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## FEVER AND HYPERPYREXIA IN CHILDREN. EMERGENCY MANAGEMENT AND CONTEMPORARY POSSIBILITIES OF TREATMENT

**Summary.** In this article practical questions of emergency care delivery to children with febrile states are being considered from a modern view. Main data on fever pathogenesis are presented. Guidelines on stratification of patients at high risk serious bacterial infections and their examination and therapeutic approach are given. Also the review of modern pharmacological possibilities of antipyretics had been offered.

**Key words:** fever, children, antipyretics.

Fever in children is one of the most frequent reasons for seeking medical advice. According to data from the USA, more than 20 % of all pediatric emergency department health encounters are fever-related [1]. Fever is one of the common responses to diverse pathological effects. Normal oral temperatures range from 35.8 to 37.2°C, and normal rectal temperatures range from 36.1 to 37.8°C. Balance between heat dissipation and heat production is settled at age of 7 – 8 years old that is why elevation of body temperature, i.e. **fever**, is more frequent in young children. **Hyperthermia** is an alteration of temperature homeostasis that results from unregulated rise in heat production, or decrease in heat dissipation, or failure of hypothalamic thermoregulation [3]. Practitioners usually understand hyperthermia as body temperature elevation above 38.5-39°C. In most cases, such temperature response is pathological and demands correction. Though, pathophysiologists, unlike clinicians, understand hyperthermia as body temperature elevation resulted from overheating. We believe this is a more justified approach. Moreover, the most of well-known and authoritative intensivists incline to the same, as evidenced by the absence of "hyperthermia" term meaning high (above 39°C) body temperature, in the most famous English and Russian pediatric intensive care editions.

By elevation degree, body temperature may be subfebrile (up to 38°C), moderate febrile (38.1-39.0°C), high febrile (39.1°C and above), and hyperpyrexia (above 41°C).

**Fever due to bacterial infection** is often accompanied by severe intoxication, rapid elevation of body temperature, delirium, lack of efficiency from centrally acting antipyretics.

**Fever due to viral infection** is usually not accompanied by intoxication signs, general state of a child remains satisfactory, and antipyretics are very effective.

Fever is always a pathological process. However, it does not always demand correction as it is also a compensatory-adaptive process that boosts the activity of immune response. Fever is likely to suppress replication of some viruses and generation of certain types of pneumococci, as well as to decrease plasma unbound iron level which is the growth factor of gram-negative bacteria. Moderate elevation of body temperature fastens important immune reactions (i.e. phagocytosis, leukocyte chemotaxis, and interferon production) [2]. Fever may be caused by any immune process that is accompanied by the production of

pro-inflammatory cytokines, namely interleukin-1, that causes the change in the thermoregulatory set zone in the preoptic area of hypothalamus, and thus leads to rise in heat production and decrease in heat dissipation. Effects of body temperature elevation are as follows: increase in basal metabolism rate by 10 – 12 %, tachypnea (4 additional breathes per minute) and tachycardia (10 – 20 additional beats per minute) for each degree Celsius over 37°C. As a result, demand for liquids, oxygen and nutrients is increased. Respiratory alkalosis is developed and cerebral blood flow decreases which could cause seizures (febrile seizures). Uncontrolled prolonged body temperature elevation leads to water-stressed dehydration, reduction of cardiac output despite persistent tachycardia, and extension of arteriovenous oxygen difference. In connection with hypermetabolism, it stimulates development of hypoxia and acidosis. Fever may be accompanied with chill, delirium and hallucinosis.

Viral or bacterial infections are the most frequent causes of body temperature rise. Viral infections account for up to 95 % of all fever causes [3]. However, this fact should not be considered as a reassuring one as, in the rest of cases, fever is a symptom of critical bacterial infections (meningococcal, streptococcal, hemophilic, pneumococcal, salmonella etc.) that could develop rapidly resulting in severe complications and even in fatal consequences [4]. According to the results of the recent prospective study, likelihood of bacterial and viral infection in children with body temperature over 41.1°C is equal and amounts to 50 % [5].

On practical grounds, it is reasonable to distinguish fever with obvious source of infection (i.e. pneumonia, influenza, tonsillitis, diarrhea, etc.) and fever without obvious source of infection (FWSI). FWSI is defined as an acute illness accompanied by fever in which provisional diagnosis is not apparent after clinical examination therefore, additional examinations are required. In foreign professional literature much attention is given to this type of fever in children as among causes of FWSI in young children bacteremia and serious bacterial infections could be occult. In case of FWSI in a young child, it is recommended to run differential diagnostics in order to choose between viral infections, meningitis, pneumonia, urinary tract infection, osteomyelitis, arthritis, gastrointestinal tract infection and already mentioned occult bacteremia. The most informative factors proving bacterial nature of fever are as follows: early

childhood (in infants below 3 months old, body temperature elevation up to 38°C must be considered as an alarm symptom), leukocytosis, especially when a white blood cell count greater than  $15 \cdot 10^9/l$  (probability of bacteriemia in children with FWSI and white count over  $15 \cdot 10^9/l$  is three times greater than with white count less than  $15 \cdot 10^9/l$ ), presence of causative organism in blood culture, pleocytosis in cerebrospinal fluid and leukocyturia. Data on WBC differential, structural changes of neutrophils, erythrocyte sedimentation rate and C-reactive protein is used as additional criteria for determination of bacterial nature of FWSI. However, it is worth pointing out that there is no absolute marker of viral or bacterial infection [6 – 8].

*Critical points to be taken into account during examination of a child with FWSI:*

1. Immunization status (recent vaccinations could cause body temperature rise) and, that is more important, immunoprophylaxis scope. These data could define probable fever factors.

2. Exposure to sick individuals and previous recent treatment with antibiotics.

3. Recent travels to other countries or regions with certain endemic areas of infectious diseases or with unfavorable epidemiological conditions.

4. Recent hospitalization, long stay in the intensive care units, prematurity and immunodeficiency state that substantially decrease the number of probable fever factors.

5. Impairment of consciousness, appetite disorders, apastia, lethargy, apnoea.

6. Signs of child abuse or neglect.

7. Temperature in the premises, duration of fever and previous fever treatment.

8. Possible factors of overheating such as prolonged exposure to the sun, long stay in hot premises in summertime or excess clothing in wintertime [6 – 8].

For evaluation of febrile in children below 2 years old, Yale Observation Scale developed in the USA is used [2]. It is applied for assessment of six parameters that allows to characterize a child's state and detect life-threatening disease (Table 1). Basing on the score obtained, further therapeutic approach to a child must be chosen (outpatient therapy or hospital care).

**Table 1. Yale Observation Scale (1982)**

Symptoms	Normal (Score = 1)	Moderate Impairment (Score=3)	Severe Impairment (Score=5)
Quality of cry	Strong or not crying	Whimpering or sobbing	Moaning, high-pitched prolonged cry, hardly responds when trying to calm the baby
Reaction to parent stimulation	Cries briefly or not crying; child looks content	Cries off and on	Persistent cry with little response
State	Stays awake; if asleep, wakes up quickly	Eyes close briefly, then wakes up with prolonged stimulation	No arousal, sleep disorders
Skin colour	Pink	Pale extremities or acrocyanosis	Pale or cyanotic or mottled or ashen
Hydration	Skin and mucous membranes moist	Skin and mucous membranes moist, but mouth slightly dry	Skin doughy/tented, dry mucous membranes, sunken eyes
Response	Smiles or alerts	Brief smile or alerts briefly	No smile, anxious/dull, no alerting

**Note: with score less than 11 – risk of life-threatening disease amounts to less than 3 %; with general score within 11-15 – possibility of serious disease amounts to 26 % and with score more than 15 – possibility of serious disease amounts to 92 %.**

It is important to emphasize that it is unacceptable to associate high body temperature (above 37.5°C) with teething. As it is absolutely physiological process and is not accompanied with fever [2]. Thus, "teething syndrome", a so widespread term in the domestic pediatrics, has no scientific justification.

For practical purposes, it is reasonable to distinguish fever accompanied by skin pallor and microcirculation disorders ("pale") when heat dissipation is inadequate; and fever without microcirculation disorders with normal heat dissipation ("pink"). "Pale" fever is indicative of serious bacterial processes and requires close medical control; pink fever is a less threatening symptom although, such a fever does not exclude the possibility of bacterial infection.

All children 2 to 36 months of age, with fever above 39°C are recommended to undergo laboratory testing, namely blood panel, coprogram, chest radiography, blood, urine and stool cultures [2, 5–9]. Taking into account the opportunities of the domestic health care system, in such cases a child is better to be taken to the specialized hospital. In case of refusal of hospitaliza-

tion, it is necessary to provide complete medical examination in the outpatient setting and prescribe empiric antibacterial treatment if there is no catarrhal symptom and it is impossible to detect a source of infection [2, 5–11]. And such an approach responds to a high risk of bacteriemia as a fever factor and to most of its serious complications (meningitis, sepsis and pneumonia).

**Principles of emergency treatment** of fever and hyperthermia are directed to lowering of body temperature. Considering that fever is an adaptive and beneficial reaction which stimulates better response to the infection, reduction of body temperature is not reasonable at any elevation of temperature. Antipyretics are administered in children whose body temperature is above 38.5 – 39.0°C and who do not have any serious premorbid background (febrile seizures, organic CNS injuries, infantile cerebral paralysis, epilepsy, chronic cardiovascular diseases, and metabolic disorders). In children with above mentioned pathological states, antipyretics are administered at body temperature below 38.0°C [2, 11].

Fever management approaches:

1. Nonsteroidal anti-inflammatory drugs are the main medicinal products used for treatment of fever and hyperthermia.

2. In case of "pale" fever it is necessary to facilitate heat dissipation that could be reached by administration of neuroleptics and vasodilators on condition of the stable blood pressure. The most frequent product administered is promethazine 0.25 mg/kg i.m. or i.v. Administration of aminazin 0.05 ml/kg is possible.

3. Physical cooling techniques may be applied at the background of neuro vegetative blockade achieved via neuroleptics administration. It could be: ice packs placed on large vessel areas, liquid application to skin with following fanning, stomach lavage and enemiasis with cooled (not icy) water, vinegary-mustard rubdown.

4. Provide sufficient amounts of liquids depending on the general state – orally or parenterally.

5. Oxygen-therapy is prescribed in case of fever with hypoxemia (septic shock, pneumonia, bronchiolitis).

Rational selection of antipyretics is of high importance. Medicines administered in children are inhibitors of cyclooxygenase enzymes (COX), acetaminophen (paracetamol) and ibuprofen. Take note, that paracetamol is a central acting agent (inhibits prostaglandin synthesis in the hypothalamus) and it has no effect on COX in the peripheral tissues and thus, has potent analgesic and antipyretic actions without anti-inflammatory activity. For the first time it was used by von Mering in 1893. Ibuprofen, a non-selective COX inhibitor, exerts potent anti-inflammatory activity but due to its effect on prostanoids synthesis in the peripheral tissues, it is associated with certain unwanted side effects, such as irritation of gastrointestinal mucosa, erosion development and gastrointestinal haemorrhage. Paracetamol is administered in a dose of 10 – 15 mg/kg up to 3 – 4 times a day (daily dose must not exceed 60 mg/kg). Ibuprofen is administered in a dose of 10 – 15 mg/kg with repeated administration in 8 hours, i.e. 3 times a day but daily dose must not exceed 45 mg/kg [5 – 11]. Discussion on higher or lower efficiency of paracetamol and ibuprofen should be considered closed as it has been proved that both substances have equal efficiency if taken in doses of 15 and 7 mg/kg respectively [11]. Notwithstanding the widely spread opinion, paracetamol as well as ibuprofen are effective for alleviation of moderate and severe pain in children. However, it is reasonable to emphasize that paracetamol is considered to be much more safer than ibuprofen as it causes fewer dyspeptic disorders, stomach bleedings and it does not affect renal blood flow (some investigators believe that administration of ibuprofen in the state of shock is one of factors leading to severe renal impairment). Moreover, paracetamol, in contrast to ibuprofen, more seldom causes "aspirin-induced asthma" attacks, which is conditioned by central activity of paracetamol and no effect on prostaglandin synthesis beyond CNS. In chickenpox, administration of ibuprofen may cause development of extremely threatening complication, namely necrotizing fasciitis. Therefore, taking into account enumerated disadvantages of ibuprofen usage, paracetamol is considered to be a product of first choice for fever management in children. Ibuprofen should be taken only with due regard to its possible adverse effects in children with significant inflammatory component of infectious disease (arthralgia, myalgia, neuralgia). Ibuprofen is contraindicated in patients with chickenpox and severe dehydration [11, 12]. However, it is worth noting, that meta-analysis of 24 randomized controlled studies demonstrated absence of significant differences in quantity of adverse effects between placebo, acetaminophen and ibuprofen [13].

Acetylsalicylic acid is contraindicated due to possibility to provoke development of Reye syndrome. Nimesulide, due to high risk of hepatitis development with potentially lethal complications, should be used in children over 12 years old.

Analgin (metamizol) is a common antipyretic product used in emergency care in Ukraine, which is primarily conditioned by availability of its parenteral form. First of all, it is important to specify that metamizol provokes neutropenia, and sometimes (1 : 1500) – agranulocytosis. Other side effects are anaphylaxis and hypothermia with development of collaptoid state. The WHO, in its special letter dated 08.10.1991, does not recommend administration of analgin as an over-the-counter antipyretic medicine [11]. Thus, analgin (metamizol) is banned to administer in the most developed countries due to its acute toxicity and a great number of adverse effects that sometimes have fatal nature. However, in Ukraine, it is administered very frequently due to availability of its parenteral form and rapid and potent antipyretic activity.

Emergence of parenteral forms of acetaminophen gives new opportunities for fever treatment in children with special needs related to administration of oral and/or rectal forms of antipyretics (i.e. impaired ability to swallow, diarrhea and vomiting, seizures, chock states with microcirculation disorders, unconsciousness). Taking into consideration greater safety compared to analgin, acetaminophen for intravenous administration has to take a proper position in pediatric emergency care [14, 15]. A row of randomized controlled studies demonstrated its efficiency and safety as both antipyretic and analgesic medicine in children. It was shown that, compared to placebo, it significantly reduces body temperature and does not have a large number of side effects that appear with frequency less than 1 : 10 000 [16–18]. Basing on first-hand experience of administration of intravenous acetaminophen in the emergency departments, Australian physicians recommend adding this medicinal product to the updated guidelines on pediatric emergency care [19]. A new domestic product of acetaminophen Infulgan, is 10 % solution for intravenous administration in bottles of 20, 50 or 100 ml. It is administered in doses of 15 mg/kg, i.e. 1.5 ml/kg (a single dose), and 60 mg/kg, i.e. 6 ml/kg (maximum daily dose) as an infusion for 15 minutes to children above 1 year old and with body weight above 10 kg.

Summarizing the above, it is necessary to emphasize that, though fever in children is a very frequent state, it is only a symptom of great number of diseases. Thus, any antipyretic drug is only symptomatic and able to reduce discomfort conditioned by progression of the disease. Main task for a physician, who examines a child with fever, is not only to prescribe symptomatic treatment but to determine the nature of fever and subgroup patients with high risk of bacterial infection who demand antibiotic therapy and often hospitalization. Special attention is required at fever with purpura, fever with stiff neck and red dermographism as such a fever may be a sign of meningococemia or meningitis. Fever accompanied with abdominal pain and vomiting requires exclusion of appendicitis and urinary tract infections. Fever lasted for more than 1 week demands close examination in order to exclude infectious mononucleosis, yersiniosis, sepsis, connective tissue diseases, immunodeficient diseases, Kawasaki disease, and malignant diseases [11]. From the other hand, if fever is a symptom of a viral infection, it is important to explain to child's parents the inappropriateness of fever phobia, as unjustified treatment of moderate fever is sooner harmful than healing.

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