

Peculiarities of the Pathogenesis of Fever in Childhood

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Abstract

Fever is one of the most common symptoms of childhood illnesses and the most common chief complaint in pediatric outpatient departments, especially in emergency departments. Fever is an increase in the hypothalamic set point temperature caused by various pathogenic factors, resulting in an abnormal increase in body temperature [1]. Acute fever (<1 week) and fever of unknown origin (FUO, inability to establish a diagnosis after 1 week of inpatient investigations) are types of fever [2]. Pediatricians are especially vigilant for high fever in children (axillary temperature up to 103.5 °F (39.5 °C)) which is more likely to cause serious adverse outcomes such as childhood pneumonia and febrile seizures.

Keywords: pathogenesis; fever; childhood

Introduction

Fever is one of the most common symptoms of childhood illnesses and the most common chief complaint in pediatric outpatient departments, especially in emergency departments. Fever is an increase in the hypothalamic set point temperature caused by various pathogenic factors, resulting in an abnormal increase in body temperature [1]. Acute fever (<1 week) and fever of unknown origin (FUO, inability to establish a diagnosis after 1 week of inpatient investigations) are types of fever [2]. Pediatricians are especially vigilant for high fever in children (axillary temperature up to 103.5 °F (39.5 °C)) which is more likely to cause serious adverse outcomes such as childhood pneumonia and febrile seizures. In addition, fever is one of the main symptoms of coronavirus disease 2019 (COVID-19), which has gradually attracted global attention. However, fever in children often causes anxiety and fear among parents and health care providers, which is called "fever phobia" [3]. During fever, children will be awakened and examined, and they will be given antipyretic drugs, antipyretic needles, external cooling, or even unjustified hormonal drugs without diagnosis. Reducing the temperature of children is not the only goal of pediatricians when they have fever. The main goal of antipyretic treatment is to restore children's comfort [4]. Therefore, it is very important to clarify the current situation of fever control and medication in children, and adopt accurate diagnostic tools and safe therapeutic agents for the diagnosis, treatment, and prognosis of febrile children. The distinctive physiological functions and additional needs of the target group of children are significantly different from those of adults, which makes it difficult to develop pediatric drugs [5]. In the past, the lack of pediatric-appropriate formulas on the market led to off-label drug use and the splitting of commercial adult tablets, resulting in unstable dosages for children. The same problem has arisen with pediatric antipyretic drugs.

Administration of medications divided into small doses and swallowed or crushed into powder and mixed with fruit juice has become the "common method" for children. Uneven tablet splitting can lead to significant variations in the administered dose. Furthermore, some prescription instructions for children do not specify the exact dose [6] or the instructions do not comply with expert consensus. The dosage of acetaminophen (paracetamol) tablets is 0.5-1 tablet at a time for children aged six years and older, which can lead to tablet splitting and inconsistent dosing. Similarly, palatability is a determinant of patient acceptability of dosage forms and compliance, especially in children. Splitting of adult dosage forms can lead to bitterness and discomfort. Although palatability is not the only factor influencing drug acceptance, inappropriate pharmaceuticals are frequently cited as a leading cause of treatment failure in young children [7].

In addition, some pharmaceutical institutions have been hesitant to conduct studies to obtain new information on labeling or dosage forms for children due to high costs, low profits, and problems with clinical trials, reflecting the neglect of clinical drugs in the pediatric population [8].

Classification of fever

Fever can be broadly classified as acute, subacute, and chronic based on their duration. Acute fevers (<7 days in duration) are typical of infectious diseases such as malaria and viral upper respiratory tract infections, while subacute fevers (usually <2 weeks in duration) may be seen in cases of typhoid fever and intra-abdominal abscess, among others [9]. Chronic or persistent fevers (>2 weeks in duration) are typical of chronic bacterial infections such as tuberculosis, viral infections such as HIV, cancer, and

connective tissue diseases [9]. However, any cause of acute fever can become persistent or chronic if left untreated.

Temperature threshold for antipyretic treatment: evidence versus clinical practice

Most clinical guidelines recommend against treating fever per se, regardless of temperature. Guidelines that set a threshold for antipyretic therapy show little agreement on temperature, with values ranging from 37.5°C to 40.5°C, and no rationale is provided. The need for a threshold remains unclear because adequate research is lacking. Although most guidelines recommend against giving antipyretics based on body temperature, surveys of health care workers have shown that most believe the risk of adverse heat-related outcomes increases at temperatures above 40°C (104°F), and that more than 90% of physicians prescribe antipyretic therapy for temperatures >39°C [10, 11]. Even in the UK, a country with long-standing guidelines that recommend only treating distress, a large study of paediatric intensive care units found that the threshold for treating fever was still 38°C, and 58% of healthcare workers surveyed considered a temperature of 39°C unacceptable [12].

Pathophysiology of the febrile response

The development of the febrile response is similar to the normal thermoregulatory processes that follow exposure to cold temperatures. However, in fever, the heat balance point is reset to a higher level such that normal peripheral and central body temperatures are now perceived as cold temperature signals by the thermoregulatory circuitry [13] [14] [15] [16]. Therefore, fever is distinct from heat stroke and hyperthermia, in which body temperature increases without a corresponding increase in the heat balance point. Similar to thermoregulation, evolving evidence suggests that the onset of fever follows multiple independent afferent and efferent mechanisms depending on the site, nature, and severity of inflammation. The various biological molecules involved in the onset of the febrile response and the pathways involved in these responses are discussed in the next section. The initiation, manifestations, and regulation of the febrile response depend on the pyrogenic and antipyretic properties of various exogenous and endogenous substances [13] [17] [18]. While pyrogens directly or indirectly cause fever, cryogens prevent excessive temperature rise.

Mechanisms underlying fever

The mechanisms underlying the specificity of fever patterns to certain diseases are not fully understood. For some infectious diseases, it may be related to the life cycle of the pathogen. For example, in malaria, parasites enter the bloodstream 48-72 h into the erythrocyte cycle of *Plasmodium falciparum/ovale/vivax*. The released parasites activate pyrogenic cytokines, which then lead to fever cycles every 48-72 h (tertian fever) [19]. However, *Plasmodium falciparum*, unlike other species, can infect multiple erythrocytes in a non-selective manner, each with independent erythrocyte parasite life cycles [19]. Consequently, fever caused by this parasite is often diurnal (daily fever spikes) [20]. *Plasmodium vivax/ovale* and *P. malariae* infect young and senescent red blood cells, which rupture to release pyrogens after 72 and 96 hours, respectively. These events partly explain the cyclic nature of fever in these malarial fevers. Downregulation of cytokine release after repeated exposure to pyrogens such as LPS may result in remission or intermittency of fever [21]. Recurrent fevers may be caused by partial healing of deep-seated infections such as abscesses or by repeated exposure to new antigens (eg, allergens in hypersensitivity pneumonitis) [22]. Such drugs (allergens) may manifest as eosinophilia in patients with drug-induced fever. In cyclic neutropenic fevers, febrile episodes correspond to periods of neutropenia and are caused by repeated bacterial infections [23]. In cancer

and pulmonary embolism, recurrent fever is partly explained by tissue necrosis, since phagocytosis of necrotic tissue results in the periodic release of pyrogenic cytokines [22]. Recurrent fevers may be related to the pathogenesis of the disease, as demonstrated by relapsing fevers caused by spirochetes, where episodic spirochetemia results in episodes of fever followed by afebrile periods, coinciding with the disappearance of the spirochetes from the circulation [24]. Night sweats are common in healthy adults, but they become clinically significant when associated with fever and exposure to moisture [25]. They may be explained by the pyrogenic properties of certain diseases, which result in early morning fever spikes followed by remission of fever a few hours later, manifesting as night sweats [25].

The role of pyrogens

Pyrogens are classified into exogenous (produced outside the host) and endogenous (produced within the host) pyrogens based on their site of production. Exogenous pyrogens are essentially parts or whole microorganisms or microbial products such as toxins. The cell wall component of Gram-negative bacteria, lipopolysaccharide (LPS), remains the most widely studied exogenous pyrogen, and most current data on febrile response are based on studies using LPS as the pyrogenic agent. Other clinically important endogenous pyrogens include muramyl dipeptidase, a component of cell walled organisms, and the enterotoxins of *Staphylococcus aureus* and groups A and B *Streptococcus*, collectively referred to as superantigens [26], [27]. Endogenous pyrogens are mainly pyrogenic cytokines including interleukins: IL-6, IL-1, interferon gamma (IFN- γ) and ciliary neurotropic factor (CNTF) and tumor necrosis factor (TNF α) and others [26], [27]. However, TNF α has both pyrogenic and antipyretic effects depending on the experimental conditions [28]. Endogenous pyrogens are produced by immune cells such as neutrophils, macrophages and lymphocytes, as well as endothelial cells, astrocytes and glial cells in response to exposure to exogenous pyrogens. Some endogenous substances such as antigen-antibody complexes, inflammatory bile acids, complements and various lymphocyte-derived molecules can, however, serve as pyrogens without induction by exogenous pyrogens [26].

Paths of fever

Fever signals carried by exogenous and endogenous pyrogens ultimately lead to resetting of the thermoregulatory circuitry via two main pathways, namely humoral and neural.

Humoral pathway

In this pathway, fever signals are carried by components of microbial products called pathogen-associated molecular patterns (PAMPs) or pyrogenic cytokines. Circulating microbial PAMPs, typified by gram-negative LPS, are known to bind toll-like receptors 4 (TLR-4) on various cells [22]. By binding to and activating TLR-4 located on the fenestrated capillaries of the circumventricular organ in the blood-brain barrier, they lead to the release of prostaglandin E2 (PGE2) from the arachidonic acid pathway in the cytoplasmic membranes [29], [30], [31]. Prostaglandin E2 is a small molecule that readily diffuses across the blood-brain barrier, binds to specific PGE2 receptors (EP3 receptor) in the preoptic area, and then activates warm neurons in the anterior hypothalamus to a higher warm balance point [32], [29], [30], [31]. It is unclear whether microbial products also increase the warm balance point by gaining direct access to the brain through disruption of the BBS. The febrile response is characterized by an early rapid phase and a delayed late phase. Based on studies in animal models of LPS-induced polyphasic fever, the first phase of this febrile response is thought to be dependent on PGE2 synthesized in the liver and lungs before migrating to

the brain, whereas the latter phases are mediated by centrally synthesized PGE₂ [33], [34]. Therefore, while peripherally synthesized PGE₂ may act to initiate the febrile response, centrally synthesized PGE₂ may be largely involved in its maintenance.

The second humoral pathway is driven by circulating pyrogenic cytokines. They transmit fever signals to the thermoregulatory circuitry by both indirect and direct pathways. In the indirect pathway, pyrogenic cytokines act outside the brain by binding to and activating cytokine receptors located on the fenestrated capillaries of the circumventricular organ, resulting in the release of PGE₂ [32], [35], [36]. In the direct pathway, circulating cytokines breach the blood-brain barrier, gaining direct access to cytokine receptors expressed on vascular, glial, and neuronal structures of the brain [36]. Activation of these central receptors stimulates further PGE₂ synthesis or again promotes the synthesis of more cytokines by the brain. Although PGE₂ remains essential in the febrile response, some cytokines and many other inflammatory mediators can activate the febrile response independently of PGE₂ [37]. Direct PGE₂-independent activation of warm neurons by cytokines may be responsible for the hyperpyrexia observed in CNS infections and hemorrhages, the latter also called central fever [35]. Under these conditions, the antipyretic properties of the CNS are impaired, leading to an unregulated increase in body temperature. Examples of non-PGE₂ inflammatory mediators that can reset the heat balance point independently of PGE₂ include bradykinin, corticotropin-releasing hormone, nitric oxide, MIP-1, IL-6 and IL-8, preformed pyrogen factors (PFPF), substance P, and endothelin-1 [37].

Neural Pathway

Peripheral fever signals can communicate with the CNS via peripheral nerves such as cutaneous sensory nerves and the vagus nerve. Activation of the neural pathway is thought to be another mechanism by which fever is rapidly initiated [38], [39], [40]. It has been proposed that localized production of PGE₂ at sites of inflammation promotes fever by activating cold-sensitive cutaneous nerves, which in turn transmit fever signals to parts of the brain responsible for fever generation [41]. Fever signaling via the vagus nerve follows a more complex pathway. Circulating pyrogens such as LPS activate complement, and complement products in turn stimulate hepatic Kupffer cells to produce endogenous mediators including pyrogenic cytokines. These cytokines activate the hepatic branch of the vagus nerve, which then transmits fever signals to the central projection area of the vagus nerve in the nucleus of the solitary tract (NST). From the NST, the signal passes to the preoptic and hypothalamic areas via the ventral noradrenergic bundle, causing intrapreoptic release of norepinephrine [38], [40].

Norepinephrine mediates the vagal pathway, causing a distinct increase in core temperature. The first of these is mediated by alpha(1)-adrenergic receptors (ARs), is rapid in onset, and is independent of PGE₂, whereas the second is mediated by alpha(2)-ARs, is delayed, and is dependent on PGE₂ [38], [40]. The role of vagal afferents in fever generation was based on experimental studies in rats, which showed that surgical vagotomy resulted in attenuation or complete cessation of febrile responses to pyrogenic cues [38], [39]. However, more recent studies have challenged this view, attributing the lack of febrile response to pyrogenic cues to side effects of vagotomy, such as malnutrition [42], [43]. Experimental studies in rats show that, while such side effects of vagotomy are avoided, total or partial vagotomy does not abolish the febrile response to pyrogenic cues, such as intravenous PGE₂ [42].

Fever with lymphadenopathy

It is a common clinical syndrome in children as it is often associated with upper respiratory tract infections. An estimated 38-45% of healthy children have cervical lymphadenopathy [44]. The threshold for lymph node enlargement varies among lymph node groups and ages. The normal lymph node size in neonates is < 1 cm in diameter. In older children, inguinal, epitrochlear, and other site nodes are < 1.5 cm, < 0.5 cm, and < 1 cm in diameter, respectively. In the strictest sense, lymphadenitis refers to enlarged lymph nodes with inflammation, but is commonly used interchangeably with lymphadenopathy. It is important to distinguish children who require detailed evaluation for lymphadenopathy as 67% of cases are caused by minor viral, bacterial, or reactive lymphadenitis [44]. Infections at lymphatic drainage sites should be carefully sought. The presence of associated symptoms such as persistent fever, weight loss, evidence of bleeding, night sweats, as well as features such as size, consistency, fixation to deeper tissues, tenderness of the lymph nodes and/or associated organomegaly, etc., will help to identify the subgroup of children who require evaluation. The approach to fever with lymphadenopathy can be based on generalized (enlargement of two or more non-contiguous groups) or localized/regional lymphadenopathy. Children with localized or regional lymphadenopathy can be further subdivided based on the duration of illness into acute (7 days) and subacute or chronic (>1 week). Acute cervical lymphadenitis may accompany pharyngitis, such as viral or bacterial infections. Nasopharyngeal or throat swab culture/PCR may help identify common viruses associated with pharyngitis such as adenovirus, coxsackie, influenza, Epstein-Barr virus (EBV), etc., and bacteria such as *Streptococcus pyogenes*. Cervical lymphadenitis without pharyngitis may be seen in infections caused by *Staphylococcus aureus*, anaerobes, *Yersinia pestis*, melioidosis, and syphilis. It is advisable to examine the lymph node drainage area for signs of infection such as dental caries, skin and soft tissue infections of the head and neck, or abscesses involving the salivary glands, oral cavity, retro- and parapharyngeal spaces. Diagnostic imaging may be helpful, and specific diagnoses can be made by fine-needle aspiration cytology (FNAC)/node biopsy and aspirate culture.

Most lymphadenopathies are caused by benign, self-limited diseases such as viral or bacterial infections. In addition, lymph nodes <1 cm are usually present in most children even without any disease. Therefore, evaluation and additional studies are indicated only in select cases.

The two main differential diagnoses of subacute or chronic febrile lymphadenitis include tuberculosis and malignancy. Constitutional symptoms such as weight loss or failure to thrive, prolonged fever, night sweats, and exposure to an open case of tuberculosis provide clues to the diagnosis of tuberculosis. Definitive diagnosis is made by culture or cartridge nucleic acid amplification tests (CBNAAT) performed on lymph node aspirate/biopsy, sputum, or gastric juice. Atypical mycobacterial infections should also be considered, especially in immunocompromised states. Malignancy should be suspected in subacute or chronic lymphadenopathy with a fixed or opaque quality, painless enlargement, supraclavicular location, any associated signs of airway obstruction, and prolonged constitutional symptoms. Common malignancies to consider include Hodgkin lymphoma, non-Hodgkin lymphoma, and leukemia. Diagnosis is usually made by complete blood count, lymph node biopsy, and/or bone marrow studies. Generalized lymphadenopathy refers to enlargement of two or more noncontiguous groups of lymph nodes. Diagnoses in children with generalized lymphadenopathy can be divided into infectious diseases, immunologic conditions, storage disorders, or malignancies. The duration of lymphadenopathy, although useful, is difficult to establish because generalized lymphadenopathy is largely an investigation that is often unknown to the child's parents. Viral infections (eg, EBV) and malignancies

tend to have a shorter duration to presentation than chronic infections (TB), storage diseases, and immunologic conditions. Clues in the history and physical examination described previously should be reviewed for malignancy.

Symptoms of fever

Resetting the heat balance point to a higher level by the humoral and neural fever signals described above initiates a feedback loop that results in a sequence of clinical and behavioral manifestations that characterize the febrile response. To achieve a new balance point, heat loss is inhibited by cutaneous vasoconstriction (resulting in shivering and goose bumps) and by behavioral mechanisms such as adopting a fetal position to reduce body surface area or wearing thick clothing and seeking a warmer environment [45], [46]. Various heat-gaining mechanisms are then activated, including increased muscle contraction (resulting in shivering). When the fever signal is no longer present in the CNS, the balance point falls to normal with activation of heat-loss mechanisms such as sweating. Consequently, fever is often characterized by shivering, a rise in body temperature, and subsequent sweating and a fall in body temperature. Systemic symptoms such as headache, malaise, anorexia, and other morbid manifestations may also accompany fever. These symptoms are caused by systemic exposure to microbial products and pyrogenic cytokines, which lead to various acute phase reactions mediated by the neuroendocrine system [45], [46].

Pharmacological treatment: choice of drug, dosage, side effects

Paracetamol is the only drug recommended by all guidelines, and 17 of them recommend it over ibuprofen. Although high-quality evidence has shown that both are effective in reducing fever, the evidence for effectiveness in reducing distress (the more meaningful outcome) is weaker. There is no basis for paracetamol to be the sole or, arguably, even first choice antipyretic, as no systematic review comparing it with ibuprofen has shown a superior effect or safety profile. Of the 30 committees comparing paracetamol and ibuprofen, 15 concluded that ibuprofen was superior, while the remainder found no significant difference in either effect or safety profile. This raises the question of whether paracetamol should be considered a second-line drug, as although the safety profiles of both drugs are equivalent at therapeutic doses, toxic levels of paracetamol are reached much earlier and cause more deaths than supratherapeutic doses of ibuprofen. Adverse effects due to ibuprofen usually resolve, although there have been deaths due to asthma and long-term complications from toxic epidermal and soft tissue necrosis. Furthermore, despite high levels of evidence that combining/alternating antipyretics provides little additional benefit in temperature control, is associated with a higher risk of supratherapeutic dosing and has not been shown to reduce discomfort, the rate of antipyretic alternation in clinical practice is 67%. Given that parents incorrectly dose antipyretics in almost half of cases and 15% use supratherapeutic doses, reaching a consensus on drug choice and dosing, and methods of communicating this to parents, would be a valuable contribution to standardizing fever management.

Antipyretics for the prevention of febrile seizures: no evidence!

Several systematic reviews have found that antipyretics are ineffective for the prevention of febrile seizures. Interestingly, one study showed that antipyretics are generally ineffective in reducing temperature during febrile episodes associated with febrile seizures. However, a recent study concluded that rectal paracetamol significantly reduces the incidence of recurrent febrile seizures during the same febrile episode. In a child with fever and suggestive clinical signs and/or a positive urine dipstick or microscopy result, antibiotic therapy should be initiated soon after obtaining a urine

specimen for UC. Prompt antibiotic treatment is necessary to eliminate the infection, prevent bacteremia (especially in the first months of life), and improve the clinical status. Regarding the risk of renal scarring associated with UTIs, it is now established that the timing of antibiotic treatment does not affect the incidence and severity of scarring if it is started within 3-4 days of the onset of fever. Many studies have shown that initiating treatment either orally or parenterally has equal efficacy, and the clinician should base the choice of route of administration on practical considerations: if the UTI is complicated, that is, when the child appears septic or severely dehydrated or is vomiting, or if there is concern about compliance, treatment should be initiated parenterally and continued with an oral antibiotic as soon as the child's clinical condition allows; if the UTI is uncomplicated, that is, when the febrile child is in good clinical condition and is able to tolerate oral fluids and medications, and compliance is expected, treatment should be given orally. The outcomes of the oral and parenteral routes do not differ in terms of duration of fever, recurrence of UTI, or incidence of UTI-associated renal scarring.

Clinicians should also base their antibiotic choice on local antimicrobial susceptibility patterns (if available) and adjust it according to susceptibility testing of the isolated uropathogen. *Escherichia coli* remains the predominant uropathogen isolated from acute uncomplicated community-acquired infections (80%), followed by *Klebsiella*, *Enterobacter*, *Proteus* species, and *Enterococci*. Many characteristics of these pathogens are changing, particularly due to antimicrobial resistance. 50-56 Our national resistance pattern recommends amoxicillin-clavulanic acid as the first-line oral antibiotic and ampicillin-sulbactam or amoxicillin-clavulanic acid if the intravenous route is indicated. The increasing resistance of *Escherichia coli* to third-generation cephalosporins (around 30% in Italy) is mainly due to the widespread and not always appropriate use of this class of antibiotics. We therefore suggest considering cephalosporins (cefixime or ceftibuten for oral administration and cefotaxime or ceftriaxone for intravenous administration) in children with severe infections. In fact, cephalosporins have superior efficacy and rapidity of action, making the possible emergence of resistance less of a concern. Since ceftriaxone is known to cause cholestasis, it should be used with caution in infants with jaundice or in children younger than 3 months. If the UC results show resistance to the prescribed antibiotic, but the patient's condition improves, treatment should be continued without modification. In children with beta-lactam allergy, an aminoglycoside such as amikacin or gentamicin is the best choice, given that *Pseudomonas Aeruginosa* rapidly develops antibiotic resistance when aminoglycosides are used as monotherapy.

Due to the high rate of resistance, empirical use of co-trimoxazole should be avoided; it should be used only based on susceptibility patterns. The use of ciprofloxacin in children is controversial. The use of quinolones should be limited to patients with severe clinical conditions or those who do not respond to other antibiotics, based only on susceptibility patterns, as stated in the latest guidelines. The alarming increase in resistance due to the widespread use of quinolones in adults should also be taken into account.

In recent years, the focus of pediatric antipyretic drugs has shifted to the development of new technologies for the preparation of diagnostic wearable sensors and new drugs suitable for pediatric patients. New temperature sensors, sweat sensors, heart rate sensors and blood sensors facilitate the accurate diagnosis of pathological parameters in pediatric patients. Tablets, microneedles, liquid suppositories and other new dosage forms printed on 3D printers have excellent potential for the effective and safe use of pediatric drugs, and can meet the need for dosage accuracy and palatability of antipyretic drugs for children. The clinical use of antibiotics, antipyretics and glucocorticoids for fever is often empirical, which may lead to irrational use

of medical resources, increased drug toxicity and harm to the growth and development of children. The World Health Organization (WHO) recommends only two over-the-counter fever reducers for children, namely paracetamol and ibuprofen.

What to do after your first febrile UTI?

Most febrile UTIs in children are uncomplicated infections occurring in otherwise normal children with an excellent prognosis. A relatively small number of children (6-10%) experience recurrences, usually within the next year. Risk factors for recurrence include high-grade reflux, age <1 year in boys, female gender, and bladder and bowel dysfunction.

Overall, it is important to instruct parents to recognize symptoms of UTIs and to prevent modifiable risk factors for recurrent UTIs, particularly constipation and bladder and bowel dysfunction.

Circumcision is an option in selected males with high-grade VUR and with recurrent febrile UTIs despite other infection prevention efforts. As for antibiotic prophylaxis, it has been used for decades in children with VUR, with the assumption that renal injury and its progression could be prevented if recurrent UTIs could be avoided. Its effectiveness is currently debated. Several recent randomized controlled trials have shown no or minimal effect of antibiotic prophylaxis in reducing recurrent UTIs. Various meta-analyses have been published; among them, the one published by De Bessa et al. seems particularly interesting as the authors differentiated between expanding (grades III-IV-V) and non-expanding (grades I-II) VUR with respect to breakthrough infections.

Non-pharmacological measures

Fluid intake, baths, rubs and compresses. Many guidelines recommend adequate/increased fluid intake to avoid dehydration. Caution should be exercised in universally recommending increased fluid intake as this may be harmful. No direct published evidence was found regarding the optimal amount or type of fluid intake during fever. Proctolysis is mentioned in only one guideline, although the literature suggests that it may be useful in maintaining hydration status, leading to improved well-being and fewer hospital admissions. Nutrition is mentioned in 25% of guidelines and most agree that children should not be forced to eat during fever.

Regarding other physical recommendations, several seemingly opinion-based, conflicting approaches are mentioned: cool or warm room temperature, ventilated or unventilated rooms, wrapping the child up or undressing him completely and bed rest or normal activity. A systematic review that attempted to analyse these factors found that there were no studies examining physiological interventions or environmental cooling measures as stand-alone interventions. Given the lack of evidence, knowledge of the fever process can be used to determine that the appropriate use of physical measures depends on the phase of fever: as the temperature increases, the child should be kept warm or even actively rewarmed, thereby reducing the energy required to develop fever and hence discomfort. Once the child is warm to the feet and begins to sweat, layers of sheets and clothing can be carefully removed.

Despite the high level of evidence that cool sponge baths increase discomfort and should be avoided, 61% of guidelines still support their use. Recommendations for compresses show a similar distribution (63% in favour), although fewer guidelines address this topic and little directly relevant research is available. The temperature reduction that results from external cooling is short-lived. The discrepancy between the hypothalamic point and skin temperature results in peripheral vasoconstriction and metabolic heat production, resulting in shivering and increased discomfort in

the child. An initial small decrease in body temperature may not be worth the potential discomfort, and the use of these methods indicates a consistent focus on reducing body temperature rather than distress.!

Additional recommendations

Only three guidelines recommend complementary therapies, despite their widespread use by parents and health professionals. The evidence for the proposed treatments is low, perhaps in part because most forms of alternative medicine do not promote fever suppression as a treatment goal. In terms of well-being, the scientific literature suggests greater or equal efficacy and satisfaction compared with conventional therapies, with high safety and tolerability.

Other potential issues not yet included in published guidelines Digital media: None of the guidelines mention screen exposure. Most countries are beginning to formulate guidelines on screen exposure in children. We highlight the need for guidelines on screen use during illness. Parental care through interaction, empathy and relationships: None of the guidelines mention the quality of parental care during illness, which may be the most important factor for both immediate well-being and long-term health. Finding ways to reduce fever phobia through education or counseling interventions may help develop compassionate and empathic fever management and significantly reduce distress.

Conclusion

In this article, fever was analyzed as an important clinical symptom reflecting the body's response to various pathogenic agents and inflammatory processes. We reviewed the pathophysiological mechanisms leading to the development of fever, as well as its diagnostic value in clinical practice.

Fever, as a protective mechanism, plays a key role in the immune response, promoting the activation of protective cells and the synthesis of cytokines. However, despite its physiological function, fever can lead to significant discomfort in patients and, in some cases, to serious complications, especially in children, the elderly, and people with weakened immunity. We also identified a variety of causes of fever, including infectious and non-infectious factors, which emphasizes the importance of an integrated approach to diagnosis and treatment. Clinical algorithms, including a detailed anamnesis and a complete examination, are vital for an accurate assessment of the patient's condition and the choice of treatment strategy. It is also necessary to note the importance of further research in this area. Studying new pathogens and mechanisms of drug action, as well as developing more effective methods for monitoring and assessing the severity of fever, will help improve the quality of medical care.

In conclusion, fever is a complex and multifaceted symptom that requires careful attention from health care professionals. Understanding its causes and consequences, as well as understanding the pathophysiological mechanisms underlying it, play a key role in the diagnosis and treatment of various diseases associated with hyperthermia.

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