

Original Research Article

Clinical profile and etiology of children presenting with prolonged fever in tertiary care centre of Southern Rajasthan

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ABSTRACT

Background: Fever is the most common complain of a child presenting to a health care setting. A prolonged fever however, is an intriguing challenge for clinicians and remains overly medicated and inappropriately worked up, provided a systemic approach is not followed. Our study aims to find the etiologic diagnosis in these cases of prolonged fever.

Methods: The present study was conducted in a tertiary care hospital in southern Rajasthan over a period of 12 months from November 2021 to October 2022. Our descriptive, observational study enrolled 150 children who were prospectively followed during their stay in hospital. Each patient was subjected to a set of mandatory investigations followed by other investigations as per the diagnostic clues. Patients were monitored closely during their course of stay until discharge, at which the final diagnosis was charted.

Results: A diagnosis could be reached for 138 patients (92%) and in 12 patients (8%), the cause of fever remained undiagnosed until discharge/death. Out of the 138 patients diagnosed, 118 patients (85.5%, 78.6% overall) had an infection as the cause of fever and 20 cases (14.49%, 13.3% overall) had a non-infective etiology.

Conclusions: Infections are the most common cause of prolonged fever in pediatric population - tuberculosis being the most frequent infection. Hematological malignancies were found as an emerging cause of prolonged fever in our study.

Keywords: Hematological malignancies, Prolonged fever, Prolonged undiagnosed fever

INTRODUCTION

Fever is defined as a rectal temperature of more than 38 degrees Celsius or 100.4°F.¹ It is differentiated from hyperthermia since it occurs in conjunction with an elevation of hypothalamic set point.² It is a general symptom of many diseases and is a very common reason for a child to seek medical care.³ It accounts, by some estimates, for one-third of all presenting conditions in children.^{3,4} Most febrile illnesses either resolve before a diagnosis can be made or develop distinguishing

characteristics that lead to a diagnosis. However, a persistent fever is a source of great anxiety to physicians and parents alike. A fever persisting beyond 1 week is an intriguing challenge for clinicians and remains overly medicated and inappropriately worked up provided a systemic approach is not followed. The non-specificity of symptoms and signs along with lack of availability of accurate diagnostics often leads to irrational use of antibiotics. A systematic approach to prolonged fever is therefore prudent. There have been many studies contributing data for etiology of prolonged fever in

pediatric population, however, most of it, being western data, it is difficult to apply these studies to countries with resource-limited settings where there is limited availability of expensive serological and other specific tests. Therefore, the present study was conducted to investigate the etiology of prolonged fever in children admitted in a tertiary care hospital in southern part of Rajasthan.

METHODS

This prospective observational study was conducted in Balchikitsalaya, Maharana Bhupal Hospital - a tertiary care hospital in southern part of Rajasthan, India, from November 2021 to October 2022 after receiving ethical clearance from the Institutional Ethics Committee. We enrolled 150 in-patients, aged 3 months to 18 years, fulfilling the inclusion criteria. Patients with a known immunocompromised status at presentation were excluded from the study.

The enrolled children were prospectively followed during their stay in hospital. Each patient was evaluated systematically as per a predesigned proforma. Prolonged fever was defined as a fever (perceived and expressed by parents or caretakers) of more than 7 days at presentation to the hospital. A detailed clinical history was taken regarding the symptom profile of the patient. Details were noted about the onset, duration, type of fever and associated symptoms if any. Exposure to wild or Domestic animals, history of Pica, travel history and medication history if any, were specifically asked for. Fever was documented by healthcare worker and parents-both, to rule out fraudulent fever. Axillary and/or Oral temperatures were recorded. Serial temperature recording and charting was done during their course of stay. A complete physical examination was done to search for Potential Diagnostic Clues (PDCs). Positive findings were noted for the same.

All the selected children underwent the following mandatory investigations to reach to the etiology of fever -CBC, PBF, CRPq, ESR, Urine Routine and Microscopy, Malarial Parasite Card Test, ELISA for Dengue, ELISA for Scrub, SGOT, SGPT, Chest Xray, Blood Culture etc.

In selected patients, we performed specific tests like serology for Brucellosis, Leptospirosis, Chikungunya; Lumbar puncture for CSF analysis, 2D Echocardiography, Serology for Rheumatological disorders, regional imaging using CT scan, MRI scan etc, regional biopsy, Covid test (as per latest national guidelines) etc based on PDCs.

Patients were monitored closely during their course of stay until discharge, at which the final diagnosis was charted. The final diagnosis was classified broadly as Infectious and Non-Infectious. Each broad category was further subclassified based on the specific etiology.

RESULTS

The mean age of our study population was 8.6 years. Among the 150 patients enrolled, there were 84(56%) males and 66 (44%) females, with a Male: Female ratio of 1.27:1 (as depicted in Table 1).

Table 1: Demographic data of the study population (n=150).

Demographic data	Number of patients
Age group	
3 to 12 month	9 (6%)
1 to 5 year	44 (29%)
5 to 10 year	37 (25%)
10 to 15 year	47 (31%)
>15 year	13 (9%)
Gender	
Males	84(56%)
Females	66(44%)

Table 2: Etiologies of prolonged fever along with their frequencies (n=150).

Etiology	N (%)
Tuberculosis	33 (22)
Scrub typhus	23 (15.3)
COVID-19	18 (12)
Malaria	15 (10)
UTI	9 (6)
Enteric fever	6 (4)
Pneumonia	5 (3.3)
Brain abscess	2 (1.3)
Dengue with complications	3 (2)
Supradiaphragmatic abscess	1 (0.6)
Pyothorax	1 (0.6)
HAV	3 (2)
HIV	3 (2)
Infectious endocarditis	2 (1.3)
HHV-6 + meningoencephalitis	1 (0.6)
Brucellosis	1 (0.6)
Leukemia/lymphoma	13 (8.6)
Rheumatic fever	2 (1.3)
Thyrotoxicosis	1 (0.6)
Munchausen syndrome by proxy	1 (0.6)
Kawasaki	1 (0.6)
SOJIA	1 (0.6)
Neuroblastoma	1 (0.6)
Undiagnosed	12 (8)

Our study population majorly covered patients from rural areas of Rajasthan wherein an overall out-patient as well as in-patient M:F ratio bends more toward male child population. A diagnosis could be reached for 138 patients (92%) and in 12 patients (8%), the cause of fever remained undiagnosed until discharge/death. Out of the 118 patients with an infectious etiology of fever,

maximum number was contributed by Tuberculosis patients -33 cases (28%, 22% overall). Second most common condition was Scrub typhus accounting for 23 cases (19.5%, 15.3% overall). It was followed by COVID-19 infection-consistent with 18 cases (15.2%, 12% overall) (Since our study was conducted during COVID-19 outbreak, a significant number of admissions corresponded to COVID-19 patients); Malaria-15 cases (12.7%, 10% overall); UTI-9 cases (7.6%, 6% overall) (Table 2).

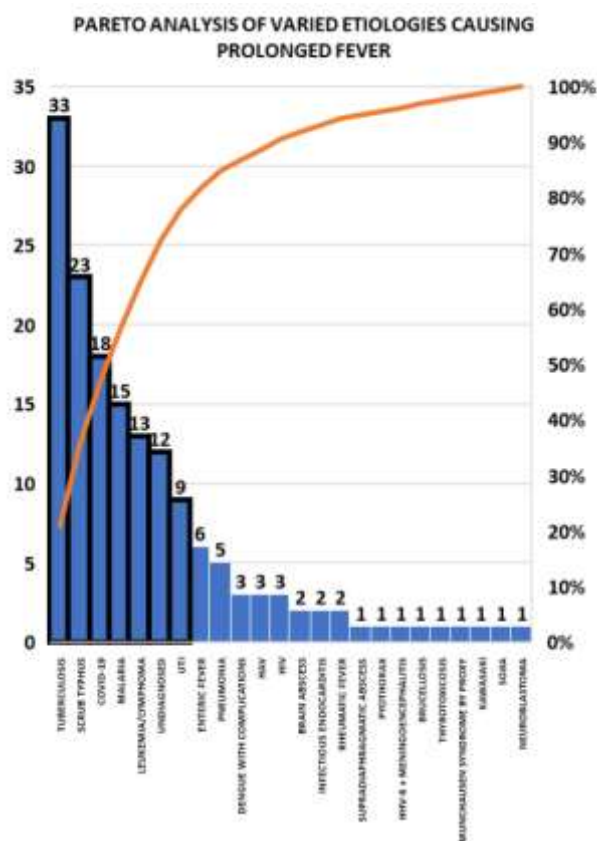


Figure 1: A pareto diagram representing the etiologies of prolonged fever (n=150).



Figure 2: The clinical findings along with the diagnosis of some of the cases enrolled in our study.

20 out of 138 diagnosed cases had a non-infectious etiology of fever accounting for 14.49% of the diagnosed cases and 13.3% of the overall cases enrolled. Malignancies formed a major fraction of non-infectious etiologies (14 out of 20 cases - 70%, 9.3% overall). Most of these cases (13 out of 20 cases - 65%, 8.6% overall) had a haematological malignancy associated- leukemia (12/13) being more common than lymphoma (1/13) at presentation. Besides hematological malignancies, one case presented with mass per abdomen and was diagnosed as having neuroblastoma.

An interesting finding we observed, was that- for every 5 patients of Tuberculosis (33), we had 2 patients of Hemato-reticular malignancies (13). Hemato-reticular malignancies contributed to a major fraction in the top 20 percent etiologies causing morbidity in 80 percent of our patients (Figure 1). Even though as a group, infections still remain the most common etiology of prolonged fever, individually taken, malignancies like leukemia/lymphoma contribute to a major fraction of morbidity in pediatric population.

DISCUSSION

Our study shows that infections are the predominant cause of prolonged fever in pediatric population- Tuberculosis being the most common infection accounting for twenty two percent of all the cases enrolled. Our study population hailed predominantly from a rural background. However, similar results have been demonstrated in a study conducted by Avinash et al. in a predominantly urban population, wherein the commonest infection still remained tuberculosis (TB) accounting for 12 out of 49 cases (24.5%).⁵ Similar results were also demonstrated in an adult population-based study conducted by Sharma et al. at PGIMER Chandigarh, in the diagnosis of prolonged undiagnosed fever, wherein, tuberculosis, was the most dominant cause of prolonged undiagnosed fever.⁶ However, the percentage of patients was even higher in this population and Tuberculosis contributed to the diagnosis of 50% of the patients enrolled.

According to the study conducted by Joshi et al. in 2008, Enteric fever was the most common infection (14 cases).⁷ This is in contrast with our study wherein enteric fever is accounting for 6 cases and tuberculosis is the commonest cause, accounting for 33 cases. The study by Joshi et al. was conducted in 2008 when the mainstay of typhoid treatment was a parenteral therapy with antibiotics.⁷ However, we now treat majority of typhoid cases on an out-patient basis with oral drugs and only the complicated patients get admitted. Also, with advent of newer and better diagnostic modalities, more and more Tuberculosis cases get diagnosed, accounting for the high number of TB cases in our study.

In the patients diagnosed with Tuberculosis at our centre, CBNAAT was positive in 22 out of 33 cases while

Mantoux was positive in 17 out of 33 cases. CXR findings could be demonstrated in 21 patients. MRI findings were positive in 2 patients, both these patients also had CBNAAT positivity. FNAC was suggestive of tubercular etiology in 4 patients and was the sole modality of diagnosis in 1 patient who also had coinfection with HIV. AFB is usually not done in our centre as CBNAAT is considered a first line investigation. However, AFB positivity was corroborative evidence in one patient. 2 cases had TB-HIV coinfection. 1 case had TB-COVID-19 coinfection and yet another had P.Falciparum-TB coinfection.

CT scan was done for 4 patients and was the sole modality for diagnosis in 3 patients with normal CXR and sputum/GA for CBNAAT. Similar observation was noted in the study conducted by Avinash et al., wherein Contrast enhanced computed tomography emerged as an important diagnostic investigation, picking up findings suggestive of TB in 6 patients who had normal X-rays and ultrasound scans.⁵

The second most common infection responsible for prolonged fever was Scrub Typhus. In this part of western India, Scrub typhus is a very common infection in children. In our study, it accounted for 23 cases- 15.3% of all the cases enrolled. There was an overlap/ coinfection of P.Vivax -Scrub Typhus and Dengue-Scrub Typhus.^{1,3} Out of all the tropical infections prevalent in our region, Scrub typhus was the most common cause of prolonged fever requiring admission to hospital- either for evaluation of the cause or for the complications associated with the disease.

Second to infections, the predominant cause of prolonged fever in the non-infectious etiology group was malignancies- especially haemato-reticular malignancies. 20 out of 138 diagnosed cases had a non-infectious etiology of fever accounting for 14.49% of the diagnosed cases and 13.3% of the overall cases enrolled. Malignancies formed a major fraction of non-infectious etiologies (14 out of 20 cases - 70%, 9.3% overall). Most of these cases (13 out of 20 cases - 65%, 8.6% overall) had a haematological malignancy associated- leukemia (12/13) being more common than lymphoma (1/13) at presentation. Besides haematological malignancies, one case presented with mass per abdomen and was diagnosed as having neuroblastoma.

Similar results were demonstrated by Joshi et al. wherein after infections, malignancies (12%) were the most common cause of prolonged fever.⁷ Our findings were also consistent with Sharma et al. who found an even higher percentage of patients with haematological and lymphoreticular system malignancies.⁶ Cruz et al. also concluded that malignancies, mostly Leukaemias were the predominant cause of prolonged undiagnosed fever in children, after infections.⁸ In a study from Turkey, Ergin et al. concluded that malignancies were the second most common cause of FUO in children, contributing 11.7

percent of all cases, the first common cause being infections.⁹ Contrary to this there have been studies which found that collagen vascular diseases were more common than malignancies. For instance, Avinash et al. found that 14 percent of cases were contributed by collagen vascular diseases, making them the second most common cause of FUO, after infections, in their study.⁵

The most common complaints of patients diagnosed with hemoreticular malignancies in our setting were difficulty in breathing and/ or swelling/mass. This was followed by pain abdomen and rash. Other presenting complaints were cough, joint pain, body ache, blood in urine and nasal bleeding. Out of the 13 cases diagnosed with hemato-reticular malignancies, we had 4 cases of Acute Lymphoblastic Leukemia - 2 diagnosed by bone marrow, 1 each by flow cytometry and FNAC. We also observed 1 case each of CML and AML, both diagnosed on flow cytometry. There was yet another case of Non-Hodgkin's Lymphoma, diagnosed on FNAC. The remaining 6 cases were not subtyped (owing to mortality/patients being referred to higher centres with pediatric hemato-oncologic setup) but were diagnosed either based on bone marrow examination or peripheral films.

We noticed a few unexpected causes of prolonged fever such as a case of Thyrotoxicosis in a known case of sickle cell disease who presented in sickling crisis with unremitting fever not responding to antipyretics and antibiotics. Fever was thought of to be due to an infectious etiology, but the child instead was in thyrotoxic storm causing hyperthermia. The patient responded to Propranolol and Methimazole and is on regular follow up for her TSH levels (Figure 2).

We also came across a case of Munchausen syndrome by proxy who presented with prolonged unremitting fever and had no episode of documented fever during the hospital stay and a completely normal clinical and laboratory profile. There was history of hospitalisation multiple times in the past along with regular OP visits for the same.

We had 12 patients with prolonged fever for whom the cause could not be diagnosed until death or discharge. This contributes to 8 percent of the total cases. A viral etiology had, in most cases been suspected but specific tests could not be carried out due to financial constraints and limited availability of tests. Similar percentage was observed by Avinash et al. and Joshi et al., each having about 12 percent of the total cases with undiagnosed cause of fever. Ramachandran et al., on the other hand, observed 4 percent of patients with an undiagnosed etiology of prolonged fever.^{5,7,10}

We performed a pareto analysis of all the etiologies of prolonged fever and found that twenty percent of etiologies (Tuberculosis, Scrub Typhus, COVID-19, Malaria, Hemato-reticular malignancies and Urinary

Tract Infections) were the cause of prolonged fever in eighty percent of our study population and rest eighty percent etiologies accounted for the remaining twenty percent of the study population (Figure 1).

CONCLUSION

Infections have been found as the most frequent cause of prolonged fever (>7 days' duration) in pediatric patients between the age of 3 months and 18 years, presenting to our center. Tuberculosis was the leading cause of the infections diagnosed while Tuberculosis, Scrub Typhus, COVID-19, Malaria, Hematological malignancies, and Urinary Tract Infections contributed to eighty percent etiologies of prolonged fever in pediatric population at our center (Figure 1). Hematological malignancies were found as an emerging cause of prolonged fever in our study.

Recommendations

Repeated, thorough clinical examination and carefully selected laboratory examinations proved useful in the diagnosis of prolonged fever.

Availability of specific serological/PCR based laboratory tests would help yield better outcomes by providing accurate diagnosis and targeted therapy along with demoting antibiotic abuse.

In a setting where we rarely think beyond infections, an unbiased approach helps yield rarer diagnosis and establish accurate management plans. However, sensitization of a primary health worker about certain commoner etiologies is a key element in diagnosing and better managing most cases of prolonged fever. Further, multi-centered studies should be carried to know whether our results are replicable and to formulate diagnostic guidelines in pediatric patients with prolonged fever.

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