia)

Indications for hospitalization are - patients with organ dysfunction, unstable vitals in need of supportive therapy, shock, respiratory distress, massive third spacing, severe thrombocytopenia, mental status changes, inability to take oral medications, unreliable caregiver and uncertain follow up.

Drugs: Therapy is inexpensive and includes drugs like doxycycline, chloramphenicol, azithromycin and tetracycline. Fluoroquinolones are not recommended for treatment.[16] Sulfonamides are contraindicated. Doxycycline is the drug of choice. Use of doxycycline for treatment of rickettsial diseases in children of any age is no longer a matter of controversy. It should be used orally or intravenously in the dose of 2.2 mg/kg twice daily for children <40 kg and 100 mg twice daily for children above 40 kg, for 3 days after subsidence of fever or a total of 7 days. Severe or complicated cases may need 10 days therapy. IV infusion should last at least for 1-2 hours. The response to doxycycline is dramatic and fever subsides within 24-48 hours. Hence, fever persisting beyond 48 hours of initiation of doxycycline should prompt consideration of alternative or additional diagnosis, including co-infection[15] Alternative effective drugs are macrolides (oral clarithromycin or oral/intravenous azithromycin), chloramphenicol and rifampicin. Azithromycin is used in the dose of 10 mg/kg/day for 5 days. Rickettsial strains with reduced susceptibility to doxycycline are reported[16,17] and alternative drugs can be used in such a situation.[18] It is recommended that rifampicin should not be routinely used for treatment of rickettsial diseases in India.

Supportive management: Severely ill patients may need other supportive measures as dictated by the clinical situation. Rickettsial encephalitis is treated with methyl prednisolone in the dose of 30 mg/kg/day for 3-5 days.

Malaria

Malaria is caused by plasmodia commonly known as malarial parasites. Several dozen species of plasmodia have been described but only five are known to cause disease in man viz. P. falciparum, P. vivax, P. ovale, P. knowlesi and P. malariae of which only the first two species are commonly seen in India.

Treatment of uncomplicated malaria

Treatment of P. vivax malaria

Chloroquine has still retained its effectiveness against P vivax infection in our country. Dosage schedule is given in Box 1. Chloroquine should not be given in empty stomach and if child is having high fever, paracetamol should be given first. If vomiting occurs within 45 minutes of a dose of chloroquine that particular dose is to be discounted and should be repeated.

In about 8 to 30% cases, P. vivax may cause relapse and can be prevented by primaquine given in dose of 0.25 mg/kg body weight daily for 14 days. National anti-malarial programme recommends a 5 day course of primaquine for risk of toxicity and operational feasibility.[19,20]

Primaquine is contraindicated in pregnant women, infants and G6PD deficient patients. Primaquine can lead to hemolysis in G6PD deficiency which can present with any of the following symptoms dark coloured urine, yellow conjunctiva, bluish discolouration of lips, abdominal pain, nausea, vomiting and breathlessness, etc. Patient should be advised to stop the medication immediately in such instances and report to hospital immediately.

Treatment of P. falciparum malaria

Both the Directorate of National Vector Borne Disease Control Programme (NVBDCP) and the WHO recommend use of combination therapy, one of which should be artemisinin derivative. Combination therapy aims at simultaneous use of two or more blood schizonticidal drugs with different mode of action and they act on unrelated biochemical targets in the parasite. This improves efficacy and also delays development of resistance.

Advantages of artemisinin

Artemisinin is a very potent antimalarial. It reduces parasite number by 10,000 fold per cycle which is quite high as compared to other antimalarial drugs which reduce it by 100 to 1000 fold per cycle, with lack of serious side effects. There is less chance of resistance to it, as it is rapidly eliminated from the body so that parasites are not exposed to sub-therapeutic level of the drug for longer time. This is of paramount importance to prevent development of artemisinin resistance.

Importance of combination therapy

Artemisinin derivatives should not be administered as monotherapy. The residual parasites which are not killed

Box 1. Malaria Treatment regime in different situations[23]

Situation	Treatment and dose
P.vivax malaria without complication	Chloroquine total dose 25 mg/kg. Day 1: 10 mg/kg, Days 2: 10 mg /kg and day 3: 5 mg/kg in a single dose. Primaquine-0.25 mg/kg body weight daily for 14 days under supervision
P.falciparum malaria without complication	i) Artemisinin combination therapy (ACT) for 3 days with single dose of primaquine (0.75 mg/kg body weight) on day 2 ii) Artesunate 4 mg/kg of body weight once daily for 3 days + a single dose of SP as 25 mg/kg of sulfadoxine and 1.25 mg/kg of pyrimethamine on day 1 OR Artesunate as above + mefloquine 25 mg/kg of body weight in two (15 + 10) divided doses on day 2 and day 3. OR Artemether + lumefantrine co-formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine given twice a day for 3 days. For 5-14 kg body weight: 1 tablet twice a day for 3 days For 15 to 24 kg body weight: 2 tablets twice a day for 3 days For 25-35 kg body weight: 3 tablets twice a day for 3 days More than 35 kg : 4 tablets twice a day for 3 days Note: on day 1 second dose to be given 8 hours after the first dose.
Mixed infection-both P.F and P.Vivax	Artemisinin-based combination therapy (ACT) for 3 days. Primaquine (0.25 mg/kg body weight) daily for 14 days.
Severe malaria- P.F./P.Vivax	Artesunate* - First dose 2.4 mg/kg IV followed by 2 doses at 12 and 24 hours, then once a day for total 7 days. Give IV at least for first 24 hours. Then switch to oral once feasible (ACT- full 3 day course). OR Artemether First dose -3.2 mg/kg (loading dose) IM, followed by 1.6 mg/kg daily for 6 days. If the patient is able to swallow, then the daily dose can be given orally. Tetracycline or doxycycline or clindamycin is added to the above regimens as soon as the patient can swallow and should be continued for 7 days. Always add primaquine too.

"The dose of IV artesunate in a child < 20 kgs is 3 mg/kg to ensure equivalent exposure to the drug". (WHO 2015)

by artemisinin will be taken care by other partner drug present in the combination. It should be combined with rapidly eliminated drugs like (clindamycin, tetracycline) or with slowly eliminated antimalarials (sulphadoxine-pyrimethamine (SP), mefloquine (MQ) or lumefantrine). When it is thus combined with rapidly eliminated drugs, a longer course i.e. 7 days course of treatment is required. This has a disadvantage of poor adherence to treatment. For slowly eliminated antimalarials, shorter courses of treatment (3 days) suffice, which ensures better treatment adherence. Combination therapy also takes care of resistance to other antimalarials. For example, in Thailand, use of artesunate - Mefloquine (MQ) combination has been proved quite effective in curtailing further MQ resistance.[21] Treatment failure with artesunate (AS)+sulphadoxine-pyrimethamine (SP) in P.falciparum malaria has been reported in many Asian countries like Bangladesh, Bhutan, Myanmar and Nepal and also in North Eastern parts of our country sharing international border with them.[22]

Dosage and schedule of various antimalarials and Artemesinin combination therapy (ACT) are given in Box 1.

Artemisinin Combination Therapy (ACT) should be given to all the confirmed *P. falciparum* cases, mixed infections and severe malaria. AS+SP is recommended in the National Programme all over India except northeastern states. In the northeastern states of Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland and Tripura), due to the reports of late treatment failures to combination of AS+SP in *P. falciparum* malaria, a fixed dose combination (FDC) of Artemether-lumefantrine (AL) is recommended. Artesunate- mefloquine combination has limited safety data and is contraindicated in child with CNS manifestations.

Special situations

For uncomplicated *P. falciparum* malaria, in infants less than 5 kgs., the dose of ACT is the same as that of children weighing 5 kgs.

In HIV positive people with uncomplicated P. falciparum malaria, avoid AS+SP if on treatment with co-trimoxazole and avoid artesunate + amodioquine (AS+AQ), if on treatment with efavirenz.

Treatment of mixed infections

Mixed infections should be treated as falciparum malaria with any ACT except AS+SP. Primaquine should be given for 14 days.

Severe malaria due to P. vivax

It should be treated in the same line as severe P. falciparum malaria and primaquine should be given for 14 days to prevent relapse.

Table II. Recommended treatment in failure with artemisinin combination therapy (ACT)

Drug	Dose	Remarks
Quinine + Tetracycline or Doxycycline or Clindamycin	Quinine 10 mg salt/kg/dose 3 times daily for 7-10 days. In case of cinchonism, Quinine, 10 mg salt/kg/dose 3 times daily for 3-5 days+ Tetracycline 4 mg/kg/dose 4 times daily for 7-10 days OR Doxycycline 3 mg/kg/day divided 2 times daily for 7-10 days OR Clindamycin 20 mg/kg/day divided 3 times daily x 7-10 days	Tetracycline or doxycycline is not recommended for child <8 years
Artemether - lumefantrine combination	If not used earlier	
A single dose of primaquine above 1 year age (0.75 mg/kg) is given for gametocytocidal action.		

Treatment failure with chloroquine in P. vivax malaria is rare in India.

Follow-up, monitoring and treatment failure/drug resistance

All cases should be subjected to clinical and parasitological assessment as per WHO new system of monitoring.[20]Absence of fever and parasitemia till day 28 after treatment is defined as cure. Parasite count of day 0 is taken 100% for that particular child.[19,20] Following that, serial microscopic examination is desirable to ascertain treatment failure which may be early or late treatment failure. They are designated as per the day of development of danger signs, height of fever and density of parasitemia as compared to day 0. Late parasitological failure (LPF) is described as presence of parasitemia on any day between Day 7 and Day 28 with axillary temperature >37.5°C in patients who do not have criteria of early treatment failure or late clinical failure. Table II presents management of cases of treatment failure.

If symptoms persist or worsen after 3 to 14 days of treatment, it is considered treatment failure and one has to ensure drug tolerance, adherence and compliance to determine whether patient has vomited previous treatment or did not complete a full course. If these factors are ruled out, an alternative drug should be used. If symptoms develop 14 days after initiation of therapy following initial clearance of symptoms, consider it as a new infection and treat with first line ACT.

Treatment of severe malaria

Main objective is to prevent death. Secondary objective is to prevent recrudescence, resistance, transmission and disability. Mortality in severe malaria is directly related to timing of administration of first IV dose of artesunate as it helps to ensure therapeutic concentration of antimalarials as soon as possible. If untreated, severe and complicated malaria carries significant risk of mortality of nearly 100%, but with proper treatment this falls to 15-20%.

Principles of management

Specific antimalarial treatment of severe malaria: Parenteral artemisinin derivatives should be used as soon as possible. To achieve quick therapeutic concentration, IV route should be preferred over intramuscular. Artesunate is the drug of choice. First dose is given on admission (time=0), then at 12 and 24 hours, then once a day. Parenteral treatment should be continued for minimum of 24 hours. Then, oral ACT should be started as soon as possible and full course is completed. Use of mefloquine should be avoided in cerebral malaria due to neuropsychiatric complications. In first trimester of pregnancy, parenteral quinine is the drug of choice.

Pre-referral treatment

First dose of one of the recommended treatments as pre-referral treatment is very crucial to reduce the risk of death or permanent disability. It is indicated if referral time is more than 6 hours till patient reaches to higher center. Recommended options include - intramuscular artesunate 2.4 mg/kg IM, artemether 3.2 mg/kg IM, quinine 10 mg/kg on each thigh or rectal artesunate 10 mg/kg.

Supportive management and treatment of complications

Of the various complications of falciparum malaria the common and important ones in children are as follows: cerebral malaria, severe anemia, respiratory distress (acidosis) and hypoglycemia.

Table III. Drugs for chemoprophylaxis[23]

For short-term chemoprophylaxis (less than 6 wks)			
Doxycycline	100 mg daily in adults and 1.5 mg/kg body weight for children more than 8 years old	Take 2 days before travel and continued for 4 weeks after leaving the malarious area.	Contraindicated in pregnant and lactating women and children less than 8 years.
Long-term chemoprophylaxis (more than 6 wks)			
Mefloquine	5 mg/kg body weight (up to 250 mg) weekly	Administered two weeks before, during and four weeks after leaving the area	Contraindicated in cases with history of convulsions, neuropsychiatric problems and cardiac conditions.
Atovaquone /Proguanil		Start one or two days before travel., to be continued for 7 days after leaving malaria zone	Contraindicated in renal insufficiency

Stabilization of airway, breathing circulation, seizure control and maintaining euglycemia are the cornerstones for successful outcome. Intravenous antibiotics after drawing samples for blood culture is indicated in cases where secondary infection is suspected. If lumbar puncture is delayed, proper antibiotic cover for meningitis must be given. Hydration is to be maintained. Hyperpyrexia should be treated with tepid sponging, fanning and paracetamol. Packed red cell transfusion is indicated when PCV is 12% or less, or hemoglobin is below 4 gm%.

Blood sugar should be monitored - if this is not possible, symptomatic patient should be treated for hypoglycemia. Daily clinical follow up should include intake output chart and close watch for hemoglobinuria. Monitoring of the response to treatment is essential. In case of artemisinin derivatives, parasite count usually comes down within 5 to 6 hours of starting therapy and hence repeat smear examination every 6 to 12 hours for first 48 hours is needed. Asexual parasitemia generally disappears after 72 hours of therapy.

Drugs used as chemoprophylaxis for malaria is summarized in Table III.[23]

Points to Remember

- ***Third generation cephalosporins are the drug of choice for multidrug resistent typhoid currently and azithromycin is to be reserved for XDR enteric fever.***
- ***In mild cases of leptospirosis, doxycycline is to be used and in severe cases IV penicillin or ceftriaxone if allergic to penicillin.***
- ***Doxycycline is the drug of choice irrespective of the age of the child in Indian tick typhus and scrub typhus and treatment should begin promptly without waiting for confirmatory laboratory results.***
- ***For uncomplicated vivax malaria chloroquine is the drug of choice.***
- ***Artemesinin combination therapy is the treatment of choice in all cases of falciparum malaria.***
- ***All cases of severe and complicated malaria should be treated as falciparum malaria irrespective of the species of malarial parasite on smear examination.***
- ***For rapid killing of malaria parasites, IV artesunate is a must at least for the first 24 hours, even if the child is able to take orally.***
- ***Primaquine is recommended in appropriate dose and duration for prevention of relapses in malaria.***

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CLIPPINGS

The Value of Calretinin in the Diagnosis of Hirschsprung's Disease.

Diagnosis of Hirschsprung's disease is based on clinical, radiological and histological evidence. The aim of our study is to evaluate the calretinin in the diagnosis of Hirschsprung's disease.

This was a retrospective and descriptive study from 1st January 2018 to 31st August 2019, conducted at the pathology laboratory where 51 paraffin blocks from suspected Hirschsprung's disease cases were included. These were immunohistochemically studied with anti-calretinin antibody. The diagnosis of Hirschsprung's disease on standard histological examination was based on the absence of lymph node cells in the submucosal and myenteric plexuses. Calretinin immunoreactivity was shown by nuclear and cytoplasmic labelling of ganglion cells and nerve nets and there is an absence of labelling of the nerve plexuses in Hirschsprung's disease.

The majority of patients (73.5%) were aged 2 years or older with a mean age of 3.4 years. The sex ratio was 2. Biopsies constituted 56.86% of the specimens and surgical specimens 43.14%. Concordance between haematoxylin-eosin examination and calretinin immunohistochemistry was observed in 47 cases (92.15%) and discordance in 4 cases (7.15%). The sensitivity of calretinin was 93.75% and the specificity 89.47%. The kappa index was 0.92. The recto-sigmoid form was the most frequent topographic form observed in 83.3% of patients.

Morphological examination with haematoxylin-eosin remains a good diagnostic method for Hirschsprung's disease. Calretinin immunohistochemistry is necessary in equivocal cases, in neonates and infants and in case of superficial biopsies.

Gaye AM, Deguenonvo GNC, Thiam I, Raafa S, Dieme-Ahouidi MJ, Dial CMM. The Value of Calretinin in the Diagnosis of Hirschsprung's Disease in Dakar. Am J Pediatr 2021; 7(3):pp178-181. doi: 10.11648/j.ajp.20210703.27.

GENERAL ARTICLE

DENGUE VACCINES UPDATE

***Shyamala J**

Abstract: *Dengue is a widely prevalent arbovirus infection with a large number of symptomatic infections occurring every year across the world. Severe dengue can contribute to significant morbidity and mortality and has no specific treatment. With the non-availability of an effective vaccine, the only known preventive measure was mosquito control which was difficult to achieve. The first vaccine that was licensed, Dengvaxia, brought many safety issues to the fore, on account of antibody dependent enhancement. Many newer vaccines are currently being developed, keeping these issues in mind - some in phase III and phase I trials, some in the pre-clinical stage. It is a matter of time before a safe and effective dengue vaccine becomes available.*

Keywords: *Dengue, Vaccine, Safety, Pre-clinical, Antibody dependent enhancement, Dengvaxia, TAK 003, Virus like particles.*

Dengue causes the greatest human disease burden of any arbovirus, with an estimated 10,000 deaths and 100 million symptomatic infections per year in over 125 countries.[1] The number of dengue cases reported to WHO has increased over 8 fold in the last two decades, from 505,430 cases in 2000, to over 2.4 million in 2010 and 4.2 million in 2019,[2] with fatality rates of over 20%.[3] Most mosquito control measures currently available have not proved very efficacious due to many logistic constraints. Safe and effective dengue vaccines may be the only way to control dengue infections.

The dengue virus is an enveloped virus with a single stranded RNA genome that encodes for a single open reading frame and can be translated into three structural proteins, that is, the core, (C), premembrane / membrane (prM/M) and envelop (E) proteins and seven non-structural (NS) proteins (Fig.1). Its structural glycoprotein E is responsible for cell recognition and for promoting host entry, which is mediated by a fusion process between the viral envelope and the cell membrane, while the NS proteins aid viral genome replication.[4]

Dengue is a unique and complex disease. Hence developing a vaccine against this disease has been very challenging. The infection is caused by a flavivirus with four serotypes (DENV-1 through DENV-4), all of which frequently cocirculate in endemic areas and are antigenically distinct. Each serotype is known to have several different genotypes. Antibody response to dengue infection differs according to the immune status of the host. Primary infection with one dengue virus serotype confers protection to the host against the infecting serotype (homotypic protection). While such protection is generally presumed to be life-long, protection against a different serotype (heterotypic DENV) is transient. When such cross-protection wanes, a subsequent infection (secondary infection) by a heterotypic DENV serotype can actually result in severe dengue disease due to antibody dependent enhancement (ADE). Antibodies against the primary infecting DENV serotype are unable to neutralize the secondary DENV serotype, but opsonize it and mediate increased infectivity of Fc gamma receptor (FcγR) bearing monocytes and macrophages to drive up virus production.[5,6]

Various dengue vaccines have been developed, one of which was licensed (but evaluation is ongoing because of post launch issues), some in phase III and phase I trials, some in pre-clinical trials. They have been summarised in Table I and II.[7]

1) Dengvaxia

The first dengue vaccine, Dengvaxia (CYD-TDV) was developed using recombinant DNA technology (Fig.2). Here, the genes encoding non-structural (NS) proteins of yellow fever virus serve as the vector or "backbone".[8]

CYD-TDV was recommended as a three-dose series at 0, 6 and 12 months as 0.5 ml dose subcutaneously. It was touted to provide effective protection against all 4 serotypes in individuals from 9 to 45 years of age. It is a sterile and freeze-dried product reconstituted before injection with a sterile solution of 0.4% sodium chloride. It contains no adjuvant or preservatives.[9]

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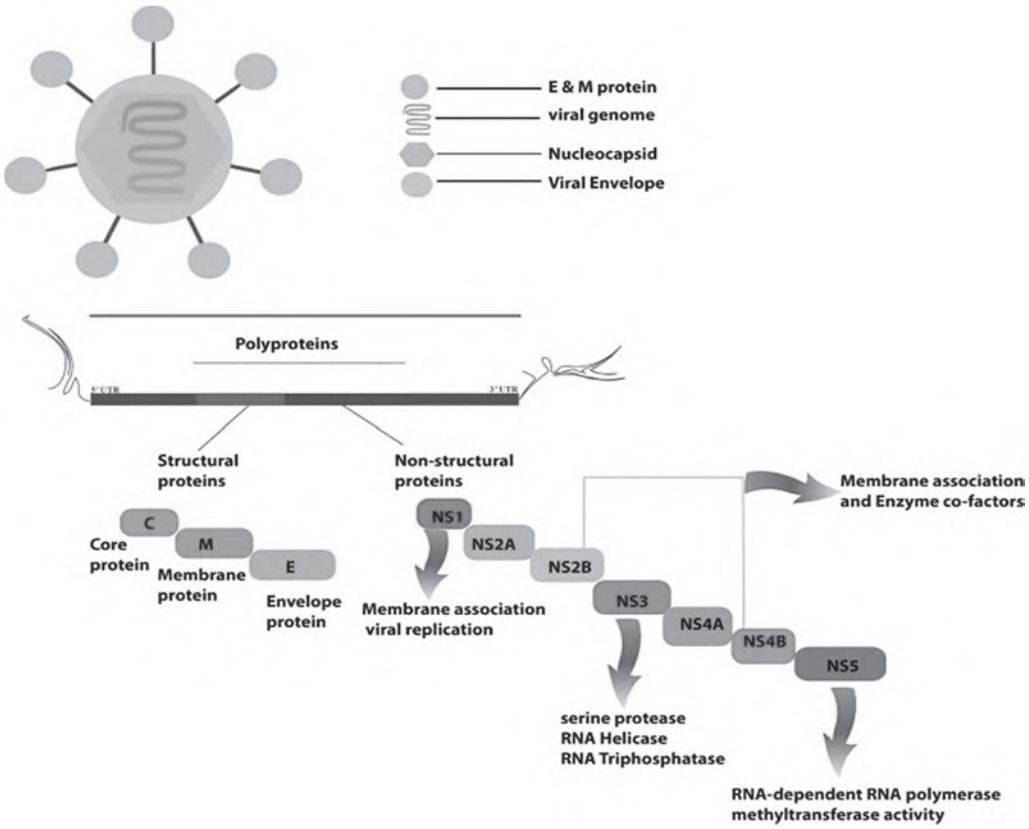

Fig.1. Structure of dengue virus and associated proteins[6]

It was initially licensed in Mexico in December 2015 and made commercially available in 2016 in Philippines and Indonesia. Though registered in more than 20 countries, immunization is limited to sub-national public health programs in only two countries, Brazil and the Philippines.[9] Low vaccine uptake has been fuelled by concerns about the increased risk of severe dengue in vaccinated dengue seronegative individuals.[10]

A recent paper provides an overview of Dengvaxia's development and product performance since its licensure in 2015. The vaccine had been studied in 26 clinical trials including more than 41,000 volunteers. The development and licensure of Dengvaxia spanned more than 20 years and cost more than 1.5 billion U.S. dollars. Of the 2.9 million doses of vaccine which were distributed worldwide, approximately 2.3 million doses were used in the Philippines and Brazil. A surveillance system was in place in Philippines and Brazil to detect adverse events following immunization (AEFI).[9]

Between December 2015 and March 2018, 1876 adverse events were reported to the manufacturer, mainly from Brazil and the Philippines. The most frequently reported AEFI were fever, headache, dizziness, vomiting and rash. Of the 211 serious AEFI reported, most were consistent with an underlying infectious disease, including dengue fever. By 20 March 2018, 87 cases of dengue infection had been reported after vaccination with CYD-TDV, of which 14 were fatal (6 had completed the vaccinated schedule, 3 had received 2 doses and 5 had received only 1 dose). In 9/14 fatal cases, the interval between vaccination and disease onset was less than 6 months from the last dose.

As per analysis by Sanofi, after Dengvaxia 'roll out and the fall-out', the vaccine performed differently, from both a safety and efficacy perspective, in different age groups. Younger vaccine recipients (<9 years of age) appeared to experience lower overall vaccine efficacy, reduced benefit related to prevention and increased relative risk of hospitalization and/or severe disease compared to control/placebo recipients. These trends peaked at study year 3 and then declined over years 4 and 5. Superior efficacy and a beneficial vaccine effect were noted in seropositive versus seronegative vaccine recipients and in older children compared to the younger age groups. Protective effects were noted against any dengue caused by all DENV types as well as severe and hospitalized dengue. [9]

Table I. Dengue vaccine candidates currently on trial[7]

Vaccine type	Vaccine name/Strategy	Manufacturer	Clinical Trial Phase
Attenuated chimera*	**CYD - TDV, Dengvaxia** Yellow fever 17D vaccine virus backbone chimerized with prM and E proteins from DENV-1-4	Sanofi-Pasteur	Licensed, Post license evaluation on-going
	DENVax, TAK 003: Attenuated DENV-2 PDK-53 (primary dog kidney-PDK) virus as the backbone and replaced with prM and E of other serotypes (DENV-2/-1, -2/-3 and -2/-4 chimeras)	US CDC/Inviragen/ Takeda	Phase III
	Tetravax DV, TV003/TV005 Attenuated by deletion of 30 nucleotides from 3'UTR of DENV-3 DENV-4 and a chimeric DENV-2/DENV-4	US NIH	Phase III
Live attenuated	**TDENV-LAV** Empirical attenuation of each of the 4 DENV strains by passaging in PDK and fetal Rhesus lung cells	WRAIR/GSK	Phase I/II
Inactivated virus	**Purified formalin-inactivated virus (PIV)** formulated with adjuvants	WRAIR/GSK	Phase I
DNA vaccine	**Monovalent DENV-1**prME delivered by needle-free biojector **Tetravalent prM/E** formulated with Vaxfectin	US NMRC	Phase I
Subunit vaccine	**V180:** 80% of N-terminal E protein produced in insect cell formulated with ISOCOMATRIX and alhydrogel	Hawaii Biotect Inc. and Merck	Phase I
Heterologous prime/boost	**TLAV-prime/PIV-boost and vice versa**	US Army Medical Research and Material Command	Phase I

**Chimeric Vaccines* are produced by substituting genes from the target pathogen for similar genes in a safe, but closely related organism.*

WRAIR - Walter Reed Army Institute of Research; NMRC- Naval Medical Research Center

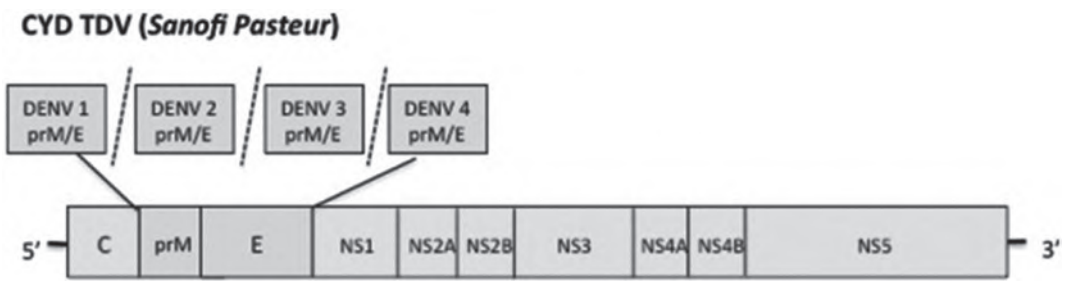

Fig.2.CYD TDV, a recombinant live-attenuated chimeric yellow-fever-dengue virus tetravalent vaccine was produced by replacing the prM and E of the 17D yellow fever vaccine virus with the prM and E proteins of DEN-1, -2, -3 or -4 viruses.[8]

Table II. Dengue vaccine candidates in preclinical trials[7]

Vaccine type	Strategy	Agency involved	Animal model used
Live attenuated virus	Dengue with host range mutation	Arbovax, USA	African Green monkey (genus Chlorocebus)
	KD 382	Kaketsuken and Mahidol University	Cynomolgus monkey
Inactivated virus	Purified psoralen inactivated virus	US (NMRC)	Aotus nancymaae monkey
Recombinant protein	Consensus EDIII Expressed in E.coli	Taiwanese National Health Research Institutes (NHRI).	BALB/c mice and NHPs (Macacacyclopis)
DNA vaccine	Tetravalent dengueprME	ChulaVRC, ChiangMai University, NSTDA	ICR[$] mice and NHPs (Macacafasicularis)
Viral vector vaccine	VEE-Dengue VRPs	University of NorthCarolina at Chapel Hill (UNC)	Rhesus macaque
	MV-DEN	Themis Bioscience, the Institute Pasteur	Transgenic mice(susceptible to measles virus infection)
Virus like particles	DSV4[*](dengue subunit vaccine)	NCR Biotech Science Cluster/International Centre for Genetic Engineering and Biotechnology, India and Emory University	Immunogenicity: BALB[#]/c mice and Rhesus macaque Challenge model: AG129 mice
	DENV-2 VLPs	Chiang Mai University, Mahidol University, NSTDA, Thailand	BALB/c mice and NHPs (Macacafascicularis)
Heterologous prime/boost	Chimeric YF 17D/DEN2- prime/ pE1D2boostor vice versa and simultaneous immunization	FIOCRUZ (institution for research and development in biological sciences, Brazil)	Preclinical (mice)

$ICR mice - strain of albino mice; NHP- non human primate

**DSV4 - Dengue subunit vaccine*

BALB - Bagg and albino (B for Halsey J. Bagg of Memorial Hospital, New York; ALB or albino)

The majority of fatal cases occurred in children (9-13 years) in the Philippines and the Global advisory committee on vaccine safety had reported causality determination as indeterminate.[11] It was evident that three years post vaccination, the risk of hospitalization with dengue was higher in vaccine recipients as compared to controls and more so in children <9 years of age.[12]

Various theories have been proposed for the variable efficacy and safety of Dengvaxia[9]:

i) vaccination mimics a primary infection in seronegative recipients, causing clinically apparent and/or severe disease on exposure to subsequent sequential infection.

ii) failure of vaccine to elicit potent cellular immune responses despite high, post-vaccination antibody titers.

iii) failure of DENV components in the vaccine to target relevant epitopes for protection from natural infection with a wild-type virus.

iv) waning immunogenicity as evidenced by low antibody titers measured by ELISA and low DENV specific memory cells in phase 2 trials.

v) pre-existing immunity to non-DENV flaviviruses and

vi) possibility of vaccine missing relevant DENV genotypes needed to mount adequate immune response.

The WHO issued two position papers[10,13] on Dengvaxia. The recent paper recommends vaccination from 9-45 years and only in people with evidence of past dengue infection based on an antibody test or on documented lab confirmed dengue infection in the past. It emphasized the development of highly specific and sensitive rapid diagnostic tests (RDTs) for determination of dengue sero status. According to the United States Food and Drug Administration (USFDA), Dengvaxia can currently only be used in individuals aged 9 to 16 living in parts of the United States where the dengue virus is endemic (Puerto Rico and a few other U.S. offshore territories) and only in children and teens who have had one previous episode of laboratory-confirmed dengue.

The Indian government, thankfully, had expressed concern about introducing the vaccine in our country, though Sanofi had sought exemption from carrying out Phase III clinical trials citing prior extensive evaluation.[14]

2) DENVax (TAK-003)

This is a new tetravalent dengue vaccine candidate. It is based on a live attenuated DENV-2 virus that provides the genetic backbone for all four of the viruses in the vaccine, which were originally designed and constructed by scientists at the Centers for Disease Control and Prevention (CDC).[15]

Biswal et al reported on TAK-003 use in children aged 4 - 16 years in the TIDES (Tetravalent Immunization against Dengue Efficacy) study. Efficacy of the vaccine was high against both symptomatic and hospitalised dengue irrespective of baseline serostatus, with rapid onset of protection after one dose - 97.7% efficacy against the dengue 2 serotype, 73.7% for serotype 1 and 62.3% for serotype 3; there were too few infections with serotype 4 to reach any conclusions. In participants who had confirmed dengue infections, the vaccine reduced the risk of hospitalization by 95.4%.[16] The TIDES trial is ongoing and safety and efficacy will be assessed over a total of four and a half years.[17] There was a further report on safety and immunogenicity of TAK-003 in children aged 2-17 years. The vaccine was immunogenic and had an acceptable safety profile, including in young children aged 2-5 years for whom no vaccine is currently available.[18] Further studies with TAK-003 are ongoing and though the vaccine seems to have better efficacy than Dengvaxia, it is not currently licensed anywhere in the world.

3) TetraVax-DV (TV003): TV003 is a live attenuated tetravalent dengue vaccine that contains a mixture of all four dengue serotypes as separate vaccine formulations. It is undergoing Phase III clinical trials in Brazil.

4) TDENV-LAV: This is a tetravalent dengue live-attenuated vaccine (TDENV - LAV).[19] Currently available data reveal that humoral immunity is not durable. Results published reveal that the type-specific neutralizing antibody response elicited by this vaccine is restricted only to DENV-2 and DENV-4.[20]

Inactivated virus vaccine

Tetravalent dengue purified inactivated vaccine (**TDENV-PIV):** Phase 1 trial has been conducted in 100 healthy volunteers in the age group 18-39 years in the USA and no results are available yet.[14]

DNA vaccine

Tetravalent dengue DNA vaccine (TVDV): A plasmid DNA vaccine elicited predominantly anti-DENV T-cell interferon-gamma responses in a dose-dependent manner.[21]

Dengue subunit vaccine (DSV)

V 180: a recombinant protein vaccine, based on insect cell-expressed C-terminally truncated versions of the DENV E proteins. Preliminary reports from studies were published in 2015,[22] after which not much data is available.

Issues in current dengue vaccines

Based on the available data on various dengue vaccines, the following issues are of concern:

i) There is no appropriate animal model of dengue infection to assess candidate dengue vaccines.

ii) Efficacy trials of Dengvaxia failed to establish nAb titers as surrogates of protective efficacy for DENV-2. This may mean that cellular immunity is also important.

iii) For a dengue vaccine to be effective and circumvent ADE, it should elicit immunity to all four DENV serotypes, against multiple genotypes and morphologically diverse forms of each serotype.

iv) An ideal dengue vaccine needs to be equally effective in both seronegative as well as seropositive recipients (unlike Dengvaxia).

v) Current tetravalent LAVs are made from physical mixtures of empirically determined amounts of four monovalent vaccine viruses - here viral interference occurs where one virus tends to replicate more at the expense of the others, simulating a monotypic infection and predisposing to ADE on encountering natural DENV infection in seronegative recipients.

vi) LAVs against DENV when deployed in regions with *Zika virus (a related flavivirus)* prevalence, antibodies to the Zika virus, can mediate ADE of DENVs and conversely, DENV antibodies can potentially cause ADE of Zika virus infection.

vii) Recombinant subunit vaccines may side step viral interference as they are non-replicating. They can be designed to eliminate epitopes implicated in the induction of enhancing antibodies. However, the immune response they generate may not be as durable as that elicited by LAVs.[19]

Dengue vaccine research in India

The Indian vaccine producers Panacea Biotech, Serum Institute, and Biological E have secured non-exclusive licenses for the clinical development and commercialization of the live attenuated dengue vaccine TetraVax-DV.[19] To date, none of the Indian vaccine manufacturers have initiated phase I trials.

The other vaccine is a tetravalent (4-in-1), single-component, non-replicating, protein-subunit dengue vaccine termed **"DSV4"** being developed by the International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi and Sun Pharma, Mumbai.[14] This vaccine was designed to eliminate epitopes implicated in the induction of infection-enhancing antibodies.[23] The authors focused their attention on a small domain of the dengue virus surface protein known as envelope domain III (EDIII). Humans make only a small amount of antibodies against EDIII, but these antibodies are effective in blocking dengue virus from entering cells. They used a yeast expression system to display EDIIIs of all four types of dengue viruses on the surface of non-infectious virus-like particles (VLPs) derived from *Pichia pastoris*, which is a methylotrophic yeast. The hepatitis B surface antigen (HBsAg), is also a component of the VLPs. These VLPs elicited antibodies, in mice and monkeys, which blocked all four dengue virus types and their variants from entering cells in culture. Importantly, these antibodies did not enhance dengue infection in a mouse model.[23]

Researchers' findings on DSV4 vaccine from various animal models provide proof-of-concept data supporting its use as a tetravalent dengue vaccine candidate with significant protective efficacy and low enhancement capacity.[23] It will next be evaluated in human clinical trials. Researchers indicate that this "Made-in India" vaccine could be available within the next 4-5 years.[14]

Conclusion

There are many challenges to developing an ideal dengue vaccine, it should be effective in all age groups, should work for a prolonged time period without causing immune enhancement (which may lead to increased severity of subsequent dengue infections) and should be equally protective against all 4 serotypes of virus. Research is ongoing with various formulations of dengue vaccines and with current advancements in vaccine technology, a safe and effective dengue vaccine should be available in the near future.

Points to Remember

- ***Dengvaxia was the first dengue vaccine to be licensed. Though the response was good in the first 2 years, it was mired in controversy after many deaths were noted among vaccinated children in the Philippines.***
- ***No dengue vaccine is yet approved for widespread use.***
- ***Several vaccines - live attenuated, inactivated, DNA vaccines, subunit vaccines are in advanced stages of trial and many in pre clinical trials.***
- ***Burgeoning vaccine technology in recent times may help develop an effective vaccine against all serotypes of dengue with minimal side effects in the near future.***

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DRUG PROFILE

MEDICATIONS TO MANAGE ACUTE EXACERBATION OF ASTHMA IN CHILDREN

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Abstract: *Acute exacerbation of asthma is one of the common pediatric emergencies that require early identification and prompt management. There are number of reliever medications that are recommended for use during these episodes, of which short acting beta-2 agonists and systemic corticosteroids are the established first line agents. When these medications fail, second line agents should be administered without delay since risk of mortality is high once the child progresses to respiratory failure. Careful dosing of medications and monitoring for side effects are important for successful management.*

Keywords: *Acute asthma, Children, Beta agonists, Corticosteroids, Anticholinergics, Magnesium sulphate, Aminophylline*

Asthma is a common, chronic inflammatory disorder of the airways associated with airway hyperresponsiveness resulting in bronchospasm and mucosal oedema. Acute exacerbation of asthma, due to various reasons, is a leading cause of hospitalization in children. The mortality associated with asthma has now drastically reduced due to better understanding of the pathophysiology and availability of specific medications to handle life threatening exacerbations.

Red flag signs of acute exacerbation of asthma in children include altered sensorium, bradycardia, poor pulse volume, cyanosis, pulsus paradoxus, excessive use of accessory muscles of respiration, state of exhaustion, limited vocalization, silent chest and hypoxia with oxygen saturation less than 92% in room air. If any of these red flag signs are present, oxygen supplementation should be immediately initiated along with beta-2 agonist inhalation and systemic corticosteroids.[1] After the initial resuscitation, the exacerbation may be then classified as mild, moderate or severe to plan further treatment. Various scoring systems are available but periodic clinical assessment of risk factors is of utmost importance. Once the patient is stabilized, the medications maybe weaned off one after the other based on the 'last-in first out' principle. It is extremely important that the patient should be discharged home with a written asthma action plan.[2] This article summarizes the important medications used in the management of an acute asthma exacerbation in children.

Oxygen

Oxygen is the most important drug in management of acute asthma as hypoxia is inevitable due to ventilation perfusion mismatch which results in hypoxia.[3] Beta agonists if given alone without supplementing oxygen may further worsen the mismatch by increasing the cardiac output and causing pulmonary vasodilatation eventually increasing perfusion to poorly ventilated areas of the lung.[4] The oxygen saturation should always be maintained ≥92%. High flow oxygen at 10-15 L/min via non rebreathing mask is administered when necessary.[1] When nebulizer is used to deliver medicines, one must ensure oxygen at a rate of minimum 6-8 L/minute to generate sufficient flow.[5]

Hydration

Children with acute asthma flare up usually have higher insensible fluid loss due to increased work of breathing. Hence, maintaining adequate hydration is extremely important. Hydration also helps to make the secretions less viscous. If the patient is in shock, resuscitation should be done with intravenous boluses of 0.9% saline 20 ml/kg. Maintenance fluids is restricted to 2/3rd with 5% DNS and 40-60 mEq of potassium per litre. Over hydration is avoided as there is risk of syndrome of inappropriate antidiuretic hormone secretion (SIADH) and pulmonary oedema especially if the patient is on positive pressure ventilation. Appropriate reduction of fluids should be is ensured when the patient is ventilated.[6]

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Short-acting β2 agonists (SABA)

Salbutamol is the most common bronchodilator used in asthma exacerbation and preferably by the inhaled route. The most cost-effective and efficient delivery of salbutamol is by pressurized metered dose inhaler (pMDI) with a spacer and should be initiated at the onset of symptoms.[7] However, when tidal volumes are severely reduced, MDI with spacer is ineffective and nebulised SABA with oxygen is indicated. In the current scenario of COVID-19 pandemic, it is recommended to avoid nebulizers wherever possible, since it is an aerosol generating procedure.[8] Dry powder inhalation (DPI) may be used in mild to moderate exacerbations of asthma but is inferior to MDI.[9] DPIs should be avoided in severe flare ups, especially in young children where hand-breath coordination is difficult.[10]

Terbutaline has similar efficacy, actions, kinetics and adverse effects as salbutamol.[11] Levosalbutamol, an isomer of salbutamol, is equipotent to salbutamol at half the dose but offers no additional advantage as regards side effects

Table I.Formulations and dosages of beta agonists in acute asthma

Drugs	Formulations	Doses
Short acting β2 agonists (SABA)		
Salbutamol	MDI (100 mcg/dose)	2-4 puffs SOS. May be repeated thrice at 20 minute intervals and then 1-4 hourly as needed
	DPI Rotacap (200 mcg/dose)	1-2 rotacaps SOS.May be repeated frequently as a rescue for a mild attack (as for MDI)
	Respiratory solution for nebulisation (5 mg/ml)	0.15 mg/kg, (minimum 0.25 ml) <6 months age: 0.25 ml 6 months-6 years: 0.5-1 ml >6 years age: 1 ml Dose for continuous nebulisation 0.15-0.5 mg/kg/hour
	Respule for nebulisation (2.5 mg/2.5 ml) (5 mg/2.5 ml)	Use equivalent doses as respirator solution (minimum- 2.5 ml) or <4yrs:2.5 mg ≥4yrs: 5 mg
	Syrup (2 mg/5 ml) Tab (2 mg, 4 mg, 8mg)	0.15 mg/kg/dose 3-4 times a day
Levosalbutamol	Respule for nebulisation (0.31 mg/2.5 ml) (0.63 mg/2.5 ml) (1.25 mg/2.5 ml)	0.075 mg/kg usage similar to Salbutamol
Terbutaline	Respiratory solution for neb (10 mg/ml)	2–5 mg diluted and nebulised
	Syrup (1.5 mg/5 ml) Tab (2.5 mg, 5 mg)	0.075 mg/kg/dose may be repeated TDS
	Inj. (0.5 mg/ml)	2-10 mcg/kg loading dose, followed by continuous infusion at 0.1 to 0.4 mcg/kg/min, titrate up in increments of 0.1 to 0.5 mcg/kg/ min every 30 minutes (Maximum: 3 to 5 mcg/kg/min)
Non selective β2 agonists		
Adrenaline	Inj. (1 mg/ml) (1:1000 solution)	0.01 mg/kg SC.(1:1000 solution) can be repeated upto 3 times in 20 minutes interval (only if red flag signs are present)

or efficacy.[12] Inhalation is the preferred mode of administration of SABA - dose and frequency needs to be adjusted according to clinical response. Oral SABA is not recommended during an acute flare up but may be considered if symptoms are mild.[13] Continuous nebulisation of salbutamol has a slight edge over high dose frequent nebulisation in severe exacerbations; but the patient should be monitored for development of life threatening hypokalemia.[14] Current evidence does not support the use of intravenous salbutamol in patients with severe asthma exacerbations.[15] Long-acting β-2 agonists, by themselves, do not have a role in the management of acute episodes in view of slower onset of action.[16] In children above 12 years of age, a combination of low dose inhaled corticosteroid (ICS) - formoterol combination may be used as a reliever medication.[8]

Adrenaline is a non-selective beta agonist (both alpha and beta action). There are conflicting evidences regarding benefit of nebulised adrenaline.[17] However, intramuscular or subcutaneous adrenaline is indicated in addition to standard therapy for acute asthma associated with anaphylaxis and angioedema. It is not routinely indicated for other asthma exacerbations unless not responding to nebulised salbutamol. It has superior bronchodilatory properties compared to terbutaline but may cause more tachycardia.[18]

Terbutaline is effective as a nebulising solution and as a parenteral agent. Subcutaneous terbutaline is considered when inhalation is not possible due to any reason or in case of a silent chest. However, it is not recommended in children below the age of 2 years. Intravenous terbutaline drip requires continuous heart rate and ECG monitoring. In case of tachycardia or ECG changes, the drip rate is reduced to half. Nebulised beta agonist is discontinued if using high infusion rates of terbutaline. The dose of terbutaline should be halved if concurrently used with theophylline drip.[1]

Table I shows the available formulations of beta agonists and the dosages.[19] Side effects of SABA in general are sinus tachycardia, palpitations, tremor, hypertension, diastolic hypotension, ventricular dysrrythmias, CNS stimulation, nausea, vomiting, hypokalemia and hyperglycemia.[1]

Rescue steroid

Initiation of a rescue steroid is equally important to maintain sustained bronchodilation by reducing the underlying inflammation. It has proven benefit in minimising the morbidity and hospitalisation due to worsening of the exacerbation.[20] In addition to the anti-inflammatory properties, steroids also induce the expression of β-2 receptors in airways thus enhancing the action of SABA agents.[21] Irrespective of the route of administration, steroids take 4-6 hours to exert their effect. Therefore, early initiation of rescue steroids is a must for improved response to therapy in moderate to severe exacerbation.[22]

Oral prednisolone is the best option if the child can take oral medications. Intravenous steroids do not have any added advantage but can be considered in hospitalised children who are severely distressed, drowsy or unable to retain oral medication.[23] Depending on the severity of exacerbation, steroids should be given for 3-7 days and can be stopped once the child is better without any dose tapering. Parenteral agents that can be safely used with almost similar efficacy are methylprednisolone, dexamethasone and hydrocortisone.[24] Oral dexamethasone is more potent and longer acting than prednisolone with

Table II. Available formulations and dosages of steroids in acute asthma

Systemic corticosteroids		
Drugs	**Formulations**	**Doses**
Prednisolone	Tablet (5 mg, 10 mg, 20 mg, 40 mg) Syrup (5 mg/5 ml, 15 mg/5 ml)	1-2 mg/kg/day for 3-7 days (Max dose 20 mg in children under 2 yrs. 30 mg in 2-5 yrs. and 40 mg in 6 years and above)
Hydrocortisone	Inj. (100 mg/vial)	4 mg/kg, 6 hourly (Maximum 100mg)
Methyl prednisolone	Inj. (40 mg, 125 mg, 500 mg, 1g)	2 mg/kg initial dose followed by 0.5-1 mg/kg/ dose 6th hourly
Dexamethasone	Oral, IM or IV	0.6 mg/kg once daily for 1-2 days (Maximum 15 mgm / dose)

similar efficacy and lesser side effects. Studies show that treatment with 1-2 days of dexamethasone has similar relapse rate compared to those children treated with 5 days of prednisolone. Oral dexamethasone should not be continued beyond 2 days because of concerns of its metabolic side-effects. Consider switching to oral prednisolone if there is failure of resolution, or relapse of symptoms with dexamethasone.[8] If the child is on IV steroids, consider changing to oral prednisolone after 48 hours. Inhaled steroids can be used along with inhaled SABA but cannot be considered as a replacement for systemic steroids in an acute exacerbation.[25]

Table II shows the available formulations of steroids that can be used in asthma exacerbation and their dosages.[19] Side effects of steroids are rare with short term use. There can be increased appetite, abnormalities in glucose metabolism, fluid retention, hypertension and mood alteration.[1]

Ipratropium bromide

Ipratropium bromide is an anticholinergic bronchodilator that is commonly used to treat acute asthma. Although ipratropium is not usually considered as a first-line bronchodilator, it can be considered as an adjunctive therapy that improves lung function and reduces hospitalisation.[26] During acute exacerbation, repetitive dosing of ipratropium in addition to β-2 agonists produces better bronchodilation than either drug alone.[27] However, the drug should not be used beyond 48 hours to minimise incidence of atropine-like side-effects. It is the drug of choice in bronchospasm due to beta blocker medication.[28] Table III shows the available formulations of anticholinergics and their dosages.[19] Side effects of anticholinergics are dryness of mouth, increased wheezing in some, blurred vision if sprayed in eyes and fever due to atropinisation.[1]

Magnesium sulphate

It is an excellent drug with anti-inflammatory and bronchodilator properties and is now recommended in moderate to severe exacerbations not responding to first line conventional therapies. It causes smooth muscle relaxation by inhibition of calcium uptake, resulting in decreased acetyl choline and histamine release. Minor side effects are reported with normal dosing, such as epigastric or facial warmth, flushing, pain and numbness at the infusion site, dry mouth, malaise, and hypotension.[29] It is usually given in a dose of 25-50 mg/kg as an infusion in 30 ml of maintenance fluid or normal saline over 20-30 minutes. Repeated dosing is possible if necessary with monitoring for toxicity. Care should be taken when administering >1gm (maximum 2gm may be given).[1] The role of nebulised magnesium sulphate in children is not well established but may be considered as an adjuvant to standard treatment with nebulized salbutamol and ipratropium in the first hour of treatment for children ≥2 years old with acute severe asthma, particularly those with symptoms lasting <6 hours.[30] Table IV shows details of formulations and dosage of magnesium sulphate.[19]

Aminophylline

Aminophylline is still considered as an acute asthma medication especially in an ICU setting. Improvement of diaphragmatic contractility and mucociliary clearance are the other notable beneficial effects of methylxanthines.[31] However, the current guidelines do not recommend routine use of intravenous aminophylline and theophylline in the management of asthma exacerbations, in view of their poor efficacy and safety profile and the greater effectiveness and relative safety of drugs like SABA. The side effects can be potentially fatal particularly in patients already treated with sustained-release theophylline. Loading dose

Table III. Formulations and dosages of anticholinergics in acute asthma

Drug	Formulations	Doses
Ipratropium bromide	MDI (20 mcg/dose, 40mcg/dose)	2-4 puffs (80-160 mcg) thrice at 20 minute interval and then 6-8 hourly as needed
	DPI rotacap (40 mcg/dose)	1-2 rotacaps SOS
	Neb respiratory solution (0.25 mg/ml)	<1 year - 0.5 ml; >1 year - 1 ml. Use every 20 minute for 3 doses, then every 6-8 hours for 24-48 hours
	Neb respule (250 mcg/2.5 ml) (500 mcg/2.5 ml)	Use equivalent doses as respirator solution or <1 yr: 125 μgm >1-12 yr: 250 μgm >12 yr 500 μgm

Table IV. Formulations and dosage of magnesium sulphate in acute asthma

Drug	Formulations	Doses
Magnesium sulphate	Intravenous Inj 50% (500 mg/ml)1 ml ampoule 25% (250 mg/ml)	25-50 mg/kg in normal saline infused over 30 minutes
	Nebulising solution	Isotonic magnesium sulphate 150 mg, 3 doses in first hour of treatment inchildren >2 years with severe exacerbation

Table V. Formulations and dosage of aminophylline in acute asthma

Drug	Formulations	Doses
Aminophylline	Inj. (250 mg/10 ml)	Bolus Dose: 5 mg/kg diluted in 5% dextrose - slow IV over 20 minutes (skip if already on theophylline) Maintenance Dose:1 mg/kg/hour continuous infusion in 5% dextrose

should be avoided in such patients. A calculated intravenous drip rather than a bolus dose is a safer option.[1] Dosage of aminophylline is described in Table V.[19]

Ketamine

Ketamine is also used as an adjunctive therapy in the management of refractory asthma exacerbation. It has a direct bronchodilatory effect as it stimulates catecholamine release. It is a good sedative for children requiring rapid sequence intubation for life-threatening asthma.[32] The dosage of ketamine is a loading dose of 0.2 to 2 mg/kg followed by continuous infusion at a rate of 0.2 to 3.6 mg/kg/hour.[33]

Heliox

Heliox is a mixture of helium and oxygen in the ratio 70:30. Inhalation of heliox reduces the air flow turbulence in the narrowed air ways, thus providing a temporary beneficial effect in terms of reduction of dyspnea, improved gas exchange and increased peak expiratory flow. The temporary reduction in muscle fatigue and improved ventilation achieved with heliox disappears as soon as it is discontinued. Heliox also helps to improve the distribution of inhaled medications. The limitation with heliox is that it cannot be used when the FiO2 requirement is more than 30%.[34]

Points to Remember

- ***Treatment of acute asthma exacerbations should target the bronchospasm as well as the underlying airway inflammation.***
- ***Short acting beta-2 agonists and corticosteroids are the first line medications used.***
- ***Whenever possible pressurized metered dose inhaler is the ideal device to deliver beta-2 agonists and in severe exacerbations when nebulizer is used, oxygen must be supplemented.***
- ***Early initiation of systemic steroids reduces the need for hospitalization.***
- ***Ipratropium, an anticholinergic bronchodilator can be considered along with short acting beta-2 agonists to improve their efficacy.***
- ***Magnesium sulphate is more recognized as a second line agent in severe asthma exacerbation not responding to first line agents.***

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CLIPPINGS

Concentration levels of serum 25-Hydroxyvitamin-D and vitamin D deficiency among children and adolescents of India: a descriptive cross-sectional study.

Vitamin D is an essential micronutrient for strong musculoskeletal and neurological development of human body and vitamin D levels during childhood and adolescence are important.This is the first national-level study that analyzes the deficiency and concentration of serum 25-Hydroxyvitamin D [25(OH)D)] among Indian children and adolescents with respect to various demographic and socioeconomic characteristics.

Data of Comprehensive National Nutrition Survey (CNNS, 2016-18) was utilized for the present study. Vitamin D levels were assessed based on serum 25-hydroxyvitamin D concentration. Prevalence of vitamin D deficiency has been shown for the three age groups: 0-4years (*n* =12,764), 5-9 years (*n* =13,482), 10-19 years (n=13,065). Vitamin D deficiency was defined as: serum 25(OH)D<12 ng/mL; and insufficiency as: 25(OH) ≤12 ng/ml to <20 ng/ml. 25(OH) D level higher than 20 ng/mL was accepted as adequate. Random slope multilevel logistic regression models were employed to assess the demographic and socioeconomic correlates of vitamin D deficiency.

Mean serum 25(OH)D concentration level was found to be 19.51±8.76, 17.73±7.91 and 17.07±8.16 ng/ml in age group 0-4 years, 5-9 years and 10-19 years respectively. 49.12% of the children aged 0-4 years were having insufficient level of vitamin D. Prevalence of vitamin D deficiency was comparatively higher among female adolescents (76.16%), adolescents living in rural region (67.48), Sikh individuals (0-4 years: 76.28%; 5-9 years: 90.26%; 10-19 years: 89.56%) and adolescents coming from rich households. North-Indian individuals were having substantially higher odds of vitamin D deficiency in all the three age groups.

The present study demonstrated that the prevalence of vitamin D deficiency is considerably high among children and adolescents of India. The study highlights high-risk group which require prompt policy interventions.

Mustafa A, Shekhar C. Concentration levels of serum 25-Hydroxyvitamin-D and vitamin D deficiency among children and adolescents of India: a descriptive cross-sectional study. BMC Pediatr 2021; 21:334. https://doi.org/10.1186/s12887-021-02803-z.

ADOLESCENCE

BODY IMAGE DURING ADOLESCENCE

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Abstract: *Body image plays an important role in identity development during adolescence. It is influenced by pubertal changes and various psychological and socio-cultural factors. Negative body image during adolescence can be associated with risky behaviours and poor health outcomes. Pediatricians should screen for body image concerns and promote development of healthy body image during annual health visits. Referral to mental health specialist must be made when indicated.*

Keywords: *Body image, Adolescence, Screening.*

Body image is a crucial part of adolescent development and has an impact on overall health.[1] Importance of body image increases during adolescence as they become more body conscious. It plays an important role in identity development. Pediatricians should screen for body image issues during annual adolescent health visits and give anticipatory guidance to build a positive body image. This review outlines the vulnerability of adolescents to negative body image, factors affecting body image development and approach to an adolescent with body image concerns.

Definition

Body image is a dynamic concept and is defined as the internal representation of one's external appearance.[2] It is made up of 4 components which include

- Perceptual (perception of size and shape of body and body parts)
- Cognitive (thoughts and beliefs about the body)
- Affective (feeling about the body)
- Behavioral (actions taken to attain 'ideal' body image)

Positive body image is having realistic perception of one's body and feeling good about it as it is. It facilitates psychosocial functioning.[3] Negative body image is a distorted perception of a person about his/her body with associated feeling of shame or anxiety and leads to low self-esteem.

Body image development during adolescence

Rapid and diverse pubertal changes occurring during adolescence along with increased media usage and emphasis on 'ideal body' (thin for girls and muscular for boys), have led to increase in body image problems.

Table I. Factors affecting body image

Physical and biological factors	Body weight Body shape Pubertal changes Medical diseases
Peer factors	Pressure to fit in Fat talk (conversation stressing the importance of weight loss) Bullying at school for body size
Familial factors	Parent's concern about weight and appearance Obsession about exercise Negative comments about body from family members
Psychological factors	Low self esteem Depression Perfectionist attitude Body comparison tendencies Athletics
Traditional and social media	Seeing ideal body in media Public opinion, judgment, comparison Number of 'likes' on social media platforms (face book, Instagram etc.)

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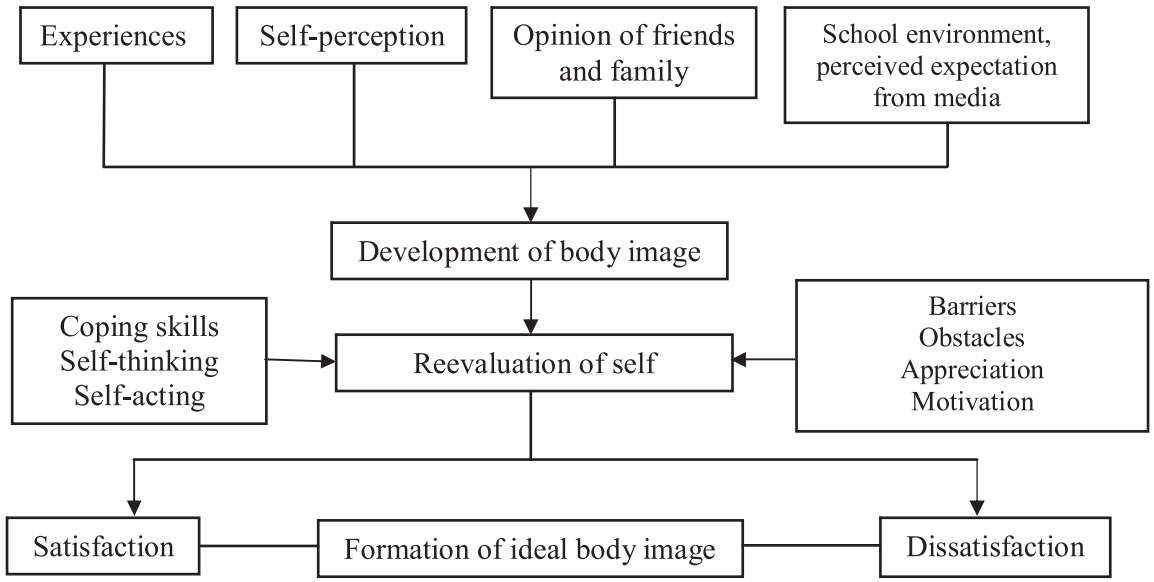

Fig.1. Development of adolescent body image[2]

Early puberty in girls and late puberty in boys increases the risk. Neurodevelopmental immaturity makes them very sensitive to body image issues and poor coping skills lead to excessive preoccupation and dissatisfaction with body image. They may explore a variety of 'looks' or appearances using jewellery, body piercing, tattoos, cosmetics and clothing styles and indulge in risky behaviour of disordered eating (like skipping breakfast, starvation followed by binge eating, diet pills, laxative pills) as well as excessive physical activity. Numerous biological, psychological and socio-cultural factors contribute to the development of body image in adolescents as shown in Table I.[4] Mental disorders like eating disorders, depression, anxiety, drug use and suicidal behaviors are known to be associated with and in some cases triggered by body image dissatisfaction. Protective factors include healthy diet, regular exercise and acceptance by family and peers. Fig.1 outlines key processes in the development of body image in adolescents[2]

As shown in Fig.1, body image development is a complex process. It is a response to the internal and external stimuli experienced by the adolescent. Reevaluation of oneself is a crucial element that influences the satisfaction level. Beliefs, emotions and life skills reinforce this reevaluation. There are barriers, obstacles and also positive appreciation for development of healthy body image.[2] An adolescent with good self-efficacy and adaptive coping skills will have positive appreciation about their body even when it does not fit into ideal standards. Those who are dissatisfied with their bodies are prone to develop disordered eating.

Prevalence of body image issues in Indian adolescents

Previously, body image concerns were thought to be a problem of the western world. Recent literature however, reveals a substantial prevalence in south east Asia and India due to changes in the traditional value system, lifestyle , globalisation and widespread media usage. Depending on the study methodology, the prevalence of body image issues in Indian adolescents is reported to be ranging from 25% to 85%.[5-8] Studies from various parts of India have shown prevalence of disordered eating behaviour to be 10-30% among adolescent girls and young adults.[9-11] This was seen more among girls, those living in urban areas, with high socio economic status and was influenced by media usage.[8,12,13]

Clinical presentation

Adolescents with body image issues usually present to pediatricians with:

1. Concerns about normal pubertal body changes and growth spurt like size of breasts and penis, gawkiness, physiological gynecomastia and acne.
2. Poor academic performance with intense desire and preoccupation to attain an ideal body image of 'zero figure' for girls and 'six packs' for boys, usually under the influence of peers and media.
3. Disordered eating behaviour like skipping meals, following fad diets (e.g. keto diet, intermittent fasting), caloric restriction, fat avoidance, binge eating and missing breakfast.

4. Performing excessive physical exercise with the aim to lose weight
5. Conflicts between parents and adolescents regarding eating habits, lifestyle, unconventional appearance and exercise patterns
6. Physical disorders like anaemia and osteoporosis
7. Mental disorders like eating disorders, depression, anxiety, body dysmorphic disorder, problematic internet use, suicidal behaviour, low self-esteem and bullying
8. Menstrual irregularity and amenorrhea
9. Use of drugs and food supplements. e.g., anabolic steroids to put on muscle mass.
10. Medical emergency with electrolyte imbalance and hypotension as in eating disorders and suicidal attempt

History taking

History should be elicited from adolescents and their parents in a sensitive, non-judgmental, empathic manner offering privacy and confidentiality. The following should be explored while taking a HEEADSSS psychosocial history from an adolescent with body image concerns (Table II).[14,15]

Asking an open-ended question like," How do you feel when you look at yourself in the mirror?" would encourage adolescents to share their body image concerns with clinicians. HEEADSSS evaluates strengths, aspirations and problem areas in an adolescent's life related to body image issues. It also reflects the influence of family, culture, peers and media on perception of body image and conflicts arising thereof. This information can be used for planning strength-based counselling.

For early detection of eating disorders, the clinical history should focus on perception of self, history of past illness or admission, patterns of eating and drinking, caloric intake, purging, restricting, binging, laxative use, exercise patterns and menstrual history. Amenorrhea for more than 3 months is commonly seen in girls with eating disorders. Co-morbidities like depression, anxiety and obsessive-compulsive disorder should be looked for and diagnosed using DSM 5 criteria. Adolescents with sexual abuse can present with body image issues.

Screening

SCOFF screening questionnaire can be used to screen for eating disorders.[16] SCOFF is an acronym standing for sick, control, one, fat and food respectively (Table III).

For those who test positive on SCOFF, EAT 26 (Eating Attitudes Test with 26 questions) questionnaire can be used to further determine risk for eating disorders.[17,18,19] An EAT score of >20 qualifies for a detailed assessment by a mental health professional. DSM 5 criteria are used to make the final diagnosis of eating disorders including anorexia nervosa and bulimia nervosa.[20] In both these disorders, self-evaluation is deeply influenced by body shape and weight. Anorexia nervosa is characterised by restriction of energy intake and intense fear of gaining weight while bulimia nervosa by episodes of binge eating followed by compensatory behaviour like diuretic use and laxatives.

Table II. HEEADSSS Psychosocial history in body image concerns

Item	Key points
Home	Socio economic status, literacy level of family members, relationship with parents and family members, type of parenting, abuse, mental and eating disorders
Education	Details of scholastic problems, recent change in school and in academic performance, peer group, bullying
Eating habits	Caloric and nutrient intake, details of body image concerns
Activities	Hobbies, type and duration of media usage and physical activity, time spent with peers and outdoors, quantity and quality of sleep, any recent loss of interest in activities
Depression	Any change in mood, behaviour and interest, duration of such change, suicide ideation or attempt
Substance use	Attitude towards drug use, drug use amongst peers, type and frequency of drug use
Sexuality	Details regarding sexual health, menstruation, intimate partners, sexual encounters, sexual violence, pregnancy, abortion, abuse
Safety	Indulgence in violent acts, run away behaviour

Table III. SCOFF Questionnaire

1. Do you make yourself **s**ick because you are uncomfortably full?
2. Do you worry that you have lost **c**ontrol over how much you eat?
3. Have you lost more than **o**ne stone (14 lb / 6.35 Kg) in last 3 months?
4. Do you believe yourself to be **f**at when others say that you are too thin?
5. Would you say that **f**ood dominates your life?
Interpretation: Each 'yes' scores 1 point and a score >2 is a pointer towards anorexia nervosa or bulimia

Examination

Important points to be noted in head to toe and systemic examination include:

- Skin, eyes, teeth and hair for issues of acne, hirsutism, dandruff, atopy, malocclusion, caries, myopia, texture, colour, body piercing, tattoo, cosmetic usage.
- Tanner staging and secondary sexual characteristics for concerns regarding pubertal changes, size of breasts and genitalia, gynecomastia.
- Body mass index (BMI), height and weight for issues of stature, weight and muscular frame.
- Detailed systemic and musculoskeletal assessment would be required for those with physical disabilities and chronic medical disorders.

Appropriate equipment to measure anthropometry, orchidometer and age appropriate IAP BMI, height and weight charts should be used. Clinical pointers towards eating disorders are highlighted in Table IV.

Table IV. Clinical pointers towards presence of eating disorders

Under nutrition, loss of fat
Bradycardia, hypotension, orthostatic pulse signs, poor capillary refill, distant heart sounds
Hypothermia
Dental erosion on molars
Sialadenosis
Facial petechiae
Sub conjunctival hemorrhage
Bruises on metacarpophalangeal joints
Caroteinemia
Edema
Xerosis
Parietal alopecia
Lanugo hair

Investigations

On clinical history and examination, suspicion of endocrinal disorders like hypothyroidism and eating disorders will entail detailed blood work up like thyroid function tests, complete blood counts, electrolytes and 2 D Echo.

Indications for referral

Indications for referral to mental health professionals and/ or for hospitalization are:

- EAT Score > 20
- Poor response to counseling even after regular sessions for 4-6 weeks
- Severe substance use disorder, severe depression, suicidal ideation and behavior
- Adolescents fulfilling DSM 5 criteria for diagnosis of eating disorders. Hospitalization is required when there are electrolyte abnormalities, physiologic decompensation, acute medical complications (heart rate <45/ min, seizures, arrhythmias), weight < 75% ideal body weight and rapid or excessive weight loss.

Management

Management of body image dissatisfaction depends on its severity and associated comorbidity. Minor concerns regarding body image can be managed by counseling parents and adolescents. Motivational interviewing technique is found to be useful. A multi-disciplinary hospital-based team including psychiatrist, psychologist, nutritionist, adolescent health specialist and intensivist is needed to manage eating disorders and its complications.

The following should be addressed while managing body image concerns and providing anticipatory guidance during annual well adolescent visits:

1.Normative pubertal changes: The adolescents and their parents should be reassured regarding changes in physique as puberty sets in, like widened shoulders for boys and broadening of hips for girls.

2.Body Mass Index: Age-appropriate charts should be used to diagnose over overnutrition, undernutrition and short stature. These charts are useful as follow up tools to assess anthropometry when the adolescent is on treatment

3.Healthy lifestyle: Adolescents are encouraged to adopt a healthy diet approach that involves eating from all food groups, avoiding diet with high fat, salt and sugar, ensuring moderate to intense physical activity for one hour every day and 8 to 9 hours of sleep. Meditation, yoga, involvement in hobbies, restricting screen time and learning stress management techniques are helpful in managing anxiety regarding body image issues.

4.Self-esteem: Importance of developing an all-round personality and a nurturing, stimulating and safe environment at home is discussed with parents and adolescents. This urges the adolescent to look beyond the 'outer/ external' beauty as the only determinant of self-worth and highlights the importance of 'inner' beauty characterized by grit, resilience, will power and psychosocial competence. The adolescent is encouraged to pursue hobbies and sports, strengths like honesty and sincerity are appreciated and use of punitive disciplinary techniques by parents are discouraged. Parents are advised to spend quality time with their children and adopt an authoritative parenting style using assertive communication.

5.Media education: Media usage, online activities and their effects on body image concerns are assessed in detail. Adolescents and parents are guided regarding healthy media usage, media literacy and online etiquette. Media literacy focuses on interpreting media messages appropriately and not getting influenced by media stereotypes. Screening is also done for social media addiction and problematic internet use.

6.Life skills: Life skill education enables adolescents to make healthy lifestyle choices and enhance self-esteem.

7.Education of parents: Parents should be role models for their children by following healthy diet and exercise pattern, focus on praise and non-appearance related positive traits and avoid harsh criticism and comparisons regarding body image.

8.Therapies: The therapeutic counselling is by using a combination of approaches which include developing acceptance, challenging sociocultural messages of "thin ideal" and targeting selective attention to disliked body parts as well as importance given for other's approval.[21] Psychological therapies include Cognitive behavioural (CBT) therapy[22], Acceptance and commitment (ACT) therapy[23], virtual reality exposure therapy[24] and mindfulness-based therapy. Yoga may be recommended as an adjunct to improve mind-body awareness.[21]

Conclusion

Adolescents are vulnerable to develop body image dissatisfaction. Adolescence is also an age of opportunity where a health professional can counsel to develop a positive body image and love their 'body' in spite of flaws and imperfections. This would enhance their self-esteem and prevent onset of serious mental disorders like eating disorders, depression and suicidal behaviour.

Points to Remember

- ***Body image is dynamic perception of one's body and is determined strongly by self-evaluation.***
- ***Development of body image follows biopsychosocial model and body image disturbance can be associated with negative health outcomes.***
- ***Adolescents should be screened for body image concerns during well visits with detailed history, HEEADSSS assessment and examination. SCOFF and EAT 26 are the common questionnaires used for screening. If indicated appropriate timely referral to a mental health specialist / Psychiatrist should be made.***
- ***Promotion of healthy body image should be included as a part of the anticipatory guidance to all adolescents. It includes explaining the normal pubertal changes, encouraging to follow healthy life style, media education and mastering the life skills.***

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CLIPPINGS

Influenza Antiviral Treatment and Length of Stay.

Antiviral treatment is recommended for hospitalized patients with suspected and confirmed influenza. Children <18 years hospitalized with laboratory-confirmed influenza in the US Influenza Hospitalization Surveillance Network included and data collected for 2 cohorts: One with underlying medical conditions not admitted to the ICU and an ICU cohort Treatment ≥3 days after illness onset had no significant effect in either cohort. Early antiviral treatment was associated with significantly shorter hospitalizations in children with laboratory-confirmed influenza and high-risk medical conditions or children treated in the ICU.

Campbell AP, Tokars JI, Reynolds S, Garg S, Kirley PD, Lisa Miller L, et.al. Influenza Antiviral Treatment and Length of Stay. Pediatrics. October 2021; 148(4) e2021050417; DOI: https://doi.org/10.1542/peds.2021-050417.

RADIOLOGY

IMAGING FINDINGS OF TUBERCULOSIS IN CHILDREN (PART-2)

***Raveendran J**

Imaging in childhood tuberculosis includes modalities like radiograph (X-ray), ultrasonogram, computed tomography (CT) and magnetic resonance imaging (MRI). Chest radiographic findings in pulmonary tuberculosis (PTB) has been discussed in the last issue. In the present issue role of other modalities such as ultrasonogram, CT and MRI are discussed. Tuberculosis in children presents in a varied manner ranging from asymptomatic to life threatening disease. In children the radiological findings are subtle and do not follow typical pattern as described in adults.

Spectrum of findings in childhood tuberculosis

1. Lymphadenopathy
2. Cavitating consolidation
3. Pleural effusion
4. Miliary tuberculosis
5. Pott's spine
6. Granulomatous lesion

The imaging modalities can provide important information about the anatomic location, size and shape of the lesions as well as their characteristic patterns described in tuberculosis infection. We will discuss in detail about the common imaging findings in tuberculosis.

Ultrasound

Cervical nodes are the most commonly affected in tuberculosis (Fig.1) and ultrasonogram is increasingly being recognized as the primary tool for their evaluation. The key features of tuberculous lymphadenitis include hypoechogenicity, strong internal echoes, nodal matting, soft tissue changes and displaced hilar vascularity.

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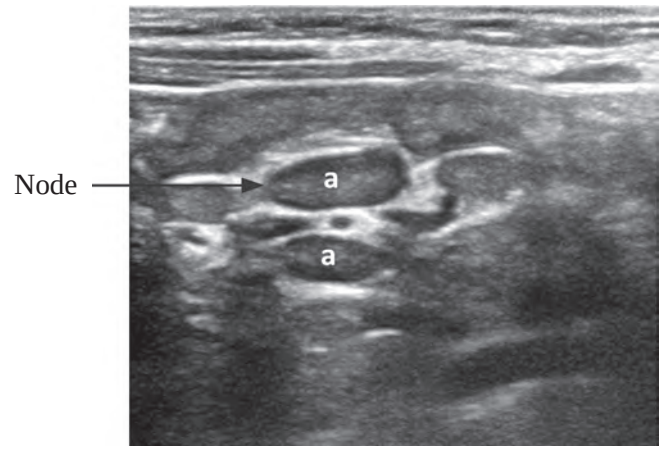

Fig.1.Multiple enlarged hypoechoic nodes (a) with posterior acoustic enhancement and loss of fatty hilum

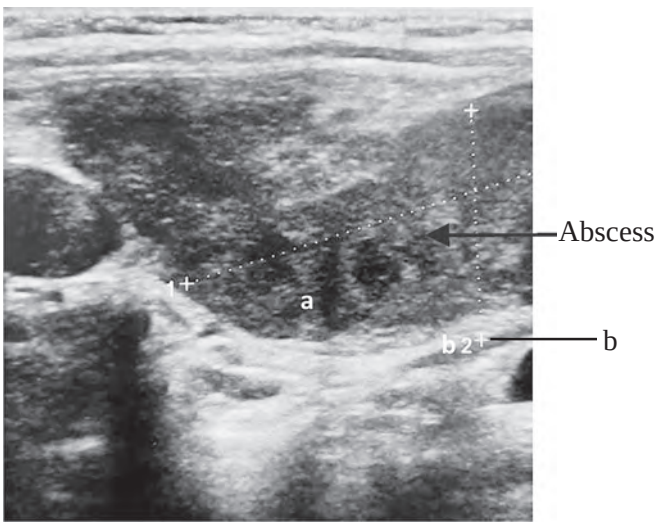

Fig.2.Ultrasonogram of cervical nodes reveals multiple enlarged hypoechoic nodes (a) with posterior acoustic enhancement, showing nodal matting and a fistulous tract (b) from the necrotic nodes leading to 'collar stud' abscess

The node under the deep fascia may undergo caseation necrosis. The caseous material may then perforate the deep fascia and escape into the superficial fascia resulting in the characteristic collar stud abscess formation (Fig.2).

Computed tomography (CT)

CT has been described as the "gold standard" for

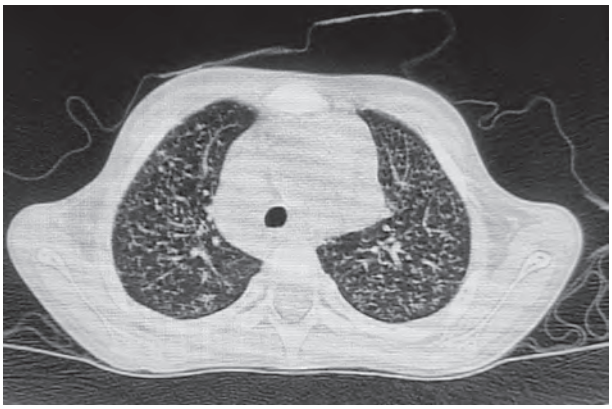

Fig.3.CT chest shows multiple disseminated small nodules in random distribution in bilateral lung fields, suggestive of military tuberculosis

demonstrating the presence of lymphadenopathy in children with primary PTB. Early features of TB (lymphadenopathy, nodules, small pleural effusion) can be made out using CT before they become apparent on chest radiograph. One of the disseminated patterns of tuberculosis described in CT chest is miliary nodules (Fig.3), widely scattered to involve all lobes without any predilection.

Endobronchial TB (Fig.4) may be a complication of cavitary disease (spread via the airways following rupture of caseous necrotic material into bronchial walls), the tree-in-bud appearance of centrilobular nodules and branching centrilobular areas of opacity is indicative of endobronchial spread and suggests active disease.

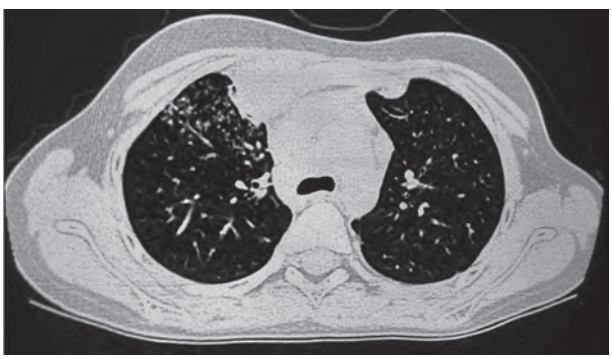

Fig.4.Tiny centrilobular nodules in linear branching or tree-in-bud pattern, suggestive of bronchogenic spread of tuberculosis

Abdominal TB is less common in children than in adults. Lymphadenopathy (Fig.5) can occur throughout the abdomen, with the most commonly involved nodes being para-aortic, mesenteric and periportal lymph nodes. Peripheral enhancement of lymph node can occur. Calcification is more likely in abdominal lymph nodes in children.

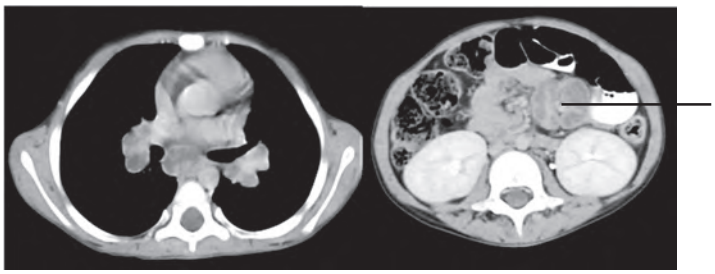

Fig.5.Contrast enhanced CT showing multiple enlarged necrotic lymph nodes with central low attenuation and ring enhancement (arrow)

Magnetic resonance imaging (MRI)

Spine is the most frequent location of skeletal tuberculosis (Fig.6 and 7). Tuberculous discitis and osteomyelitis usually affect the lower thoracic and upper lumbar vertebrae. The infection involves the anterior aspect of the vertebral body and often spreads to the disc, subligamentous space and soft tissues. MRI of the spine is critical in diagnosing spinal tuberculosis, as paravertebral and epidural abscesses can lead to cord compression.

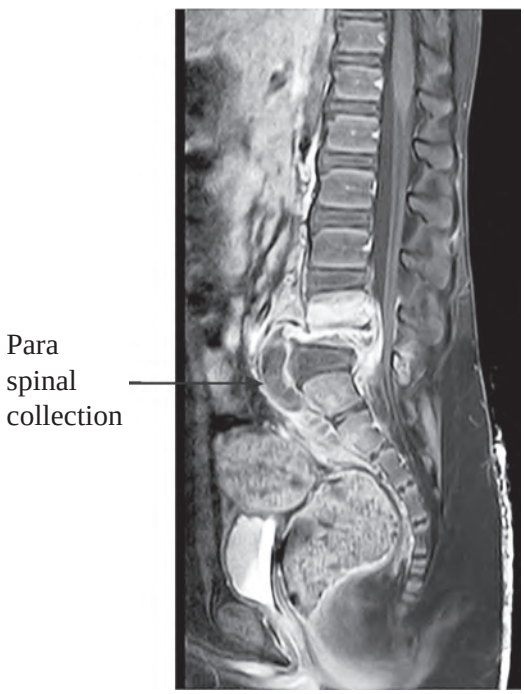

Fig.6. Contrast enhanced T1 weighted MRI, sagittal section shows vertebral body collapse of L3, L4 vertebra with bone marrow edema and peripherally enhancing hypointense paraspinal collection extending from L4 to S1 level

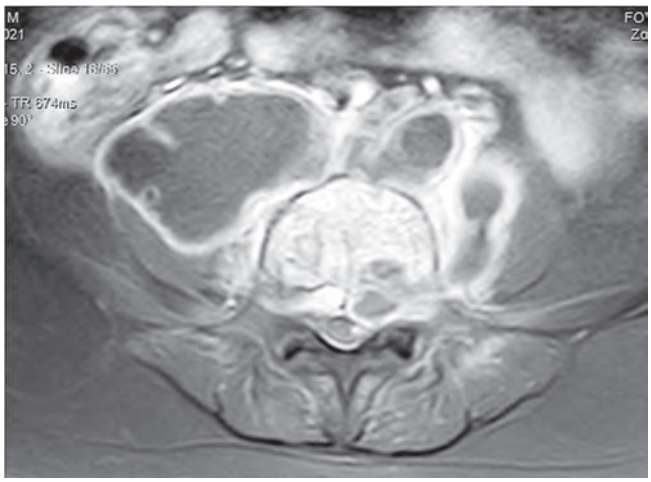

Fig.7. Contrast enhanced T1 axial section shows peripherally enhancing multiloculated paraspinal collection suggestive of cold abscess, a consequence of tuberculous spondylodiscitis

The main forms of CNS TB include tuberculous meningitis and tuberculoma. Intracranial tuberculomas originate as a conglomerate of small tubercles, which may rupture into the subarachnoid space, leading to the development of tuberculous meningitis. MRI is the modality of choice in identifying of tuberculomas which have central caseous necrosis in the background of granulomatous reaction. They usually appear as ring-enhancing lesions (Fig.8) or may appear as a conglomerate enhancing mass.

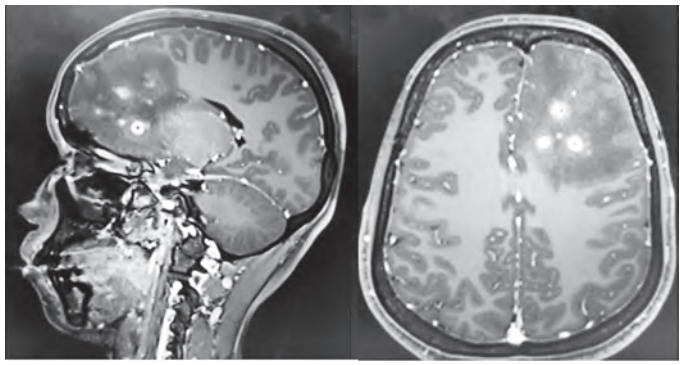

Fig.8.Contrast enhanced MRI of sagittal and axial sections showing multiple nodular and ring enhancing lesions suggestive of tuberculoma

Conclusion

In children with TB in whom microbiological confirmation is negative, the diagnosis is made clinically or radiologically. Characteristic patterns in children with TB include unilateral hilar lymphadenopathy with or without consolidation and miliary disease. Contrast enhanced CT and MRI are valuable diagnostic imaging modalities for extra pulmonary disease. Hence, radiographic images are among the most important diagnostic tools and also help in assessment of response to treatment and evaluation of complications of tuberculosis in children.

CLIPPINGS

Antimicrobial resistance in India.

Most studies are (78.7%) from NICU. Total of 50 545 blood cultures, among them, (29.1%) were positive.

S.aureus (median, 14.7%) and *K.pneumoniae* (median, 26%) were the commonest reported Gram-positive and Gram-negative pathogens. Approximately half of all *S.aureus* isolates were reported as MRSA (median, 50%; IQR, 31.4%–65.1%).

Median rate of resistance of common Gram-negative pathogens to ampicillin and gentamicin/amikacin were extremely high (*K.pneumoniae*/ampicillin 95.9%; *K.pneumoniae* / gentamicin 75%; *E.coli* / ampicillin 92.9%; *E coli*/gentamicin 55.6%). Likewise, the median resistance of Gram-neg blood stream isolates to cephalosporins were also high (K. pneumoniae / cefotaxime 62.6%; E coli/cefotaxime 47.5%).

High rates of resistance to WHO -recommended first-line treatment options for neonates and children have been identified in blood stream infections across India. There is an urgent need to enhance antibiotic stewardship and to repurpose older antibiotics back into routine care in India.

Dharmapalan D, Shet A, Yewale V and Sharland M. High Reported Rates of Antimicrobial Resistance in Indian Neonatal and Pediatric Blood Stream Infections. J Pediatr Infect Dis Soc 2017; 6(3):e62–e8.

CASE REPORT

LEFT VENTRICULAR NON-COMPACTION CARDIOMYOPATHY ASSOCIATED WITH CONGENITAL CYTOMEGALOVIRUS INFECTION

***Ram Babu Sharma**
**** Shashank Sharma**
***** Neelam Singh**

Abstract: *Left ventricular-noncompaction cardiomyopathy, is a rare and new association with congenital cytomegalovirus infection. It is characterized by distinctive trabeculated or spongy appearing left ventricle associated with left ventricular hypertrophy and systolic/diastolic dysfunction. A 3 months old infant with bilateral cataract, severe respiratory distress and congestive heart failure is described herewith. Serum ELISA of cytomegalovirus (CMV) IgM and IgG were positive. Urine for CMV PCR was positive. Echocardiography revealed grossly hypertrophied noncompacted left ventricle with multiple trabeculations and global left ventricular hypokinesia with moderate tricuspid regurgitation and pulmonary hypertension.*

Keywords: *Left ventricular-noncompaction cardiomyopathy, Congenital CMV, Bilateral cataract.*

Left ventricular noncompaction cardiomyopathy (LVNC) is a rare disorder in children. LVNC is estimated to affect 8-12 per 1 million individuals per year.[1] However, its incidence in India is not known. It has multiple inheritance patterns with mutations of MYH7 and MYBPC3 genes.[2]

Case details

A 3-months-old infant born of second-degree consanguineous marriage was admitted for evaluation of cardiac defects. This infant was born to 28-years-old gravida 2, para 2 mother with an uneventful antenatal history. No anomaly was detected on fetal ultrasonography-anomaly scan. There was no history of fever, rash, joint pains and no family history of congenital heart disease or cardiomyopathy in first and second-degree relatives. The baby was delivered by lower segment cesarean section at 37 weeks of gestation, delivery and postnatal period

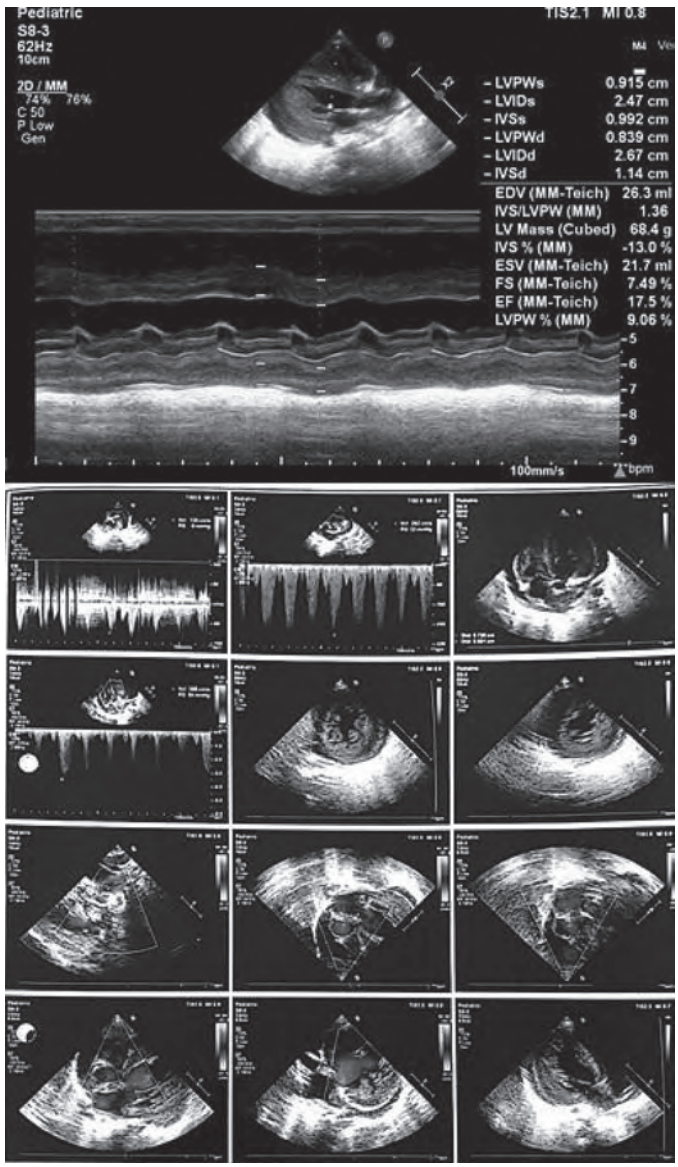

Fig. 1. Echocardiogram showing Left ventricular noncompaction cardiomyopathy (LVNC) (EF-25-30%)

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being uneventful. The baby was healthy with birth weight of 3 kgs. At 1month, bilateral congenital cataract was diagnosed. At 3 months of age, the patient presented with severe respiratory distress and congestive heart failure (CHF). Abdomen was distended with hepatomegaly, brownish macules seen on abdomen and medial side of thighs. His weight was 4.2 kg, length 58 cm and head circumference 41 cm. A pan systolic murmur of grade 4 was heard over left lateral sternal border. The developmental quotient was 50%. X-Ray revealed cardiomegaly (cardiothoracic ratio-77%). Electrocardiogram (ECG) revealed left ventricular hypertrophy with atrioventricular (AV) nodal tachycardia with pre-excitation. Echocardiography revealed grossly hypertrophied noncompacted left ventricle with multiple trabeculations and global hypokinesia with moderate tricuspid regurgitation and pulmonary hypertension (Ejection fraction-25-30%) (Fig.1). On Computed Tomogram brain imaging, subtle hypodensity was seen in bilateral frontal subcortical white matter and centrum semiovale. Complete blood count was within normal limits. Liver enzymes were mildly elevated: SGOT (81.0 U/L) and SGPT (43.0 U/L). TORCH profile revealed CMV IgM (18.40 U/ml, Normal <15.00 U/ml) and IgG (47.10 U/ml, Normal <11.00 U/ml), titers undoubtedly positive and the titers of herpes simplex virus, rubella and toxoplasmosis were negative. Urine for CMV PCR was positive. CK-MB levels was normal (18.25 IU/L). Transient evoked otoacoustic-emissions (OAE) test was negative. The patient was given oxygen support, maintenance fluid and antibiotics. Furosemide, digoxin and enalapril were given for congestive heart failure (CHF). In view of poor response and deterioration, digoxin was withdrawn and dobutamine started. Unfortunately, the patient expired due to severe respiratory distress and CHF. Genetic testing was not done due to unaffordability of the parents.

Discussion

LVNC is classified as an unclassified cardiomyopathy by WHO and Federation of Cardiology Task Force.[3] LVNC is a rare genetic cardiomyopathy which occurs as an isolated defect or associated with other cardiac or systemic conditions. According to Heart Failure Society of America (HFSA), proper family history of at least three generations and clinical screening in first degree relatives including history, physical examination, electrocardiogram, echocardiogram and creatine-kinase MM fraction is done every 3 years beginning in childhood or when signs/ symptoms appear in patients with cardiomyopathy including LVNC.[4] Treatment is based on the clinical findings associated with myocardial dysfunction or significant arrhythmias or congenital heart disease.[5,6] LVNC has been reported in a HIV positive women and is not a recognized manifestation of congenital CMV infection. However, hypertrophic cardiomyopathy has been reported with CMV in literature.[7,8] LVNC can be an emergent manifestation of congenital CMV infection. This case is being reported due to the characteristic echocardiographic findings and the new association.

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CASE REPORT

PAN OPHTHALMITIS - A RARE, YET PREVENTABLE COMPLICATION OF DENGUE INFECTION

***Mayuri Yeole**
****Himaal Dev**
*****Raghu Nagaraju**

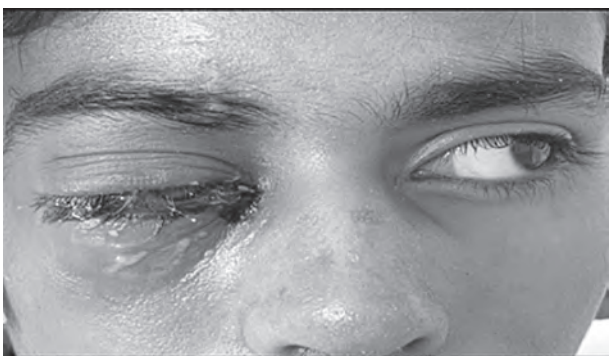
Abstract: *Dengue fever, one of the most common mosquito borne flavivirus diseases affecting humans, spreads by Aedes aegypti mosquito. A small proportion have life-threatening forms such as dengue hemorrhagic fever and dengue shock syndrome. One of the complications in dengue that is being observed more frequently in recent times is the ophthalmic manifestation. Ophthalmic manifestations can involve both the anterior and posterior segment. However, only a few isolated case reports have been published so far.*

Keywords: *Dengue, Panophthalmitis.*

Dengue fever (DF) is the most prevalent form of flavivirus infection in human beings. Worldwide, the number of cases of dengue exceed 100 million per year.[1] Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are severe and potentially fatal forms of the disease. Dengue related ocular complications range from 10% to 40%.[2,3] The ocular manifestations reported to be associated with dengue infections are mostly posterior segment manifestations like macular edema, vascular occlusions, chorioretinitis, vasculitis with retinal bleeding or cotton wool spots in addition to subconjunctival hemorrhage.[4,5] Here, we report an unusual manifestation of dengue fever presenting unilaterally with extensive panophthalmitis.

Case details

A 14-year-old boy presented as dengue shock syndrome at a remote hospital with high-grade fever of one week and associated vomiting for four days. On the second day of admission child complained of retro orbital pain and periorbital swelling over the right eye. Patient presented to us with blood and serous discharge from right eye for further intervention. Hematological investigations revealed a platelet count - 67,000/cu.mm and positive Dengue IgM. Culture swab from affected eye was negative. MRI brain with orbit was suggestive of right eye proptosis with features of panophthalmitis, orbital cellulitis and abscess of right eye. On evaluation, there was no perception of light noticed in right eye; with normal left eye. Child was treated with broad spectrum intravenous and topical antibiotics and systemic steroids. A significant improvement in restoration of eye movements in right eye except for abduction was noted (Fig.1 & 2). Proptosis had eventually reduced, with no perception to light, corneal infiltrates were present and fundus was still not visible. Systemic dengue illness improved, but with no perception of light in right eye and painful blind eye, hence he underwent evisceration.



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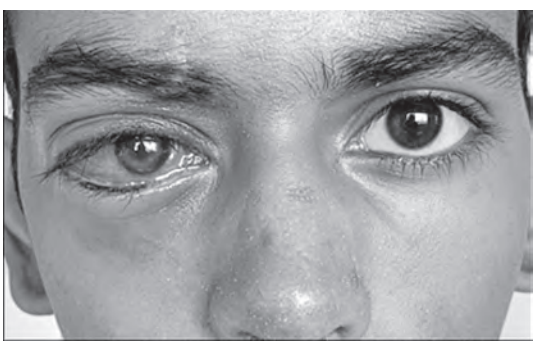

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Fig.1 & 2. Pre and post systemic steroid response

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Discussion

Ocular manifestations of dengue have been reported in all age groups, but more commonly in the age group of early thirties.[2,4] Vision threatening complications of dengue have been reported at the end of 1st week of dengue fever as this is the phase coinciding with nadir of thrombocytopenia.[4] Panophthalmitis is a rare complication, which has been reported in only few cases in literature till date.[6,7] Panophthalmitis is a severe involvement of the anterior and the posterior segments of the eye, common symptoms include ocular pain, blurring of vision and ocular discharge. Though the pathogenesis of these changes is not yet known, their clinical presentation and evolution are indicative of an immunogenic etiology rather than infective.[8] Immediate high dose steroids at presentation, followed by a rapid tapering has been suggested and tried with varying success to suppress and minimize the inflammatory damage.[9] Panophthalmitis, though rare in dengue, is vision-threatening. Hence, a systematic ophthalmic examination and intervention in dengue patients with ocular symptoms are mandatory. The onset of visual symptoms usually occurs at the lowest platelet level, blurring of vision typically coincides with the nadir of thrombocytopenia and occurs around one week after the onset of fever. Even though the disease is self-limiting and has a good prognosis it can also result in panophthalmitis resulting in vision loss. We, clinicians should have heightened awareness of dengue related ophthalmic complications and should facilitate prompt referral for ophthalmic assessment and management. Early systemic or intra vitreal administration of steroids might help in halting the ocular damage.

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CLIPPINGS

Role of prophylactic iron supplements in preventing recurrences of simple febrile seizures in infants: A prospective study.

This study recruited 101 children with simple febrile seizure (SFS), those with normal iron status (NIS) prescribed biweekly iron folic acid (IFA) supplementation. Mild, moderate and severe iron deficiency anemia (IDA) was managed using iron therapy, followed by prophylactic IFA supplementation with biannual deworming for one year. At the end of one year, serum ferritin levels, complete blood counts and the frequency of SFS episodes were documented. Incidence of IDA was 93.1%. After intervention, 63.4% showed NIS and increased serum ferritin levels. After supplementing IFA for one year the iron status improved and it was noted that 81.2% of children were void of SFS.

Nandhini K, Shanthi AK, Podhini J, Soundararajan P. Role of prophylactic iron supplements in preventing recurrences of simple febrile seizures in infants: A prospective study. Sri Lanka J Child Health 2021; 50:472-477.

CASE VIGNETTE

CANTU SYNDROME

***Senthil Kumar P**
****Ahila Ayyavoo**

A 2-year-old first-born girl of 3rd degree consanguineous parents had been admitted for respiratory illness. She was treated for pneumonia 3 months prior to this episode. Birth weight was 4.1 Kg with age-appropriate growth and development. Physical examination revealed coarse facies (Fig.1), epicanthal folds, long philtrum, short neck, hyper-extensibility of joints, hypotonia, hypertrichosis (Fig.2) over both sides of face, nape of neck, back and extremities. Examination of systems were normal. A diagnosis of mucopolysaccharidosis was considered, but urinary glycosaminoglycans were normal. X-ray of the thoracolumbar spine demonstrated vertebrae of ovoid shape (Fig.3). Chest X-ray was normal, with no evidence of cardiomegaly or skeletal malformations.

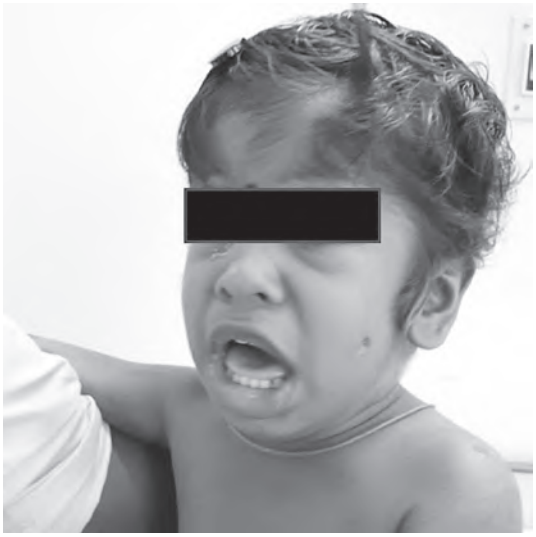

Fig.1. Coarse face, full lips and hypertrichosis over forehead, neck and trunk

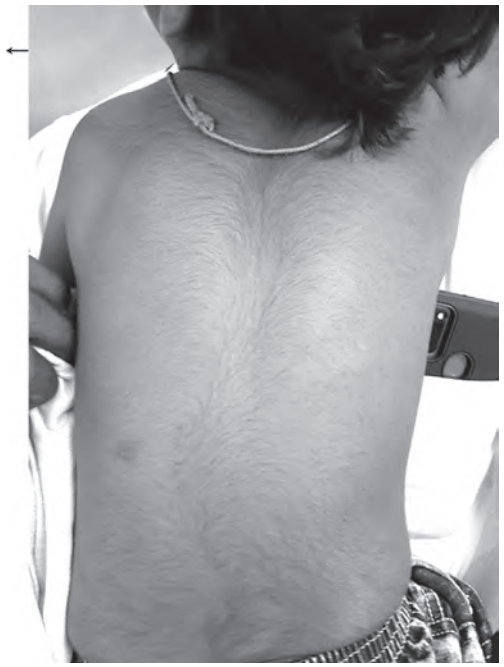

Fig.2. Hypertrichosis over back

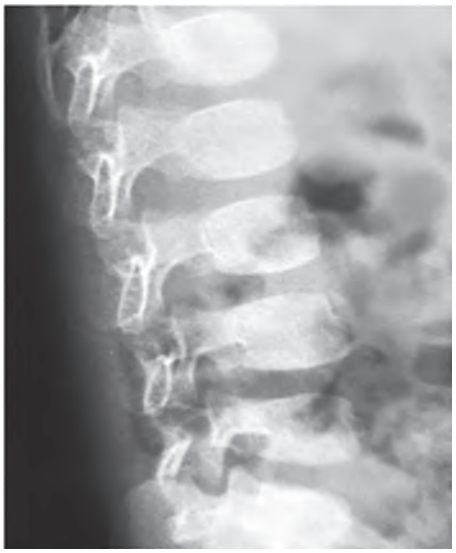

Fig.3.X-ray thoracolumbar spine: Lateral View-Ovoid vertebrae

Echocardiogram was normal. Clinical exome sequencing was done for the varied features and parental concern about the next pregnancy and it revealed heterozygous ABCC9 (-) mutation on Exon 27 - variant c.3461G>A

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(p.Arg1154Gln). This mutation results in Cantu syndrome (hypertrichotic osteochondrodysplasia) with autosomal dominant inheritance. Child was discharged subsequent to recovery from respiratory infection, with genetic counselling.

Cantu syndrome, known as hypertrichotic osteochondrodysplasia, a heterogeneous syndrome with autosomal dominant inheritance due to de novo mutations in either ABCC9 or KCNJ8, is a disorder due to potassium channelopathy.[1] These genes are expressed in tissues including skeletal, smooth and cardiac muscles. Around 70 cases with Cantu syndrome have been reported in the literature, with half being diagnosed based on clinical features.[2] Phenotypic expression of CS can be highly variable. While the facial features of Cantu syndrome could evolve over time, hypertrichosis usually persists.[3] Characteristic skeletal abnormalities include thickened calvaria, broad ribs, platyspondyly, ovoid vertebrae, scoliosis, pectus carinatum, metaphyseal flaring.[3] It is possible for some children with CS to have cardiac abnormalities such as patent ductus arteriosus, pulmonary hypertension, and pericardial effusions.[3] Less frequent features include umbilical hernia, pyloric stenosis, gastroesophageal reflux, recurrent infections and anterior pituitary hormone deficiencies. Although majority have normal intelligence, mild learning disabilities, developmental delay and behavioral problems have been observed in few cases.[4] Annual echocardiogram and electrocardiogram are recommended to monitor cardiac function and development of pericardial effusion. Periodic growth and endocrine assessment should be done for early identification of endocrine problems.

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CLIPPINGS

Concept of the "four D's" of fluid therapy.

In patients with septic shock, the administration of fluids during initial hemodynamic resuscitation remains a major therapeutic challenge. We are faced with many open questions regarding the type, dose and timing of intravenous fluid administration. There are only four major indications for intravenous fluid administration: aside from resuscitation, intravenous fluids have many other uses including maintenance and replacement of total body water and electrolytes, as carriers for medications and for parenteral nutrition. In this paradigm-shifting review, we discuss different fluid management strategies including early adequate goal-directed fluid management, late conservative fluid management and late goal-directed fluid removal. In addition, we expand on the concept of the "four D's" of fluid therapy, namely drug, dosing, duration and de-escalation. During the treatment of patients with septic shock, four phases of fluid therapy should be considered in order to provide answers to four basic questions. These four phases are the resuscitation phase, the optimization phase, the stabilization phase and the evacuation phase. The four questions are "When to start intravenous fluids?", "When to stop intravenous fluids?", "When to start de-resuscitation or active fluid removal?" and finally "When to stop de-resuscitation?" In analogy to the way we handle antibiotics in critically ill patients, it is time for fluid stewardship.

M Malbrain ML, Van Regenmortel N, Saugel B, De Tavernier B, Van Gaal PJ, Joannes-Boyau O, Teboul JL, Rice TW, Mythen M, Monnet X. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Annals of intensive care. 2018 Dec;8(1):1-6.

PICTURE QUIZ

Clinical background: This ten years old boy presented with afebrile seizures, first episode, regained consciousness. While examinning BP, he developed this movement.

1. Clinical diagnosis?

2. Two investigations?

3. Treatment?

Answers

1. Tetany

2. Serum ionized calcium, vitamin D level, PO4, alkaline phosphatase and PTH

3. IV Calcium gluconate, Vitamin D3 60,000 units weekly 4-6 doses. A short period of 2 weeks of calcitriol

NEWS AND NOTES

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Date: 16th - 19th December, 2021 **Venue:** Sangamitra Convention Centre, Puducherry

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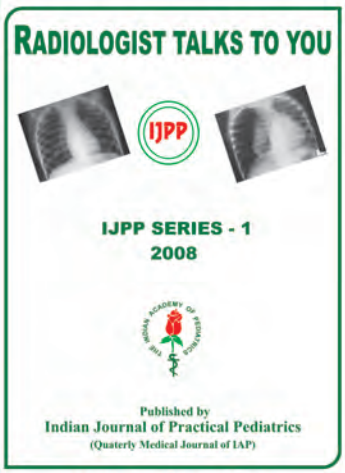

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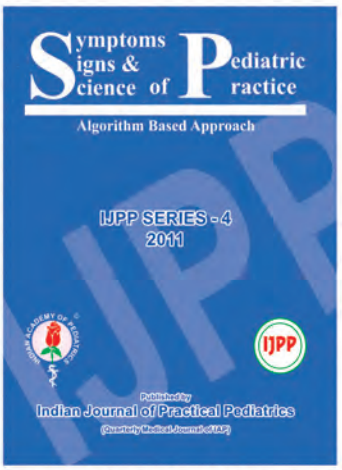

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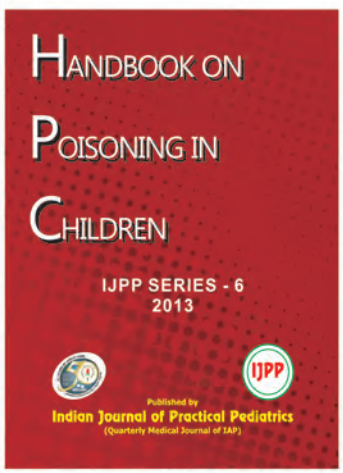

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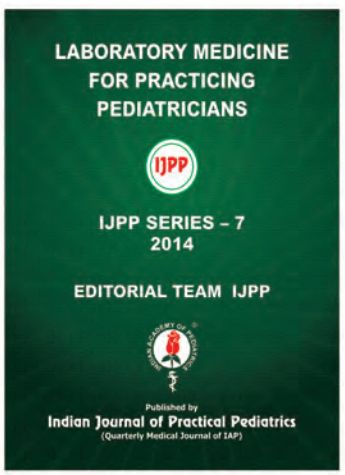

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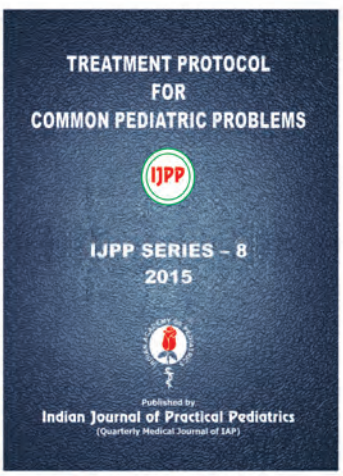

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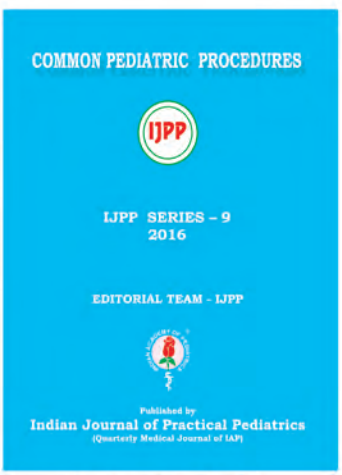

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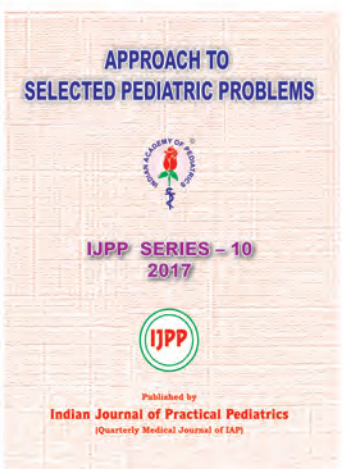

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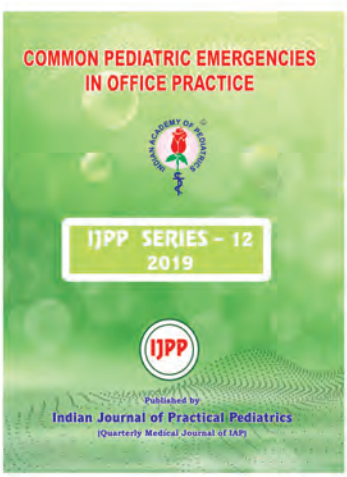

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