Fever: Pathogenesis and Treatment

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11.1 Introduction

Pyrexia (fever) refers to an abnormal increase in temperature occurring under central nervous system control as a component of a co-ordinated biological response.

The average normal temperature is usually quoted as 37 °C (98.6 °F) [1, 2], a value arrived at following research conducted in the 1800s. Newer research involving oral measurement of temperature in young adults found the usual maximum average temperature reached 37.2 °C (98.9 °F) in the morning, and 37.7 °C (99.9 °F) during the day as a whole [3]. Patients' age, the time of day, how active they are and (for women) where within the menstrual cycle, and certain other variables, all affect the normal temperature [3, 4].

The average body temperature is higher in infants and young children than in other people, a situation attributable to infants' and young children's relatively higher ratio of surface area to mass and more active metabolism. In neonates (i.e. aged 28 days or less) the average normal temperature (via rectal thermometer) is 37.5 °C. The maximum normal temperature is 38 °C (100.4 °F), allowing for two standard deviations from the mean [5].

There is variation in the normal body temperature throughout the day. The temperature is lowest in the morning and highest in the afternoon or early evening. On average, this variation is 0.5 °C (0.9 °F) [6]. During a pyrexial illness, this variation

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continues, although the baseline temperature is elevated. Diurnal temperature varies by up to 1 °C (1.8 °F) in certain cases where a pyrexial episode is resolving [1].

Since a raised body temperature may result from either pyrexia, in which the temperature rises in accordance with a change in hypothalamic thermoregulation, or hyperthermia, where the raised temperature is not accompanied by a hypothalamic thermostatic change, distinguishing between the two situations is key to understanding the pathophysiology and treating the cause [1].

11.2 Definition of Fever

Pyrexia (fever) refers to an abnormal increase in temperature occurring under central nervous system control as a component of a co-ordinated biological response. What constitutes an abnormal temperature varies according to age in children and where the temperature is recorded. The decision to search for an infective focus is informed by how old the child is and elements of the clinical presentation (such as immunodeficiency, sickle cell disorders and how grave the illness appears, amongst other factors). In the majority of cases, the degree of temperature elevation is less significant than other markers of disease severity such as irritability and meningismus [7–10].

11.2.1 Hyperthermia

Hyperthermia refers to an abnormally raised temperature that is not the result of resetting hypothalamic temperature regulation. This homeostatic dysequilibrium occurs because heat is generated more rapidly than it can be dissipated [11]. Antifever agents have no effect upon hyperthermia.

11.3 Pathogenesis

Pyrexia is the end result of an orchestrated physiological process initiated by production and secretion of the chemical mediators interleukin-1 (IL-1), IL-6, TNF, interferon-α, and other fever-promoting cytokines released by phagocytes, both in the circulation and within tissues [12]. Cytokines within the circulation reach the anterior hypothalamus, where they trigger a rapid elevation in the production of prostaglandins, notably PGE2 (prostaglandin E2). It is PGE2 which induces a higher set-point for thermoregulation.

Once the body thermostat has been reset to a higher temperature, the thermoregulatory centre sets off sequences of changes with the aim of raising body temperature to the desired level. The changes result in greater heat generation through raising metabolic activity, muscular tone and action, whilst reducing dissipation of heat by shunting blood from the skin to the deeper body structures. The temperature keeps on going up until the desired temperature is reached, after which a new

equilibrium is established. Pyrexia does not appear to generate a maximal temperature exceeding 42 °C (107.6 °F), and indeed temperatures above 41 °C (106 °F) are seldom seen unless hyperthermia is also present [3, 13, 14].

Pyrogenic cytokines, as well as provoking pyrexia, cause increased hepatic production of acute phase proteins, lower the iron and zinc level of the blood, cause recruitment of leucocytes and speed up the degradation of protein within voluntary muscle. IL-1 can bring on the slow-wave phase of sleep, which may account for the tendency to sleepiness in patients who are pyrexial. Similarly, PGE2 may be responsible for muscular and joint pains which are a frequent accompaniment to pyrexia. The cardiac rate rises to accommodate the greater metabolic demands of pyrexia [1].

The hypothalamic thermoregulatory centre controls the body temperature. Heat is generally produced by hepatic and muscular metabolism, and lost via the skin and lungs. Typically, the hypothalamus keeps the body temperature within relatively strict limits if there are not extreme environmental influences to contend with. Once the temperature of the environment exceeds around 35 °C (95 °F), heat can no longer be lost and the body temperature inevitably increases [1].

11.4 Aetiology

Pyrexia indicates the presence of disease and the reason for it needs to be investigated, especially should a child appear unwell or the pyrexia persistent. The effectiveness of antipyretic treatment has no value in discriminating infection due to bacteria from those due to viruses [15–17].

11.4.1 Neonates

Neonates (i.e. below the age of 28 days) may present with pyrexia but without clear indications in the history or on examination as to likely cause. Despite this, 3% of such cases have a grave bacterial infection. It is vital to gain a clear patient account from the child's mother about the pregnancy, delivery and life up to then of the neonate. An infection within the first week of life is usually transmitted from the mother, whilst after that point, the infection is generally from either the community or hospital environments. To be sure of the details of a grave bacterial infection, laboratory assistance is needed. The patient must be fully investigated for sepsis, including blood culture, CSF +/− urine sampling. The peak occurrence of bacterial meningitis is at age 1 month or younger. It is thought that between 5% and 10% of neonates who test positive for Group B streptococci (GBS) also have meningitis [18, 19].

11.4.2 Young Infants

Managing pyrexia in an infant between 28 and 60 days old involves remaining highly alert to possible sources of infection, since physical examination often

appears normal. In infants below the age of 3 months, a severe bacterial infection is seen in around 6–10% of cases, usually the result of urinary tract infection (UTI). Somewhat surprisingly, if a child aged below 3 months is found to have a definite viral infection, the chance that a severe bacterial infection is also present decreases compared to those without a viral infection [20]. However, infants suffering from bronchiolitis often have a UTI, too [18].

11.4.3 Children Aged Between 3 Months and 3 Years

The Agency of Health Care Policy and Research issued guidelines in 2012 [21], according to which, a rectal temperature of at least 38° in a child aged below 3 months is associated with a risk between 4.1% and 25.1% of a severe bacterial infection. These data were obtained in accident and emergency departments or primary care settings in North America.

In the past, 2–4% of patients aged between 3 and 36 months whose rectally recorded temperature was at least 38.5 °C were harbouring an occult blood-borne bacterial infection [22]. The principal pathogen was *Streptococcus pneumoniae*, with *Haemophilus influenzae* type b the second most likely cause. Vaccination has achieved great success against these organisms, with the result that only 0.5% (i.e. 1 in 200) children with pyrexia, who are otherwise immune competent, now harbour bacteria in the blood [23, 24].

Currently, occult bacterial infection of the blood is only seen in between 0.25 and 0.7% of such children, and two thirds of apparent bacteraemias are actually false positives, as a result of contamination [23–26]. The most frequent bacteria responsible (representing 2 out of 3 cases) are pneumococci or *Escherichia coli*. It is common that infants with a pneumococcal infection harbour bacterial strains of a type to which the conjugated vaccine, which targets seven different bacterial sugars, does not confer immunity [18].

Blood-borne infection by *S. pneumoniae* may appear as acute otitis media, pneumonia, sinusitis, meningitis, pyrexia-related convulsion, soft tissue infection (sometimes affecting the orbit or face), or have other features of pyrexia that do not point to a particular diagnosis. Infection with *E. coli* is usually seen in a child aged under one year and typically together with a urinary tract infection (UTI). 15% of blood-borne infections are secondary to *Staphylococcus aureus*, occurring in association with cellulitis, skin or musculoskeletal infection. The bulk of the other cases are due to Salmonella spp., *Neisseria meningitidis* or *Streptococcus pyogenes* [18].

11.5 History and Examination in Children

11.5.1 Neonates

It is vital to obtain a full history for any neonate suffering from pyrexia. The pattern of symptoms may point to an infective focus (e.g. diarrhoea, coughing) or be more

general (e.g. not feeding, being irritable, lethargy). 20–50% of neonates with meningitis have a convulsion. It needs to be established if there is anyone in contact with the child who is already sick (either at home or elsewhere), if any illness has recently occurred, any vaccination has been administered and whether antibiotics have been prescribed around the time of birth or afterwards [18].

11.5.2 Prenatal History

The pregnancy history should be reviewed, encompassing any sexually transmitted infection, such as HIV, hepatitis B or C, treponemal infection, gonorrhoea, chlamydia or herpes simplex. The mother's GBS status should be reviewed, together with any precautions taken, how the delivery occurred, if the membranes were ruptured long before birth and whether the mother suffered from any pyrexial episode.

The following are risk factors for a severe bacterial infection: a neonate weighing below 2500 g at delivery, premature rupture of the membranes, sepsis or trauma during delivery, hypoxia in the foetus, the mother having an infection around the time of birth, and galactosaemia. Gestational age needs to be calculated, since prematurity heightens the risk of a severe bacterial infection [18].

11.5.3 Household Contacts

Any family members suffering from illness need to be recorded. If the patient has been in contact with animals at home or elsewhere (such as at a nursery), this should also be ascertained. The vaccination histories of others living in the house should be documented. If another pregnancy has been lost or a baby has previously died due to an infectious disease, then a congenital anomaly or primary immunodeficiency syndrome will need to be excluded as the cause [18].

11.5.4 Review of Systems and Physical Examination

All body systems need to be carefully reviewed for symptoms to pick up any clues about the origin of pyrexia. Patients should be completely examined and vital signs noted. Oximetry should be performed, and growth checked, with the various parameters assigned to the appropriate percentile. On general examination, note how active the child is, whether skin changes are present, muscular tone, and signs of irritability. Look for a focus of infection by checking the skin, mucosal membranes, ears and limbs.

If the umbilicus persists as a stump after 4 weeks age, this can indicate a white cell adhesive deficiency syndrome. Uncircumcised boys are at greater risk of a UTI. Aside from pyrexia, it is frequent for UTI in neonates to present as failure to thrive, icterus (usually a result of a conjugated hyperbilirubinaemia secondary to cholestasis), and vomiting. The following also may indicate a severe infective

episode in a neonate: being irritability, not responding to soothing, inadequate skin perfusion, lack of tone, moving less than usual, and becoming lethargic [18].

11.5.5 History and Examination in Young Infants

As with a neonate, pyrexia in an infant may be reflected in symptoms pointing to an infective focus (diarrhoea or coughing) or be more general (e.g. not feeding, being irritable, lethargy). Identify if the infant has been in contact with anyone else suffering from illness at home or outside, such as at a nursery. Recent illness, vaccinations administered and any antimicrobial therapy all need to be noted [18].

11.5.5.1 Past Medical History and Household Contacts

In essence, the history to be obtained for an infant does not differ from that for a neonate. The history should include the pregnancy, delivery and early life. Note any other medical problems and any medication being used that might render an infection more likely. Additionally, note details of the diet and how well and long the child sleeps, as you would with any neonate. Eating less or sudden alterations in how sleep occurs may point towards a systemic infection.

If another pregnancy has been lost or a baby has previously died due to an infectious disease, then a congenital anomaly or primary immunodeficiency syndrome will need to be excluded as the cause, as is the case with neonates. It is important to establish who lives with the child and who is the main carer. Being in contact with new arrivals from overseas, and being homeless or poor are important factors to consider in assessing risk of infective illness and treating the case [18].

11.5.5.2 Review of Systems and Physical Examination

All body systems need to be carefully reviewed for symptoms to pick up any clues about the origin of pyrexia. Patients should be completely examined and vital signs noted. Oximetry should be performed, and growth checked, with the various parameters assigned to the appropriate percentile. Tachycardia (>160 bpm in infants) and tachypnoea (>60.min^{-1}) increase the risk of death occurring and are frequently associated with the onset of septic shock [18].

11.5.6 History and Examination in Children Aged Between 3 Months and 3 Years

History taking needs to concentrate on factors that put an infant or toddler at higher risk of severe bacterial infection.

11.5.6.1 History of Presenting Complaint

It is vital to record the patient's temperature and the measurement method employed. A rectally recorded temperature exceeding 38.5 °C (101 °F) indicates abnormality in a child of this age. As well as recording the temporal onset and duration of

pyrexia, any other symptoms need to be carefully enquired after. The following is a non-exhaustive list of other symptoms to consider: loose stools, vomiting, nasal discharge, coughing, skin exanthem, and alteration in weight or eating habits [18].

11.5.6.2 Past Medical History

Search exhaustively for any evidence of prior infections and risk factors predisposing to severe infections by bacteria. Underlying chronic diseases, prior surgical operations, previous urinary tract infections (UTIs), and incomplete courses of pneumococcal or hib vaccinations should particularly be asked about. In patients aged under 9 months, the neonatal and perinatal history is of especial significance [18].

11.5.6.3 Family History

If siblings or first cousins are subject to recurrent infective episodes or the mother supplies a history of miscarriage, this should alert the clinician to the possibility of a primary immunodeficiency. It is vital to learn the human immunodeficiency virus (HIV) status of the parents. If immediate or more distant blood relatives are subject to chronic infections (such as hepatitis B or C, or tuberculosis), this is also of diagnostic significance. Acute infections in family members, e.g. croup or respiratory infections, is similarly an important point to consider [18].

11.5.6.4 Social History and Household Contacts

Assess whether the child has been exposed to animals, insects or woodland environments. Has the child been near dirty drinking water or sewage? Has he/she been travelling, especially if overseas? Does the child attend a nursery? This type of question will provide vital information which may say something about a possible epidemiological or environmental cause. Being in contact with ill individuals beyond the usual family members may also offer invaluable evidence [18].

11.5.6.5 Review of Systems and Physical Examination

Asking questions about all the body systems can reveal clues that point to the origin of pyrexia. The following are especially useful in pinpointing a focus: exanthems, conjunctivitis, otalgia and otorrhoea, swollen and tender lymph glands, symptoms related to breathing, alteration in appetite, weight loss, loose stools, vomiting, alteration in how often urine is passed and whether dysuria occurs, inability to bear weight, limbs that hurt when someone else moves them, and symptoms of clear neurological origin.

In a child between 3 and 36 months old with pyrexia, the following features of the physical examination are consistent with a severe bacterial infection: appearing ill, pyrexia, vomiting, abnormally raised respiratory rate with chest retraction and slow capillary refill. These appearances are seen in cases of bacterial infection in over 39.5% of those aged 2 to 3 years and in above 39% of those aged 3–24 months.

The cutaneous system, lymph glands, eyes, ears, nose, and pharynx all need to be carefully inspected, since a viral infection is associated with an exanthem or breathing difficulties in a great many infants. The chest must be inspected and auscultated

as an invariable part of the physical examination. Inspect the abdomen to see if it is distended. Ileus or excessive intestinal activity may be apparent at auscultation. Check the capillary refill time in the fingers and toes. Check how far the joints move, look for signs of infection, and assess if there is tenderness in any particular area. Depending on the age of the patient, a neurological and developmental examination should be carried out [18].

11.6 Differential Diagnosis [18]

- Bacteraemia.
- Neonatal sepsis.
- Meningitis due to bacterial infection.
- Infection due to *E. coli.*
- Infection due to *H. influenzae.*
- Meningitis and Encephalitis.
- Bacteraemia due to *S. pneumoniae.*
- Urinary tract infection.
- Infection due to *S. aureus.*
- Infection due to Group B Streptococcus (GBS).

11.7 Diagnostic Studies

Markers of low risk are well established for a child older than 28 days. The reference range for leucocytes is 5000–15,000 cells/μL. There should be fewer than 1500 band cells/μL. Nonetheless, leucocyte count on its own is neither sensitive nor specific for bacteraemia or meningitis in young children and should not be relied on, without also carrying out a full sepsis screen [18].

11.7.1 Urine and Stool Studies

Given the fact that urinary tract infections (UTIs) are common in children of this age, urine should be collected for urinalysis and culture. In a single study, pyuria was evident in just 20% of infants with pyrexia who were found to have pyelonephritis. Urine for culture must be aspirated suprapubically or by inserting a catheter in the urethra, as urine from a collecting bag usually contains contaminating organisms [18].

11.7.2 Pulmonary Studies

If an infant presents with evidence of respiratory distress, for example, coughing, cold, abnormally raised respiratory rate, rales, rhonchi, chest retraction, grunting,

flared nostrils, or wheeze, chest X-ray may be needed. At appropriate times of the year, an identification of the viral pathogen should be attempted via direct fluorescent antigen (DFA) testing or viral DNA polymerase chain reaction (PCR) and viral culture of nasal lavage fluid [18].

11.8 Treatment

Pyrexia represents an appropriate biological response rather than a pathological process. If a child has no other health problem, the majority of pyrexial illnesses are not severe, and require no intervention, as long as the aetiology is clear and fluid levels are maintained. Pyrexia alone is not responsible for brain insults. Clinical intervention is warranted if signs of a severe kind are present. It may be appropriate to initiate an antipyretic if a child is distressed (as indicated by reduced activity, a drop in volume of drinks consumed, etc). Whether an antipyretic drug lowers the body temperature or not reveals nothing about the likely bacterial or viral nature of an infection. There is no need to waken a sleeping child merely to administer an antipyretic [1].

The correct dose of an antipyretic agent depends on weight, not patient age. If prescribing an antipyretic for use with a child, the dose will be more accurate if written guidance is given and an accurately marked syringe supplied for liquid preparations. Relying on the instructions and equipment supplied with OTC preparations to ensure correct dosing is unwise given the wide margin of error using such equipment involves [27].

11.8.1 Antipyretic Agents

Anti-fever agents resolve pyrexia by resetting the hypothalamic set-point within normal bounds. The two most frequently encountered anti-fever agents in paediatric practice are paracetamol and ibuprofen. Since aspirin has an association with Reye syndrome, it is contraindicated in children [11].

11.8.1.1 Indications

Therapeutic interventions in children with pyrexia are individually tailored to suit the clinical presentation, in particular the likely cause, level of distress and need to investigate the pattern of pyrexia seen [1].

It is appropriate to treat pyrexia in the short term in cases such as the following [3, 14]:

- Shock.
- Underlying disease of the nervous, circulatory or respiratory system, or any disorder resulting in raised metabolic demand (e.g. following burns injury, or post-surgery).
- Fluid and electrolyte not in equilibrium.

- High fever (i.e. ≥40 °C (104 °F)).
- Distress.
- Significant cerebral injury.
- Following a cardiac arrest.

11.8.1.2 Paracetamol

The author recommends paracetamol in the majority of paediatric cases of pyrexia that require treatment. This is due to the agent's well-established safety, provided the dose is not exceeded [3].

It is not usually advisable to use paracetamol in children less than 3 months old, except under medical supervision, as pyrexia may be the sole indicator of a grave infection. The dosage of paracetamol is 10–15 mg/kg per dose (maximum dosage 1 g) by mouth every four to 6 h (with no more than five doses in any 24-hour period). The maximum daily dose is 75 mg/kg per day up to a total of 4 g/day. Some paracetamol preparations recommend lower amounts. The author does not suggest routine use of a loading dose (which would be 30 mg/kg), as it may complicate further dosing and lead to error [11].

The temperature falls by 1 or 2 degrees Celsius (1.8 to 3.6 Fahrenheit) in around 80% of paediatric cases of pyrexia [11, 28]. The onset of therapeutic action is within 30–60 min, with peak effect after 3 or 4 h. Therapeutic effects last between 4 and 6 h [1].

11.8.1.3 Ibuprofen

Ibuprofen is recommended as first-line treatment in any child aged over 6 months in whom an antipyretic and anti-inflammatory action is needed. Such is the case in, e.g. juvenile arthritis. Children receiving Ibuprofen should have adequate hydration [3].

The dosage of ibuprofen is 10 mg/kg per dose (with a maximum dose of 600 mg) by mouth every 6 h. Daily, the maximum daily dose is 40 mg/kg up to a total of 2.4 g [11]. The onset of therapeutic action is within 60 minutes, with the maximum effect (a fall in temperature of between 1 and 2 °C (1.8–3.6 °F)) occurring within 3 to 4 h. Therapeutic effects last 6–8 h [11, 28].

11.8.2 External Cooling

External cooling is the best way to counter heat stroke and other forms of heat-related illness, since lowering the body temperature swiftly is needed if end-organ damage is to be avoided. External cooling is not proposed to lower body temperature in infants and children with pyrexia but who are otherwise healthy. Studies where patients were randomised to receive either tepid sponging and antipyretic therapy together or antipyretic therapy only, the additional advantage of tepid sponging in lowering the body temperature was brief in duration, and sponging brought with it a higher degree of discomfort [29–31].

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