

Febrile Child and Fever without Focus

Dear Editor

A review of pediatric diseases in the south of Iran showed that 63% of the children were referred for a disease. Respiratory tract diseases were the most common presenting illnesses, comprising 53% of all outpatient diseases.¹ Infectious diseases outnumbered noninfectious diseases, and febrile children comprised up to 40% of the referred children.¹ The objective of this study was to investigate the cause and proper management of fever without focus (FWF).

The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (code: IR.SUMS.REC.1401.311). Written informed consent was obtained from the participants' guardians. During seven years from 2015-2021, 4201 febrile children were studied among 11115 ill children (37.7%) in Shiraz, Iran. 270 (6.4%) of febrile children with a presumptive diagnosis of FWF were closely followed to discover the cause and make a final etiologic diagnosis.

There were 133 (49.2%) boys and 137 (50.7%) girls, with a boys-to-girls ratio of 0.9:1. As the findings indicated, 26 (9.6%), 43 (15.9%), 66 (24.4%), 135 (50%), 93 (34.4%), 42 (15.05%) were under the age of six months, 6-12 months, 12-24 months, 0-2 years, 2-5 years, and 5-15 years old, respectively. Half of the children were under the age of two (n=135, 50%), and about 85% were under five years of age.

The seasonal distribution of FWF patients showed that 75 (27.7%) were in spring, 95 (35.1%) in summer, 65 (24%) in fall, and 35 (13%) in winter. In general, 170 (62.9%) of the cases were in warm seasons, and 100 (37%) were in cold seasons. Spring, summer, and early fall together, comprised 235 (87%) of cases. 194 (71.8%) of the cases finally were diagnosed as self-limited febrile illness (SLFI) or self-limited viral illness (SLVI), 22 (8.1%) as Roseola infantum, and 12 (4.6%) as pharyngitis (nine groups A beta-hemolytic streptococcus (GABHS) and three non-group A beta-hemolytic streptococcus). A viral upper respiratory infection such as rhinitis, nasopharyngitis, rhinitis conjunctivitis syndrome, gingivostomatitis, vincent infection, hand-foot-mouth disease, and purulent rhinitis, was present in 10 (3.7%). There were 11 (4%) cases of viral gastroenteritis. Seven (2.6%) of the cases, all of whom were female, had urinary tract infections (UTIs), and two (0.7%) had sinusitis. Otitis media, leukemia, occult bacteremia, treated sepsis, hyper IgE syndrome, and recurrent fever were among the remaining cases (one for each condition). In addition to the final diagnosis mentioned above, six (2.2%) of the cases were diagnosed with coronavirus disease 2019 (COVID-19) during the second half of 2021.

Fever without localizing sign (FWLS) is defined as a fever of less than 10 days in which the patient does not appear seriously ill, has no abnormalities on physical examination, and has normal urinalysis as well as a negative urine culture. Viruses cause FWLS in more than 70% of cases, most commonly coxsackie and echoviruses, and less commonly parainfluenza, adenovirus, and influenza. With the viruses as a cause, the disease has a complete uneventful recovery usually in three days and is eventually labeled as SLFI or SLVI.^{2,3}

The clinical course may change features sometimes even in less than 24 hours in infants as otitis media. GABHS pharyngitis has no sign in the first 24 hours; while in 48 hours, either a distinct erythema or sometimes pinpoint exudates appear on tonsils. Rapid strep. antigen and/or throat culture even in the first 24 hours will confirm the diagnosis of GABHS. High fever, poor reaction to antipyretics, restlessness, anorexia, and sometimes vomiting are all symptoms of strep. pharyngitis.^{4,5}

Approximately 20% of children of 6-12 months infected with human herpesviruses 6B infection present with roseola infantum as well as a nonspecific febrile illness without a rash or localizing sign. Fever is often higher than 39.5 °C and lasts for 3-7 days. Roseola is distinguished by an erythematous maculopapular rash that appears on the trunk and spreads to the face and extremities, once the fever resolves and lasts for hours or days. Therefore, in any infants presenting with FWLS, especially in spring or fall, the possibility of fever progressing to roseola could be expected.⁶

Most children with fever and pneumonia usually have some abnormalities on physical examination.

Tachypnea, abnormal auscultation, or nasal flaring suggest respiratory diseases. A reliable physical examination can be a challenge. 20-30% of highly febrile young children (<5 years) with no clinical signs of pneumonia, have white blood (WBC) count of $\geq 20,000/\text{mm}^3$. In a study, a chest radiograph revealed lobar or segmental pneumonia in 41% of infants aged 3-36 months with $\text{WBC} > 25,000/\text{mm}^3$. Even in the post-conjugate pneumococcal vaccine era, there is a strong association between leukocytosis and pneumonia.^{7,8}

The most common site of bacterial infection among febrile infants and young children is UTI. The prevalence of UTI is significantly influenced by sex, age, race, and circumcision status. The prevalence of UTI is high among girls and warrants urine analysis and urine culture in all females age 3-24 months with fever $\geq 39^\circ\text{C}$ and no source.⁹

Uncircumcised male infants with fever have a higher risk of UTI than circumcised male infants, with the highest frequency in infants under three months of age. The incidence of UTI in circumcised males above the age of six months is low.⁹

The approach to the diagnosis and management of a child with FWF depends on the patient's age. For instance, it is recommended to perform blood and urine cultures, do a lumbar puncture, and also begin parenteral antibiotics in newborns less than 28 days old, who are admitted to hospital with rectal temperature higher than 38°C . Besides, for nontoxic-appearing infants 28-90 days old, and "low risk" infants, rectal temperature $\geq 38^\circ\text{C}$, who has been previously healthy, nontoxic appearance, no sign of focal bacterial infection on examination (except otitis media), $\text{WBC} < 15,000$, $\text{Bands} < 1500/\mu\text{L}$, normal urinalysis, in case of diarrhea; < 5 WBC/high power field in stool; and when respiratory symptoms are present, chest radiograph should be taken. Then, there are two possibilities for outpatient care:

1. Blood and urine cultures as well as careful observation.

2. Blood and urine culture, lumbar puncture, ceftriaxone 50 mg/Kg IM (to 1 g) and return for re-evaluation within 24 hours. At this time, if all cultures are negative, and the patient is afebrile and well-appearing, careful follow-up is essential. If the blood culture is negative, and the patient is well-appearing but febrile, the patient should be closely monitored, and a second dose of ceftriaxone may be recommended.

If the blood culture is positive, the patient should be hospitalized for sepsis/meningitis evaluation and parenteral antibiotic therapy while the findings are awaited. If the urine culture is positive and the fever persists, the patient should be admitted for sepsis evaluation and parenteral antibiotic therapy while waiting for the results. Finally, if the infant is afebrile and healthy, outpatient antibiotic therapy is recommended.^{2, 8, 10, 11}

Keywords • Fever • Child • Prevalence

Authors' Contribution

E.S: conception and design; acquisition, analysis, and interpretation of data for the work, drafting and revising. He approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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Received: 27 August 2022

Revised: 02 October 2022

Accepted: 14 October 2022

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