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Volume 2

INFECTIONS AND SYSTEMIC DISORDERS

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Chapter 28.1
Approach to a Child with Fever

Bhavna Dhingra, Piyush Gupta

Fever, in common parlance, is an elevation of body temperature above normal, but not all causes of temperature elevation constitute fever (e.g., heat stress and heat illness). Fever is an elevation of core body temperature as part of a specific biological response, mediated by cytokines and controlled by the central nervous system (CNS). It is a characteristic feature of many diseases, both infectious and noninfectious, and it involves activation of various physiological, endocrinological and immunological systems.

Normal body temperature follows a circadian rhythm and varies between 36.6°C in the morning to 37.9°C in the evening. Body temperature is controlled by the thermoregulatory center located in the preoptic anterior hypothalamus, which balances heat production, derived primarily from metabolic activity in muscle and the liver, with heat dissipation from the skin and lungs to maintain the temperature in a steady range. Oral temperature is generally 0.6°C (1.0°F) lower than rectal temperature because of mouth breathing, which is particularly important in patients with respiratory infections and rapid breathing. Lower esophageal temperature reflects core temperature, and tympanic membrane (TM) temperature readings also approximate to core temperature. Beyond the newborn period, infants and young children generally have higher body temperatures due to the greater surface area to body weight ratio and the higher metabolic rate than older children and adults.

DEFINITION

A clinically significant fever is generally defined as a rectal temperature of 38°C (100.4°F) or higher. This is equivalent to an oral temperature of 37.5°C (99.5°F), and axillary (armpit) temperature of 37.2°C (99°F). Fever above 41.5°C (107°F) is called hyperpyrexia and may lead to irreversible organ damage.

PATHOPHYSIOLOGY OF FEVER

Fever is induced by pyrogens. Bacteria, fungi, viruses, malignancies, connective tissue disorders, certain drugs, and trauma may endogenously stimulate production of pyrogens.

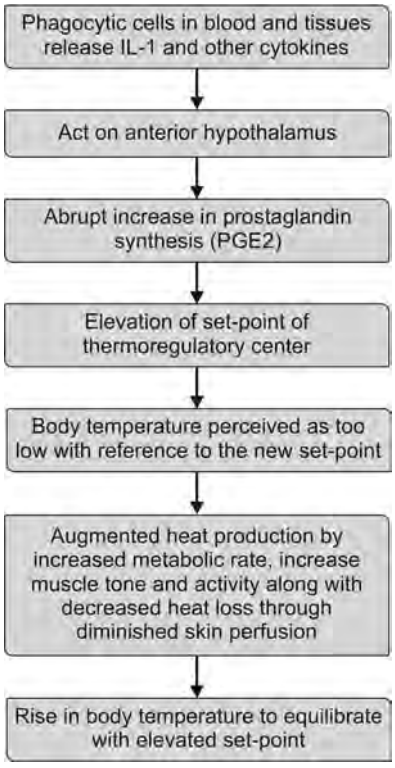
- Common *endogenous pyrogens* include interleukin 1 (IL-1), tumor necrosis factor (TNF) and interferon. Other endogenous pyrogens include IL-6, IL-11, leukemia inhibitory factor (LIF), ciliary neurotropic factor (CNTF) and oncostatin-M. Large amounts of IL-6 circulate in nearly all febrile diseases, and IL-6, induced by IL-1 or by the combination of IL-1 and TNF, accounts for most clinical fevers.
- *Exogenous pyrogens* include the bacterial cell wall component lipopolysaccharide (LPS), enterotoxins, and exotoxins. Exogenous pyrogens can induce production of endogenous pyrogens via activation of Toll signaling, and both endogenous and exogenous pyrogens stimulate the synthesis of prostaglandins (PG). Prostaglandin E2 (PGE2) is the ultimate endogenous pyrogen. It resets the temperature of the hypothalamus.

Fever is the result of a series of events that begins peripherally with the synthesis and release of IL-1 and other cytokines by phagocytic cells in the blood or tissues. **Flow chart 1** illustrates the pathophysiology of fever.

ADVANTAGES OF FEVER

The survival of some pathogenic bacteria or viruses is impaired at temperatures in the range of 40°C (104°F). Many pathogenic bacteria require iron for their growth, and fever is associated with a decrease in serum iron and a simultaneous increase in the iron-binding protein, ferritin, resulting in low levels of free iron in the blood. It has been suggested that this response is a coordinated host defense mechanism meant to deprive bacteria of free iron. Enhancement of several human immunologic functions occurs

Flow chart 1 Pathophysiology of fever



at moderately elevated temperatures, e.g., increased lymphocyte transformation response to mitogen, increased bactericidal activity of polymorphonuclear leukocytes, and increased production of interferon with increasing temperature. Beyond 40°C, most of the functions decline below baseline levels.

DISADVANTAGES OF FEVER

Fever is associated with an increased metabolic rate, increased oxygen consumption, increased carbon dioxide production, and increased demands on the cardiovascular and pulmonary systems. Fever often makes patients uncomfortable. Fever can precipitate febrile convulsions in children between 6 months and 5 years of age. Fever can aggravate cerebral injury.

ETIOLOGY OF FEVER

Fever is probably the most common presenting complaint in pediatric practice and is associated with a wide variety of illnesses. The most common cause of fever in children is a viral infection. In viral infection, fever is usually short-lived and signs are usually more generalized than those with bacterial infection. Common viral and bacterial illnesses like upper respiratory infections (URI), gastroenteritis, ear infections, croup, and bronchiolitis are the most likely illnesses known to cause fevers of short duration. Viral fevers usually resolve in about a week, persistence of fever beyond this time requires a detailed work-up. Bacterial URIs may be difficult to distinguish from viral URIs but the presence of pus points in the tonsil and unilateral involvement of ears points towards a bacterial etiology. Other common infective causes that need to be looked into are malaria, urinary tract infections, sepsis, abscesses, etc.

EVALUATION OF A FEBRILE CHILD

Performing a detailed and thorough history and physical examination is the first and most important component of the diagnostic evaluation of a febrile child. The next steps are to (*i*) localize the fever to a particular organ system by presenting complaints; and to (*ii*) identify the probable etiology of fever, depending upon its duration, pattern and clinical examination.

History

The history should include questions regarding characteristics of fever (onset, intensity, duration, frequency and pattern of fever—continuous, remittent or intermittent); how was the temperature assessed-perceived manually or documented by a thermometer along with the site of documentation; localizing symptoms of fever; recent exposures like vaccination, animal/insect bites, or receipt of blood transfusion or biological product; exposure to a family member with fever or any infectious disease; past history of any significant illnesses such as tuberculosis, urinary infections, congenital heart disease, and surgical procedure; any history of travel in the recent past; history of an underlying chronic disease, and medication history. History of recurrent episodes of fever may give a clue to certain cyclic causes of fever. Ask for other system-related symptoms. Enquiry about specific symptoms may help in localizing the disease to a particular system.

Examination

The physical examination should begin with a general assessment of the patient's appearance, activity, vital signs, and growth parameters. It is a good idea to evaluate the child during febrile period as the presence or absence of few signs during the febrile phase may provide certain clues to diagnosis, e.g., absence of sweating in anhidrotic ectodermal dysplasia. Absence of malaise or other generalized signs in a child with a history of high fevers can signal factitious fever.

Identify the Etiology of Fever

Short duration fever Fever of less than 2 weeks duration is usually infectious in origin, and due to viruses, bacteria or protozoa. Many of these patients recover completely, even before a precise diagnosis is made or treatment is given. These children may present with or without localizing manifestations. Every effort should be made to identify and localize the system involved, based on the localizing symptoms, as shown in **Table 1**.

Prolonged fever Fever lasting for more than 2 weeks requires a different approach. Infections still remain the most important cause of prolonged fever; however, noninfectious causes are also responsible. Common causes of prolonged fever are listed below:

- *Infections:* Tuberculosis, HIV, urinary tract infections, chronic fungal infections, etc.

Table 1 Determining etiology of fever based on presenting features

Cough and coryza	*Viral fever*
Rash	Exanthematous illnesses like measles, rubella, chickenpox, erythema infectiosum, roseola infantum, herpes simplex; other illnesses like meningococcemia, dengue, Henoch-Schönlein purpura, leukemia, and Kawasaki disease
Ear pain	Acute suppurative otitis media (ASOM)
Skin boils	Abscess, pustules, cellulitis, impetigo
Seborrheic dermatitis (±ear discharge)	Langerhans cell histiocytosis
Periungual desquamation with strawberry tongue	Kawasaki disease
Throat pain, difficulty in swallowing, cervical nodes	Pharyngotonsillitis
Stridor, dysphonia	Laryngitis, tracheitis, croup, epiglottitis, diphtheria
Fast breathing and cough, wheezing, chest in drawing, chest pain	Pneumonia, bronchiolitis, pleural effusion, tuberculosis
Joint swelling, pain or limited movements	Septic arthritis, rheumatic fever, tubercular arthritis, connective tissue diseases
Vomiting	Gastritis, gastroenteritis, viral hepatitis, meningitis, enteric fever, UTI
Diarrhea	Gastroenteritis, enteric fever, dysentery
Jaundice	Hepatitis, cholecystitis, malaria
Pallor, rash, bleeding, lymphadenopathy	Leukemia, infectious mononucleosis
Urinary frequency, burning micturition, crying during micturition, hematuria	Urinary tract infection, cystitis
Chills or pallor or jaundice	Malaria, hepatobiliary causes
Altered sensorium, seizures, neurological deficits, meningeal signs	Meningoencephalitis (bacterial, viral, tubercular), cerebral malaria, enteric encephalopathy, brain abscess
Abdominal pain	Gastroenteritis, appendicitis, liver abscess, hepatitis, cholecystitis, cholangitis, intra-abdominal/pelvic abscess, pyelonephritis

- *Inflammatory disorders:* Rheumatoid arthritis, systemic lupus erythematous, Kawasaki disease and other connective tissue disorders including polyarteritis nodosa, Behcet disease, Wegner granulomatosis.
- *Malignancies:* Lymphoma (including Hodgkin disease), leukemia, hepatoblastoma, Wilms tumor, neuroblastoma, brain tumors.
- *Endocrine causes:* Thyrotoxicosis, diabetes insipidus.
- *Hematological and immune deficiency disorders:* Spherocytosis, agranulocytosis, hemolytic anemia; Langerhans cell histiocytosis, disorders of T- or B-cells; disorders of phagocytosis.
- *Neurologic disorders:* Familial dysautonomia, hypothalamic and third ventricle lesions; anhidrotic ectodermal dysplasia.
- *Miscellaneous causes:* Drug fever, periodic fever, factitious fever.

Box 1 provides a detailed list of common causes of fever associated with hepatosplenomegaly, rash, or lymphadenopathy. When fever has been persistent for a week, and no cause has been found, serious consideration should be given to hospital admission to confirm pyrexia and initiate investigations. Appropriate laboratory testing as per the merit of each case may include: complete blood counts with peripheral smear, ESR, CRP, urinalysis and urine culture, blood cultures and serologic tests when appropriate (e.g., for enteric fever, malaria, dengue, leptospirosis, TORCH infections, rickettsial infections, *Coccidioides immitis, Cryptococcus neoformans, Borrelia burgdorferi, Treponema pallidum,* and HIV). Radiological investigations may include X-ray chest; ultrasonography, CT and MRI, as indicated. Other common though invasive investigations include bone marrow examination, lumbar puncture, cytopathology, and examination of ascitic/pleural/joint fluids.

BOX 1 Etiology of fever with rash, lymphadenopathy and hepatosplenomegaly

Fever with Hepatosplenomegaly

- *Infectious causes:* Malaria, enteric fever, kala-azar, tuberculosis, infectious mononucleosis, brucellosis, echinococcosis, rickettsial diseases, TORCH infections, dengue, septicemia, and infective endocarditis
- *Malignancies:* Leukemias, lymphomas, histiocytosis, infantile hemangioendothelioma, hepatoblastoma, and metastases
- *Connective tissue diseases:* Systemic lupus erythematosus (SLE); systemic juvenile idiopathic arthritis (JIA), sarcoidosis, scleroderma, and rheumatic fever
- *Chronic hepatitis/chronic liver disease:* Autoimmune hepatitis, chronic hepatitis B/C, and Wilson disease.

Fever with Rash

- *Infectious causes:* Meningococcemia, dengue, measles, rubella, varicella, roseola infantum, erythema infectiosum, herpes simplex, and lupus vulgaris
- *Malignancies:* Leukemia and histiocytosis
- *Vasculitis:* Henoch-Schönlein purpura, Kawasaki disease, rheumatic fever, systemic JIA, and SLE.

Fever with Lymphadenopathy

- Suppurative lymphadenitis (bacterial, often accompanying pharyngitis, tonsillitis, dental infections, scalp infections)
- Tuberculosis
- Lymphoma (Hodgkin and non-Hodgkin lymphomas)
- Histiocytosis
- Acute lymphoblastic leukemia (ALL)
- HIV infection
- Connective tissue disorders such as systemic JIA or sarcoidosis
- Kawasaki disease
- Rosai-Dorfman disease.

IN A NUTSHELL

1. Fever is a symptom of an underlying disease, which may be infective or noninfective.
2. Fever results due to a change in the set point of hypothalamic thermoregulatory center.
3. The most common cause of fever in the young child is usually a self-limiting viral infection.
4. A detailed and thorough history and physical examination is the most important component in the evaluation of a febrile child.
5. Duration of fever and associated symptoms aided by appropriate investigations can help in localizing cause of fever.

MORE ON THIS TOPIC

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Chapter 28.2
Fever: General Principles of Management

Piyush Gupta, Bhavna Dhingra

All fevers do not need to be treated, and when treated, the primary objective of treating fever should be to make the child comfortable, and not the normalization of body temperature. Antipyresis can be achieved by nonpharmacological measures and/or drugs. Antipyretics may help in overall management of a febrile child but do not appear to affect the recurrence of febrile seizures.

NONPHARMACOLOGICAL ANTIPYRESIS

Nonpharmacological methods include environmental modifications, increased fluid intake, and mechanical cooling.

Environmental Modifications

Place the child in cool and airy environment (21–22°C) which enhances heat loss by convection. Minimal clothing; i.e., dressing the child in only one layer, is advocated to enhance heat loss. Some theories support a gentle body massage to dilate the cutaneous blood vessels which further increases heat dissipation.

Hydration

As fever increases, the metabolic rate of the body also goes up. For each 1°C rise of temperature above 37.2°C, there is an increase in insensible water loss of 7 mL/kg body weight/day. Hence, extra fluid intake is advised in febrile patients. For each 1°C of increase in temperature, a 12% increase in fluid intake is recommended.

Mechanical Cooling (Hydrotherapy or Sponging)

It is considered the mainstay of nonpharmacological antipyresis. External cooling lowers the temperature of febrile patients by evaporation, conduction, and convection. Evaporation is rated as the most effective physical mean of promoting heat loss in febrile

children because it has the least capacity to induce shivering. External cooling acts by impairing the overwhelming effect or mechanisms evoked by elevated thermoregulatory set point, rather than by lowering the elevated set point. The capacity of external cooling to lower core temperature is limited because it induces both cutaneous vasoconstriction and shivering. Therefore, unless concomitant antipyretic therapy or other pharmacological methods are used to abolish shivering, external cooling is vigorously opposed in febrile patients by thermoregulatory mechanisms endeavoring to maintain elevated temperature.

External cooling with ice is the treatment of choice for heatstroke and other forms of heat illness, but is more discomforting. For fever, external cooling is indicated only in specific situations, and with tepid rather than cold water. Some infants with infection may also have a component of heat illness from over-wrapping, dehydration, or drugs such as atropine. Sponging should be done by continuous wiping of the body with tepid water (28–30°C) from head to toe for 15–20 min. Sponging action ensures that water film is constantly moving thus maximizing heat conduction. Tepid sponging acts by conduction of heat from the warm skin to water. An absorbent towel should be soaked, rinsed and placed on the legs, trunk and forehead in order to reduce the body temperature. Hydrotherapy should be continued till the body temperature comes down to 38°C. Indications for sponging is summarized in **Box 1**. Studies indicate that hydrotherapy alone is clearly inferior to antipyretics for reduction of fever for periods longer than 30 min after initiation of treatment. External cooling may, however potentiate the activity of antipyretics.

Results of randomized trials comparing the combination of antipyretics and physical methods with antipyretics alone have provided mixed results. In 4 out of 7 such studies the combination treatment was superior to use of antipyretics alone for reduction of temperature during first 30 min of initiation of therapy and overall. In other 3 studies both modes of treatments were equally effective in lowering temperature. It is recommended to administer antipyretic drugs at least 30 min before sponging.

The main disadvantage of hydrotherapy is patient discomfort and shivering. Shivering not only impedes cooling during fever but also imposes considerable metabolic burden. Studies in volunteers have shown that shivering increases the oxygen consumption, respiratory minute volume, respiratory quotient, increase in percentage of carbon dioxide in exhaled air during exposure to cold and increase in mean arterial pressure. Perhaps in febrile patients with cardiovascular disease external cooling can cause coronary artery vasoconstriction by cold press or response and thus decrease coronary perfusion. Sponging, though rapid in reduction of temperature, has an ill sustained effect.

PHARMACOLOGICAL ANTIPYRESIS

Antipyretic agents are administered to provide symptomatic relief in children with fever. Keeping in mind that fever results from change in the set temperature of the hypothalamic thermoregulatory center, it seems logical to bring down the temperature by restoring the hypothalamic set-point to normal.

BOX 1 Indications for sponging with lukewarm water in fever

- Febrile delirium
- Febrile seizure
- Fever > 41.1°C
- Patients with neurologic disorders, because many of these children have abnormal temperature control and respond poorly to antipyretic agents
- Children with hypersensitivity to antipyretic agents
- Children with severe liver disease.

Commonly used agents to achieve antipyresis include paracetamol, ibuprofen, and aspirin. Aspirin was the first antipyretic used in children. However, after reports of its association with causation of Reye syndrome, aspirin is not recommended for controlling fever in children. Mefenamic acid and nimesulide are the other drugs used infrequently to control fever.

Mechanism of Action

The antipyretic medications act via the arachidonic acid pathway **(Flow chart 1)**. Arachidonic acid is a substrate for both cyclo-oxygenase-2 (COX-2) and a second isoform of the enzyme, COX-1. COX-2 is the principal mediator of the inflammatory response, resulting in production of prostaglandin2 (PGE2). COX-1 products, on the other hand, function primarily in renal function, vascular homeostasis and gastrointestinal cytoprotection. Central inhibition of COX is responsible for the antipyretic effects of paracetamol. Relatively weaker inhibition of splenic COX accounts for its relatively poor anti-inflammatory response. Paracetamol is nearly as effective as aspirin and 10% as effective as indomethacin in inhibiting central COX but only 5% as effective as aspirin and 0.02% as effective as indomethacin in inhibiting peripheral COX.

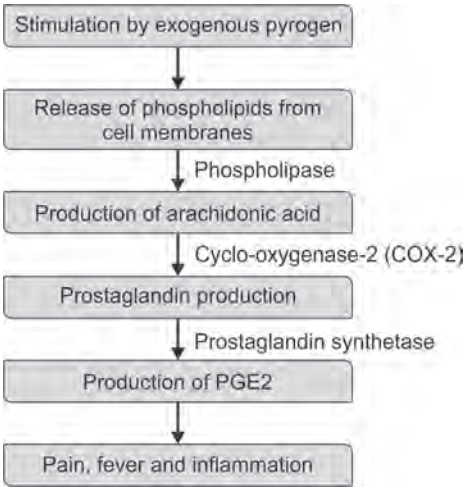
Ibuprofen is a competitive inhibitor of the COX enzymes, in that it competes with arachidonic acid for binding to the catalytic site on COX, thereby preventing prostaglandin synthesis. This is a reversible process. Unlike paracetamol, ibuprofen acts peripherally and lacks specificity for either COX isomer. Ibuprofen therefore has antipyretic, analgesic and anti-inflammatory actions.

Dosing and Toxicity

Paracetamol

Paracetamol is recommended in a dose of 15 mg/kg at 4–6 hourly intervals not exceeding 60 mg/kg/day. Antipyretic effect begins within 30–60 min, approximately 80% of children will experience a decreased temperature within this time frame. Paracetamol reduces the temperature by 1–2°C after 2 hour of intake. The rate of fall of temperature is directly related to the degrees above which initial temperature was above baseline. Greater the initial temperature, greater is the fall after drug intake and vice versa. Hence, drug administration in low grade temperature may not lead to any significant fall and antipyretic treatment in high grade fevers (> 104°F) would result in reduction of temperature by less than 1°C, failing to touch the baseline.

Flow chart 1 The arachidonic acid metabolism pathway



Ibuprofen

Ibuprofen can also be used as a first line antipyretic. Efficacy of paracetamol and ibuprofen has been compared in a number of studies, and some have shown greater antipyretic effect with 10 mg/kg of ibuprofen as compared to 15 mg/kg of paracetamol. Ibuprofen has the advantage of longer duration of antipyresis (8 h) as compared to paracetamol (4 h). Recent evidence indicates that there is no difference in the safety and effectiveness of paracetamol and ibuprofen in the care of a generally healthy child with fever. There is evidence that combining these 2 drugs is more effective than using them alone. However, this should not be followed as a routine because of associated risk of inappropriate dosages. The practice of alternating ibuprofen and paracetamol has limited value.

Nimesulide

Nimesulide has a superior efficacy when compared to paracetamol, aspirin, naproxen and mefenamic acid. Also the advantage of reduced frequency of dosing (2–3) exists with its use. However, use of nimesulide in children is associated with potentially fatal adverse effects resulting in hypothermia, hepatotoxicity, and renal damage.

Mefenamic Acid

Mefenamic acid is a reversible competitive inhibitor of COX-1 and COX-2 enzymes and has analgesic, antipyretic, and anti-inflammatory properties. It is very effective in control of high fever in a dose of 6–7 mg/kg/dose (20 mg/kg/day in three divided doses), usually a single dose suffices and can later be followed by paracetamol after 6–8 hour. Its main side effects are diarrhea, hemolytic anemia, thrombocytopenia and drowsiness.

Choice of Antipyretic

The decision regarding the choice of antipyretic should be based on personal experience, scientific data regarding efficacy, safety, duration of effect, and cost. In therapeutic dosages aspirin is more toxic and causes gastritis, gastrointestinal bleeding, impaired platelet function, diminished urinary excretion of sodium, Reye syndrome and blunted immune response. These side effects are known to occur less frequently with ibuprofen and none with paracetamol. Paracetamol can be safely used in children with asthma, with sensitivity to aspirin or ibuprofen, coagulation disorders, peptic ulcer or reflux esophagitis. Thus paracetamol is considered to be the safest antipyretic in children at therapeutic dosages. Hepatotoxicity appears to be the most serious and well-documented toxicity associated with use of paracetamol in children. Concern has been raised over the gastrointestinal disturbance and nephrotoxicity with ibuprofen; hence caution is encouraged when using ibuprofen in children with dehydration. In the overdose situation, the toxicity of paracetamol is not only reached much earlier, but is also more severe and more difficult to manage as compared with an overdose of ibuprofen.

The most commonly used and preferred mode of administration of antipyretics is the oral route. Rectal suppositories may be used in children with febrile seizures or unconscious patients. Parenteral (intramuscular or intravenous) administration of paracetamol may be used in cases where quick relief of fever is required or when oral administration is not possible, e.g., comatose children. The dose of intravenous paracetamol is 7.5 mg/kg/dose (max. 30 mg/kg/day) for neonates and infants and 15 mg/kg/dose for older children (max. 60 mg/kg/day) to be given as an infusion.

Parental Education

Fever is the most common complaint for which medical attention is sought by the caregivers. It also causes considerable parental anxiety and concern; therefore, appropriate counseling of parents and caregivers is a must. Parents need to be explained that fever is a protective response of body and helps to fight the disease. Medical personnel need to emphasize and deal with issues, such as what is fever, what is high grade fever, advantages and disadvantages of fever, when and which fever should be treated and how, the danger signs associated with fever, and when to seek medical help.

HEAT HYPERPYREXIA

Heat hyperpyrexia is not an unusual cause of fever in tropical countries where ambient temperature may go as high as 45°C. Heat hyperpyrexia may occur even without exposure of the child to the direct sunlight. The predisposing factors include high temperature and humidity in the environment, unsuitable clothing, dehydration and debilitating illness, such as malaria, pneumonia, measles, and renal disorders. Invariably, heat hyperpyrexia is associated with cessation of sweating. Children with ectodermal dysplasia and absence of sweat glands are more prone to develop episodes of heat hyperpyrexia.

The onset of high fever may be quite sudden. The rectal temperature may exceed 42°C to 43°C. The skin appears hot and dry (without sweating). Tachycardia and tachypnea are present. The loss of consciousness occurs early. The patient may develop peripheral circulatory failure and hemorrhages. Headache, faintness, abdominal discomfort and delirium are usually complained of. The liver and kidney failure may complicate heat hyperpyrexia.

Management

When the temperature exceeds 41°C, body of the child below the neck should be immersed in the cold water without further delay to prevent irreversible brain damage. The parents should be reassured that this seemingly drastic measure will not induce shock. Ice cold bath does not cause significant vasoconstriction. The rectal temperature should be recorded continuously and the hydrotherapy should be discontinued as the temperature falls below 38°C.

IN A NUTSHELL

1. Fever *per se* is just a symptom of underlying illness and not a disease itself.
2. All fevers do not need treatment. The aim of treating fever is not normalization of body temperature.
3. Febrile children should be advised to drink plenty of water and wear loose comfortable clothing.
4. Medicines should be used only when indicated. Paracetamol (15 mg/kg) is the safest antipyretic in children. Ibuprofen is an alternative. Aspirin and nimesulide should not be used in children.
5. Hydrotherapy with tepid water may be useful when used in combination with pharmacological antipyresis.
6. Explain to parents that febrile seizures occur in minority of children, are benign and do not cause any permanent brain damage or epilepsy.
7. Close monitoring is required in children with past history of febrile seizures.
8. Parents should be taught the emergency management of febrile seizures.

MORE ON THIS TOPIC

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Chapter 28.3
Fever without Focus

Piyush Gupta, Bhavna Dhingra

Fever without focus in a child is defined as a rectal temperature of 38°C or higher as the only presenting symptom and can be subcategorized into *fever without localizing signs* (FWLS) and *fever of unknown origin (FUO)*.

FEVER WITHOUT LOCALIZING SIGNS

Children presenting with history of acute onset of short duration fever (usually less than a week) as the only presenting complaint without any signs or symptoms localizing to any organ system are categorized as having fever without localizing signs. This presents a diagnostic challenge in children less than 36 months of age. These children represent an important group because of higher risk of occult bacteremia and serious bacterial infections (SBI) (range 5–20%). Therefore, it may sometimes become essential to start specific and empirical treatment without establishing an etiological diagnosis. As the etiology of this entity and risk of SBI is variable in different age groups, these children are usually subclassified into the following three categories:

1. Neonates (up to 1 month of age).
2. Infants, 1–3 months of age.
3. Infants, 3–36 months of age.

There are certain high-risk groups of children who are at increased risk of SBI and require a more aggressive outlook. These include children presenting with: hyperpyrexia (> 40°C); fever with petechiae; and immunocompromised patients with asplenia, sickle cell disease, complement deficiency states, agammaglobulinemia, hypogammaglobulinemia, congenital heart disease, malignancy, or AIDS.

Neonates (Birth-1 Month of Age)

Newborns presenting with fever without localizing signs present a diagnostic dilemma for the treating clinician. They have a very limited number of signs of infection and that too are nonspecific. Immune response is also not mature. It is difficult to differentiate between dehydration fever, a self-limited viral illness, and SBI. SBI ranges from occult bacteremia, pneumonia, meningitis, urinary tract infection, and enteritis, to osteomyelitis, and septic arthritis.

Any newborn or young infant presenting with fever should be hospitalized and after control of ambient environmental temperature and adequate hydration with increased frequency of breastfeeding, if the baby is still febrile—possibility of SBI should be entertained even in an apparently healthy neonate. All such neonates should be subject to a septic screen which includes complete blood counts with band form count, urine microscopy, blood culture, urine culture, chest X-ray, and peripheral smear for malarial parasite. Lumbar puncture and cerebrospinal fluid analysis (cell counts, glucose, protein, Gram stain and culture) should be undertaken in children with lethargy or refusal to breastfeeding.

Etiology

Haemophilus influenzae B and *Streptococcus pneumoniae* are the two most important causes of SBI in India, besides *Klebsiella*, *Staphylococcus aureus*, and *Escherichia coli. Listeria monocytogenes* and perinatally acquired *Herpes simplex virus* (HSV) infection have also been implicated. Malaria should also be considered a strong possibility in endemic areas.

Management

After obtaining relevant investigations, empirical antibiotic therapy should be initiated at the earliest with combination of ampicillin and cefotaxime or monotherapy with ceftriaxone (100 mg/kg per day) and modified later as per the reports of the sepsis screen and cultures.

Fever in the Young Infant 1–3 Months of Age

Self limited seasonal viral illnesses are the most common cause of fever without localizing signs in this age group. The possibility of SBI should always be entertained in any febrile child between 1 month and 3 months of age and the following conditions should be ruled out: otitis media, pneumonia, skin and soft tissue infections, omphalitis and urinary tract infections especially in uncircumcised boys and children with urinary tract anomalies.

Risk Stratification

Febrile infants less than or equal to 3 months with diminished spontaneous activity, lethargy, respiratory compromise (tachypnea, chest retraction and grunting), diminished muscle tone, mottled cool extremities, irritability, weak sucking are at high-risk. Infants 1–3 month of age with fever who appear well and had been previously healthy, and have a normal physical examination, can be categorized as at *low-risk* or *high-risk* for serious bacterial infections by certain investigations. **Table 1** lists the various criteria used for identifying children 1–3 months at low-risk of SBI.

Etiology

The most common implicated organisms are Group B *Streptococcus*, *E. coli*, *S. aureus*, *S. pneumoniae*, *H. influenzae*, *Neisseria meningitides* and enterococci. Pyelonephritis is the most common SBI and may be seen in well appearing as well as ill appearing children between 1 month and 3 months of age presenting with fever without localizing signs.

Management

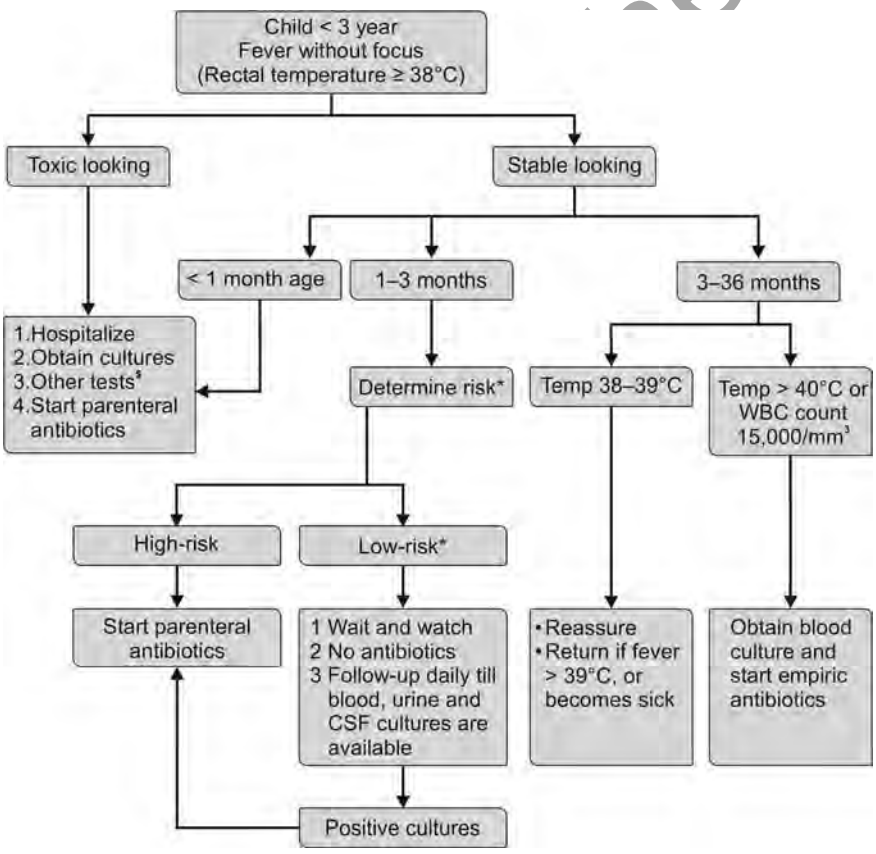
Febrile children, 1–3 months of age who present with fever without localizing signs must be evaluated for sepsis by complete blood count, lumbar puncture, blood culture, urinalysis, urine culture and chest radiograph. Ill appearing infants require immediate hospitalization and prompt institution of empirical parenteral antimicrobial therapy. Ampicillin with either cefotaxime or ceftriaxone is an effective combination. Vancomycin should be included if possibility of meningitis with penicillin resistant *S. pneumoniae* is suspected. Antimicrobials can be modified as per the culture and sensitivity reports.

Table 1 Low-risk criteria in 1–3 months old children with fever without localizing signs

	Philadelphia protocol	*Pittsburgh guidelines*	*Rochester criteria*	*Boston criteria*
General appearance	Well	Well	Well	Well
Physical examination	Normal	Normal	Normal	Normal
Complete blood count WBC/mm^3 I:T neutrophil ratio absolute band count	< 15,000 < 0.2	5000–15000 < 1500/mm^3	5000–15000 < 1500/mm^3	< 20,000
Urine examination	< 10 WBC/HPF No bacteria on Gram stain	9 WBC/mm^3 No bacteria on Gram stain	< 10 WBC/HPF at 40X	Negative leukocyte esterase
Cerebrospinal fluid (If bloody tap)	< 8 WBC/ mm^3 No bacteria on Gram stain	5 WBC/mm^3 No bacteria on Gram stain WBC:RBC ≤ 1:500		< 10 WBCs/mm^3
Chest radiograph	No infiltrates	No infiltrates		
Stool examination	No RBC, few or no WBC	5 WBC/HPF with diarrhea	< 5 WBC/HPF if diarrhea	
				Caretaker contactable telephonically

Abbreviations: WBC: white blood cells; RBC: red blood cells; HPF: high power field; I:T, immature: total.

Flow chart 1 Management of fever without focus in young children
(*Reproduced from Gupta P. Textbook of Pediatrics. New Delhi: CBS; 2013*)



*Determine risk based on history, examination, and laboratory studies:
Low-risk: Normal history and physical examination; WBC 5000–15000/mm^3; band cell < 1500/mm^3 urine pus cells < 10/hpf; stool pus cells < 5/hpf; normal chest radiograph; and CSF < 8 lymphocytes/mm^3.
$Other tests include WBC count; urine and stool microscopy; chest X-ray; CSF Gram stain.
Cultures include that of blood, urine, and CSF.

In well appearing infants a watchful observation without antibiotics may be planned and a sepsis screen obtained, although a lumbar puncture may be deferred. A mandatory follow-up after 24 hours must be ensured. Prior to initiation of antibiotics in the event of clinical deterioration, a lumbar puncture should always be done.

Fever without Localizing Signs in 3–36 Months Old Children

Viral infections are responsible for majority of children having nonlocalizing fever in this age group. Serious bacterial infection can also occur due to *S. pneumoniae*, *Neisseria*, and *H. influenzae*.

Risk factors for occult bacteremia in these children include rectal temperature > 39°C, WBC counts > 15000/mm^{3,} raised ESR, and elevated C-reactive protein. Rectal temperature > 40°C and WBC count > 25000/mm^3 indicate a higher probability of serious bacterial infection. Important bacterial infections include otitis media, pneumonia, sinusitis, enteritis, urinary tract infection, osteomyelitis and meningitis. Pneumococcal bacteremia can resolve spontaneously in about one-third of cases or can lead to development of localized infections, e.g., meningitis, pneumonia, cellulitis, pericarditis, osteomyelitis or septic arthritis. Management options are detailed in **Flow chart 1**. Infants with moderate to high risk factors should be treated with ceftriaxone (50–80 mg/kg/day in one or two divided doses IV or IM). In infants below 4 weeks of age, ampicillin (50–100 mg/kg/day IM or IV two divided doses) should also be added to cover *Listeria monocytogenes* and enterococci, which are not sensitive to ceftriaxone.

IN A NUTSHELL

1. Children presenting with fever without localizing signs carry high chances of occult bacteremia and serious bacterial infection (SBI).
2. Newborns or young infants with fever should be hospitalized and dehydration fever ruled out, before starting empirical therapy.
3. Well appearing, 1–3 months old febrile children should be categorized into low-risk and high-risk categories, based on certain criteria.
4. Empirical antibiotic therapy should be started in children at high-risk of serious bacterial infections/occult bacteremia.

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Chapter 28.4
Fever of Unknown Origin

Bhavna Dhingra, Piyush Gupta

Fever of unknown origin (FUO) is defined as fever (rectal temperature > 38°C) documented by a health-care personnel, for which no cause is identifiable after 3 weeks of outpatient evaluation and after 1 week of evaluation as an inpatient that includes a careful history and physical examination and initial laboratory assessment.

Nosocomial or health-care-associated FUO refers to hospitalized children receiving acute care in whom infection or fever were absent on admission but in whom a fever of 38°C or more occurs on several occasions, for at least a week.

Neutropenic FUO is defined as multiple readings of more than 38°C in a child with absolute neutrophil count less than 500/mm^3, after at least 3 days of investigations including at least 48 hours of incubation of cultures.

HIV-related FUO is defined as a temperature of more than or equal to 38°C on multiple occasions for more than or equal to 3 weeks as an outpatient and more than 1 week as an inpatient in a patient with confirmed HIV infection.

Fever of unknown origin needs to be differentiated from fever without localizing signs as their differential diagnoses and most frequent causes are distinct. Children with FWLS usually need immediate evaluation and empirical antibiotic therapy, whereas those with FUO generally do not need an emergency assessment and antibiotics. The major hurdle in establishing a diagnosis is that the salient features rendering specific disorders clinically recognizable are absent or subtle. There is no *one fits all* algorithm available for evaluation and the clinician needs to work-up each case on its own merit.

ETIOLOGY

Fever of unknown origin is usually an uncommon presentation of a common illness. Infectious diseases, connective tissue diseases and autoimmune disorders are the most common causes of FUO in children. Malignancies are responsible for a lesser number of cases as most children with malignancies present with other systemic signs or suggestive laboratory abnormalities. Drug fever, factitious fevers and periodic fever syndromes are responsible for a few cases of FUO. **Table 1** lists the common causes of FUO in children.

Epidemiologically relevant infections must be considered first in differential diagnosis and ruled out by appropriate clinical, laboratory and radiological evaluation. Hidden deep seated abscesses, e.g., pelvic, subdiaphragmatic, perinephric, subphrenic, psoas, retroperitoneal, mediastinal, dental, brain and hepatic should always be looked for and excluded. Subacute bacterial endocarditis should be high on the suspicion list especially in the setting of a pre-existing cardiac disease.

Nosocomial infections with unusual organisms, e.g., anaerobic bacilli should be considered in differential diagnosis of a patient having received various antibiotics, especially aminoglycosides, for several days in the hospital. Factitious fever should be considered, if fever persists for more than 6 months without diagnosis.

APPROACH TO DIAGNOSIS

Unless the child is acutely ill, the evaluation for FUO generally is done on an outpatient basis. If outpatient evaluation fails to disclose a cause for the fever, inpatient evaluation provides an opportunity to review the detailed history, physical examination, investigation reports and keep the child under close observation with an ongoing assessment to establish the cause of fever.

History

The history should include questions regarding characteristics of fever (onset, intensity, duration, frequency and pattern of fever). Intermittent fevers with a high spike and rapid defervescence suggest a pyogenic infection but can also be seen in tuberculosis, lymphoma, and connective tissue disorders. Remittent fevers are characterized by fluctuating peaks and a baseline that does not return to normal and are seen most commonly with viral infections, some bacterial infections (especially endocarditis), sarcoidosis, lymphoma, and atrial myxoma. Sustained fevers persist with little or no fluctuation but can appear to be intermittent if antipyretic agents are administered and are usually seen in enteric fever,

Table 1 Common causes of fever of unknown origin (FUO) in children

1.	*Infections* *Bacterial:* Tuberculosis, typhoid, paratyphoid, brucellosis, listeriosis, meningococcemia, yersiniosis, *Campylobacter*, relapsing fever, Lyme disease *Viral:* Infectious mononucleosis (Epstein-Barr-virus), human immunodeficiency virus (HIV)/AIDS, hepatitis, and cytomegalovirus (CMV) disease *Parasitic:* Malaria, kala-azar, amebic abscess, hepatic amebiasis, giardiasis, toxoplasmosis, trypanosomiasis, and visceral larva migrans *Rickettsia:* Scrub typhus, Q fever, Rocky mountain spotted fever *Fungal:* Disseminated candidiasis, histoplasmosis, aspergillosis, blastomycosis, disseminated coccidioidomycosis, and cryptococcosis
2.	*Connective tissue and autoimmune disorders:* Systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA), rheumatic fever, juvenile dermatomyosistis, chronic active hepatitis, polyarteritis nodosa, mixed connective tissue disorder, Behçet disease, and autoimmune thyroiditis
3.	*Hypersensitivity disorders:* Drug fever, serum sickness, hypersensitivity pneumonitis, and Weber-Christian disease
4.	*Malignancies:* Hodgkin disease, leukemia, lymphoma, inflammatory pseudotumors, pheochromocytoma, neuroblastoma, and Wilms tumor
5.	*Granulomatous disorders:* Sarcoidosis, granulomatous hepatitis, inflammatory bowel disease
6.	*Familial and hereditary syndromes:* Familial dysautonomia, familial Mediterranean fever, anhidrotic ectodermal dysplasia, Ichthyosis, and hypertriglyceridemia
7.	*Hematologic causes:* Hemophagocytic lymphohistiocytosis syndromes, cyclic neutropenias, immunodeficiency states, Kikuchi-Fujimoto disease, and Castleman disease
8.	*Endocrine causes:* Addison disease, thyrotoxicosis, hypothalamic central fever, and diabetes insipidus
9.	*Miscellaneous causes:* Factitious fevers, infantile cortical hyperostosis, pancreatitis, drug fevers, poisonings, thrombophlebitis, and pulmonary embolism

typhus, brucellosis, etc. Hodgkin disease has a typical *Pel-Ebstein* type of fever (3–10 day cycles of febrile and afebrile periods). Fever with chills and rigors suggest malaria, urinary tract infection, abscesses or nosocomial infections. Relapsing fever with periods during which patients are afebrile for one or more days between febrile episodes may be seen with malaria, rat-bite fever, *Borrelia* infection, and lymphoma.

The clinician needs to enquire about the way temperature was assessed-perceived manually or documented by a thermometer along with the site of documentation; localizing symptoms of fever; recent exposures like vaccination or animal/insect bites or receipt of any blood transfusion or biological products; exposure to a family member with fever or any infectious disease, past history of any significant illnesses such as tuberculosis, urinary infections, congenital heart disease, any surgical procedure; any history of travel in the recent past to specific disease endemic areas, history of exposure to any heavy metals or poisonous fumes and history of an underlying chronic disease and medication history. History of recurrent episodes of fever may give a clue to certain cyclic causes of fever, e.g., cyclic neutropenia, and may also be seen in immunodeficiency disorders, hyperimmunoglobulin D disease and central nervous system disorders of temperature regulation. Tick bites can lead to Rocky Mountain spotted fever, ehrlichiosis, tularemia, tick-borne relapsing fever, or Lyme disease. Ingestion of raw meat or raw shellfish may lead to brucellosis, toxoplasmosis, tularemia, or hepatitis. Familial Mediterranean fever is generally seen in Jewish, Turkish, and Arab populations. Familial dysautonomia is common in Ashkenazi Jews.

Examination

A detailed clinical examination, which needs to be repeated frequently, so as not to miss any subtle or evolving signs, remains the most important clinical tool for diagnosis. While examining the child, particular attention should be paid to evaluation of skin, fundus, throat, lymph nodes, genitalia and sinuses. Detailed eye inspection including that of cornea, conjunctiva, orbit, uveal tract and retina may point towards many infectious, collagen vascular, malignant or metabolic disorders. Absence of sweating during fever may be noted in anhidrotic ectodermal dysplasia and absence of malaise or other generalized signs in a child with a history of prolonged high fevers can signal factitious fever. Careful rectal, external genitalia, and pelvic examination (where indicated) should be performed.

Laboratory Tests

The laboratory and imaging evaluations for FUO should be directed toward the likely causes of fever based upon the patient's age, duration of fever, history and findings from the physical examination. Appropriate laboratory investigations such as complete blood counts with total leukocyte count, differential leukocyte count, erythrocyte sedimentation rate (ESR), peripheral blood smear examination for malaria and filariasis (night blood) are routinely performed. **Table 2** lists the various hematological abnormalities which may be an indicator of a specific disease condition. An elevated ESR more than 30 mm/hour suggests inflammation. ESR and C reactive protein (CRP) though nonspecific, can serve as prognostic markers and be used for monitoring purposes. Simple serological tests for typhoid, brucellosis, leishmaniasis, toxoplasmosis and amebiasis, and bacteriological culture of blood for *Salmonella and Brucella* should be undertaken.

Repeated microscopic examination and cultures of blood, urine, throat, sputum, and stool for bacterial and fungal infections should be carried out at periodic intervals. Sterile pyuria can be a clue to Kawasaki disease or genitourinary tuberculosis.

Table 2 Hematologic clues to specific disease states

Anemia	Malaria, Infective endocarditis, Inflammatory bowel disease, systemic lupus erythematosus, tuberculosis, etc.
Thrombocytosis	Kawasaki disease
Total white blood cell count >10,000/mm^3	Serious bacterial infection
Nonsegmented polymorphonuclear leukocytes > 500/mm^3	Serious bacterial infection
Eosinophilia	Parasitic, fungal, allergic or immunodeficiency states
Immature band forms	Leukemia
Activated lymphocytes	Viral Infection

Serum electrolytes, blood urea nitrogen (BUN), creatinine, and hepatic enzymes are obtained to evaluate renal and/or hepatic involvement. Hypernatremia may be seen in diabetes insipidus, elevated hepatic enzymes may be a clue to a viral infection.

Bone marrow examination can help in diagnosing leukemia, lymphoma, histiocytic disorders, and hemophagocytic syndromes. If specifically indicated, cultures of bone marrow, cerebrospinal fluid, gastric aspirate, lymph node aspirate and liver aspirate for aerobic and anaerobic bacteria, mycobacteria and fungi may prove to be invaluable. Serum antinuclear antibody should be obtained for children with a strong family history of rheumatic disease. Serum concentrations of immunoglobulins (IgG, IgA, and IgM) should be measured in children with evidence of recurrent or persistent fever and a negative initial evaluation. Hypogammaglobulinemia may indicate an immunodeficiency, while elevated levels may be seen in chronic infections, or autoimmune disorders. Serological tests should also be repeated to look for any rising antibody titers. Modern molecular diagnostic techniques; e.g., polymerase chain reaction (PCR) are now available for diagnosis of several infectious agents. A variety of immunological tests for detection of various autoantibodies is now available to rule out various autoimmune disorders.

Diagnostic imaging of the nasal sinuses, mastoids, chest and gastrointestinal (GI) tract by radiography, barium studies, ultrasonography, computerized tomographic (CT) scans and magnetic resonance imaging (MRI) as indicated, should initially be performed for specific indications, but may be done in children in whom FUO persists without a cause being established. Endoscopic evaluation of respiratory, genitourinary and gastrointestinal tract may help positron emission tomography (PET) scanning and immunoscintigraphy may be helpful in patients with persistent FUO who remain without a diagnosis after initial evaluation. Lymphangiography can be resorted to, for demonstrating retroperitoneal, iliac and periaortic lymph nodes. Biopsy (e.g., of lymph nodes, bone marrow or liver) should be reserved only for children with evidence of involvement of specific organs. If indicated, skin, pleura, muscle, kidneys, etc. can also be biopsied.

MANAGEMENT

Empirical treatment with anti-inflammatory agents (except for symptomatic relief in suspected JIA) or antibiotics should be avoided as they may mask the diagnosis or alter the course of certain conditions like infective endocarditis, meningitis or osteomyelitis and may also interfere with isolation of certain microorganisms on cultures. Disease specific appropriate interventions should be initiated soon after establishing the diagnosis.

IN A NUTSHELL

1. Fever of unknown origin (FUO) is defined as fever (rectal temperature > 38°C) documented by a health-care personnel, for which no cause is identifiable after 3 weeks of outpatient evaluation and after 1 week of evaluation as an inpatient.
2. A detailed clinical history and examination, repeated frequently, is crucial for diagnosis of FUO.
3. Infectious diseases, connective tissue diseases and autoimmune disorders are the most common causes of FUO in children.
4. Children with FUO generally do not need an emergency assessment or empirical anti-inflammatory agents and/or antibiotics.

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