Nigerian Journal of Paediatrics 2006; 33 (3&4): 65-9

An Approach to a Child with Fever of more than 72 hours' duration without Obvious Cause: a Review

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Summary

Bajraktarevic Adnan, Sporisevic Lutvo, Djurdjevic Djulepa Aida, Khatib Hakam, Hadzimuratovic Admir. An Approach to a Child with Fever of more than 72 hours' duration without Obvious Cause: a Review. *Nigerian Journal of Paediatrics* 2006;33:65.
Pyrexia of undetermined origin (PUO) is defined as fever with a temperature of over 38°C of more than three weeks' duration whose source is not determined after a careful history and physical examination. Clinical handling is different and depends on the age of the child. Acute episodes of fever represent between 10 and 20 percent of outpatient paediatric consultations, occurring on the average between four and six times annually. There is usually an increase in the winter months corresponding to an increase in respiratory and gastrointestinal viral infections. Different scales of observation have been developed that are aimed at identifying those children with underlying bacterial or viral ilnesses. The diagnosis of PUO is determined by careful evaluation of the presenting picture. The handling of a prolonged episode of fever should be on individual basis and should include the evaluation of the risks of serious bacterial infection. The use of antibiotics is generally not indicated except in the neonate when they are administered parenterally following appropriate investigations, including lumbar puncture.

Key words: Fever, child, diagnostic evaluation, therapy.

Introduction

PYREXIA of undetermined origin (PUO) is defined as fever with a temperature of over 38°C lasting for more than three weeks whose source cannot be determined after a careful history and physical examination.[1,2] It is one of the most common causes of paediatric consultations. Sometimes there is the possibility of an underlying serious bacterial infection. However, the vast majority of these episodes are benign and caused by viral infections and may not require specific treatment. The viruses most frequently encountered in children with PUO include *Herpes type 6*, *Enterovirus* and *Adenovirus*, as well as viruses responsible for respiratory infections, although these usually present with signs localized to the airways. Approach to management varies, depending on the age of the child.[3] At the moment, it is considered that between 2-3 percent of infants aged three months with fever have a bacterial infection. However, the risk increases several folds in younger babies aged less than four weeks. The bacteria more commonly encountered in the younger age group include *Streptococcus group B*, Enterobacterias and *Listeria monocytogenes*. The risk diminishes between three and 36 months, and from this age, it is considered that the risk of underlying serious bacterial infection

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is minimal, and therefore management is similar to the approach in the adult.[4] In patients between three and 36 months of age with rectal temperatures > 39°C, the potential risk of bacteremia is currently less than five percent.[5] In over 80 percent of potential bacteremias, S. pneumoniae is the likely aetiological agent. Other common pathogens are meningococcus, salmonella spp., and H. influenzae type B in unvaccinated children.

Table I shows the recommended methods of measuring body temperature in different age groups.

Table I

Recommended Modes of Measuring Body Temperature at Various Age Groups

Age	*Recommended Technique*	
Birth to 2 years	1st choice:	Rectal (for an accurate reading)
	2nd choice:	Axillary
Between 2 and 5 years	1st choice:	Rectal (for an accurate reading)
	2nd choice:	Aural, axillary
Older than 5 years	1st choice:	Oral (for an accurate reading)
	2nd choice:	Aural, axillary

Table II

Normal Temperature Ranges

Measurement Method	*Normal Temperature Range*
Rectal	36.6°C to 38°C (97.9°F to 100.4°F)
Oral	35.5°C to 37.5°C (95.9°F to 99.5°F)
Axillary	34.7°C to 37.3°C (94.5°F to 99.1°F)
Aural	35.8°C to 38°C (96.4°F to 100.4°F)

The pathological process

Fever is the consequence of an alteration of the normal thermoregulatory mechanism, with an upward displacement of the pre-established point of control of the temperature in the hypothalamus.[6] This point of thermostat increases due to the action of certain cytokines released from macrophages in response to a variety of stimuli. These cytokines in turn, stimulate prostaglandin E2 (PGE2) synthesis resulting in fever. The point of thermostatic control is consequently set at a higher level; this stimulation of prostaglandin E2 (PGE2) synthesis by cytokines takes longer to act. PGE2 is directly responsible for the occurrence of fever. The fever, which is a response to an infection, should be distinguished from an increase in body temperature, in which there is an alteration in thermoregulation, as in hyperthermia.[7]

The reason for young infants being at an increased risk of serious bacterial infection is principally the immaturity of their immune systems. In the first months of life, there is reduced opsonization and reduced functional state of macrophages and neutrophils. In addition, the production of specific IgG against encapsulated bacteria is very much diminished in the first 24 months of life.[8] Consequently, the first exposure of children to certain bacteria could result in overwhelming infection, as is the case with infections caused by *Streptococcus pneumoniae*, meningococcus and H. influenzae type b.

The clinical picture

By definition, there are no localizing signs in PUO.[9,10] Different scales of observation have been developed that attempt to predict those children with underlying bacterial disease. Among them are those of Rochester for infants of three months of age and that of Yale for older children as well. However, the sensitivity and specificity of these scales for the detection of serious bacterial infection are low. In children, bacteremia could be asymptomatic although occasionally, the presentation could resemble that of a viral infection and without a positive blood culture or a localised infection, it is usually difficult to distinguish from the latter.

Diagnostic evaluation

The differentiation of fever of viral origin from that of bacterial origin could be dificult since children with bacteremia could remain relatively well with no obvious focus of infection. The diagnostic evaluation of a child with PUO should take into consideration the clinical picture and the results of investigations such as urine and blood cultures. It is essential to obtain a detailed history targetted at identifying those pointers to potential bacterial infection.[11] The risk of bacterial infection is less in children aged between 28 and 90 days in which age bracket the level of body temperature is not necessarily a risk factor.[12] However, after the age of three months, the body temperature becomes an important risk factor for bacterial infection. For instance, there is a direct relationship between the risk of bacterial infection and temperature values above 39°C particularly if the leucocyte count is over 15,000/mm^3 and the risk further increases at temperatures over 40°C.

Meningitis should always be excluded in very young infants particularly those under three months of age. Overall, evaluation of children with fever of undetermined origin should be on individual basis.[13] After the history and physical examination, one should carry out well selected ancillary investigations before deciding on the choice of treatment, particularly the use of antibiotics.

Blood culture remains the gold standard for making a diagnosis of a bacterial cause of fever. However, the result of such culture could be delayed for up to 48 hours, thus leading to a delay in commencing appropriate therapy. In view of this inevitable delay, it is customary to identify those who are less likely to require antibiotic therapy.[14] In children below three months of age, the criteria used include a leucocyte count of less than 15000/mm^3, urine microscopy showing less than 10 leucocytes per high power field and a band count ratio of less than 0.2, among others. In children over three months of age, estimation of various acute phase reactants has been used in predicting those with bacterial cause of the fever. Still in this age group, a leucocyte count of over 15000/mm^3 increases the likelihood of bacterial infection five-fold. This is more so in fevers associated with pneumococcal infections where in 80 percent of cases, the leucocyte count exceeds this value, but not so in infections caused by H. influenzae and meningococcus where the lecucocyte count exceeds 15000/mm^3 in 50-80 percent of cases. However, the sensitivity of the use of the leucocyte count alone is low because occasionally, this count could be exceeded in viral infections. Other useful parameters in predicting fevers associated with bacteremia are absolute neutrophil count of over 10,000/mm^3, a band count of over 500/mm^3. The C-reactive protein (CRP) though useful as a predictor of bacterial infection, has not been extensively studied in investigating children with fevers of undetermined origin. Overall, in investigating children, the use of several parameters in combination rather than individually yields better results. A chest X-ray is hardly indicated in the investigation of these children except when there are signs of respiratory distress.[15] However, a chest x-ray could be carried out among children of this age group if the leucocyte count exceeds 20,000/mm^3 and the body temperature is over 39°C. Urine culture is indicated in children younger than two years and particularly those below six months of age. In this circumstance, it is advisable to obtain either a catheter specimen of urine or a specimen by bladder tap to avoid contamination.

It is important to consider non-infectious causes of fever. Such causes include high environmental temperatures especially in very young infants and neonates. Heat production in the body is a function of both metabolic and physical activities. Basal metabolic rates vary and are influenced by, for example, age, the funcitional state of the thyroid gland and environmental temperature. The highest rates are generally seen in very young infants whose surface areas are large relative to body mass. Physical activity and exercise can greatly increase heat production by muscles. Release of catecholamines during exposure to cold environment increases muscle contraction, resulting in heat production. Body temperature generally tends to be higher in children than adults and begins to approximate adult values from about the age of one year and stabilizes at puberty. Distinguishing between fevers due to high environmental temperatures and those of either viral or bacterial origin are best achieved using the results of laboratory investigations such as leukocyte count, differential blood count, C-reactive proteins, and procalcitonin level.[16]

Treatment

The antipyretics commonly used include paracetamol, ibuprofen and acetylsalicylic acid. Of the three, paracetamol has no anti-inflammatory property. It is well absorbed, reaching peak plasma concentration between one and two hours after administration and maintaining its action for four to six hours.[17] The usual dosage is 15mg/kg/day administered 4-6 hourly, but not exceeding 90 mg/kg/day. Ibuprofen as an antipyretic is safe when used for short periods. It has a prolonged action, lasting between six and eight hours.

Several simple physical methods have traditionally been used to reduce fever. Exposing the infant is usually a first action before rechecking an elevated temperature. Ensuring adequate fluid and calorie intake is also beneficial. Cooling blankets are often used in intensive care settings in which the body temperature and energy expenditure of critically ill children must be strictly controlled. The use of tepid sponging in the management of fever is controversial. It is however recommended in situations where the fever is very high. The use of antibiotics is generally not indicated except in the neonate when they are administered parenterally following appropriate investigations including a lumbar puncture. In older children between the ages of one and three months, the use of antibiotics should be decided on individual basis. If the parents could be trusted to return for follow-up and the child belongs to a low-risk category, he/she could be allowed home and reassessed 24 hours later. Otherwise, antibiotics should be administered parenterally following a lumbar puncture. One option is the administration of i.m. ceftriaxone and reassessment of the child within 24 hours. In children between the ages of three and 36 months, the decison to use antibiotics is not as clear-cut but depends to a large extent on whether the child is being managed on outpatient or inpatient basis. In those children with increased risk of occult bacteremia (leucocyte count $\geq$15000/mm^3), antibiotics could be commenced after blood culture. One should bear in mind the increasing resistance of *Streptococcus pneumoniae* to penicillin and ceftriaxone. The objective of commencing antibiotics empirically is to cover infections caused by the pneumococcus and in this regard, amoxycillin would be an appropriate choice. In those countries with a high prevalence of pneumococcal infection with reduced sensitivity to penicillin, it would be appropriate to commence amoxycilin at a higher dose (80 to 100mg/kg/day) in those children with increased risk of occult bacteremia. Generally, in the treatment of bacteremia, ceftriaxone appears more effective than amoxycillin in preventing serious complications although the difference may be mininmal in cases associated with the pneumococcus. Therefore, there is little justification for the use of ceftriaxone empirically especially since vaccines are available against H. influenzae.

Prognosis

This depends basically on the underlying bacterial aetiology of the fever. Bacteremia of pneumococcal origin could resolve spontaneously in the majority of cases, but in about 10 percent of cases, it could develop into a more serious infection. With appropriate treatment, the proportion of potentially serious bacterial complications such as cellulitis, osteomyelitis and pneumonia is considerably reduced as well as the duration of the fever. Usually infections caused by H. influenzae type b or meningococcus are associated with serious complications. In the former, 30 percent of cases could result in serious bacterial infections and from six percent to 14 percent in meningitis, while in the latter, 60 percent of cases could result in serious bacterial complications and from 25 percent to 58 percent in meningitis. In bacteremia associated with Salmonella spp, the risk of developing serious complications is found in children over the age of three months, but the risk could be considerably reduced by the use of appropriate antibiotics.[18,19]

Conclusion

Acute episodes of fever represent between 10 and 20 percent of outpatient paediatric consultations, occurring on the average, between four and six times annually. There is usually an increased incidence in the winter months, corresponding to an increase in respiratory and gastrointestinal viral infections. Clinical course depends basically on the underlying bacterial aetiology of the fever. With appropriate treatment, the proportion of potentially serious bacterial complications such as cellulitis, osteomyelitis and pneumonia is considerably reduced as well as the duration of the fever. Occult bacteremia is present in approximately three percent of children younger than three years of age. Blood culture remains the gold standard for making a diagnosis of a bacterial cause of fever. However, the diagnosis could be delayed up to 48 hours thus leading to a delay in comencing appropriate therapy.[20,21] Clinical evaluation is therefore crucial in assesing the risk of serious bacterial infection. The antipyretics commonly used are paracetamol, ibuprofen and acetylsalicylic acid. Treatment depends on the diagnosis. In children who appear well, empirical therapy may further cloud the diagnosis. Children who appear ill require hospitalization

Acknowledgments

We thank our colleagues, Dozent Dr Med Hadzo Cengic, Prim Dr Med Sabiha Skaljic, and Dr Med Zijo Begic, from Sarajevo in Bosnia and Herzegovina, and Prof Dr Med Amir Buljina from Untited States of America, for generously providing us with a copy of their manuscript on a meta-analysis of the diagnostic tests for fever in children. We would like to give special thanks to Edisa Bajraktarevic and Amra Bajraktarevic for assistance in extracting the necessary data from a Bosnian language article. We thank the technical experts Mr. Salih Hamzic and Mr Mirza Hamzic representing the partner organizations (Cad plus Bosnia) for their most valuable contributions. They provided critical insights on this topic, reviewed an earlier draft of this report, and provided prompt assistance when requested. We also thank our patients, parents and other caregivers for taking time out to provide important insights from the patient's perspective in the clinical management of this condition.

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