Original Research Article

Expert perspectives on paracetamol for managing pediatric febrile illness in Indian settings

ABSTRACT

Objective: To examine expert perspectives on the prescription practices and clinical uses of paracetamol for managing pediatric febrile illness in routine Indian healthcare settings
Methods: The study utilized multiple-response questionnaires distributed electronically to clinicians via email or online platforms. The survey comprised 30 questions pertaining to current clinical feedback, observations, prescription practices, clinical use of paracetamol, and experiences related to pediatric febrile illness in routine clinical settings. Descriptive statistics were used to analyze the data.
Results: The study included 341 experts, and the majority (72.43%) identified upper respiratory tract infections as the most common cause of pediatric acute febrile illness. About 50.73% of physicians encountered 40-50% of pediatric patients with fever in outpatient clinics, and seizures were the most commonly reported complication (66%). Oral temperature measurement (53.08%) and digital thermometers (67%) were commonly preferred for fever assessment. Paracetamol (49.56%) and paracetamol with mefenamic acid (42.82%) were the most commonly prescribed antipyretics. Viral infections were cited as the leading cause of fever cases (71%). About 60.41% clinicians reported low incidence of hepatotoxicity due to paracetamol and refrained from prescribing N-acetylcysteine for paracetamol toxicity (63%). Majority (66.57%) of the respondents reported the paracetamol suspension to be satisfactory, with strawberry (31.09%) and mango (32.55%) being the preferred flavors among pediatric patients.
Conclusion: According to the survey results, paracetamol was favored as the first-line antipyretic, with many clinicians opting for combination therapy with mefenamic acid. Viral infections are highlighted as the primary cause of pediatric fevers. The survey also revealed positive perceptions regarding the flavor and packaging of paracetamol suspension.

Keywords: Paracetamol suspension, pediatric febrile illness, upper respiratory tract infections, antipyretics

1. INTRODUCTION

Fever, commonly described as a body temperature higher than 38.0°C (100.4°F), is a common clinical symptom, particularly in children. Pediatric febrile illnesses pose a major diagnostic challenge in routine clinical settings and are a leading cause of hospital admissions. Febrile illnesses in children and infants constitute 20% of pediatric consultations. In developing countries, unaddressed comorbidities, reduced immunization rates, and delayed medical interventions add to the associated burden [1]. Fever incidence varies widely, with country-specific reports showing between two to nine febrile episodes per child under age five per

year, averaging around 5.88 episodes annually [2]. Multiple studies have also highlighted fever as the most common presenting symptom in pediatric health facilities and communities [3,4].

In India, very little research has been conducted on fever without a clear source, and there was no definite data on the prevalence of severe bacterial infections in this population subset. According to the National Family Health Survey round 4 (2015–2016) in India, 12.8% of children under five had experienced fever in the two weeks prior to the survey date [5]. Studies suggest that acute respiratory infections are the major cause for 50%–75% of febrile episodes noted in children under 5 years visiting outpatient settings [6].

The drugs frequently employed for pediatric fever treatment include paracetamol, aspirin, and ibuprofen. These medications exert their effects by targeting various points along the biochemical pathway leading to fever [7,22,23,24]. Major guidelines for pediatric fever management and paracetamol use include recommendations from the American Academy of Pediatrics (AAP), National Institute for Health and Care Excellence (NICE), and Centers for Disease Control and Prevention (CDC). These guidelines emphasize weight-based dosing, appropriate monitoring, and caution against overuse or misuse of antipyretics like paracetamol in children [8,9]. Paracetamol exerts its analgesic and antipyretic effects by the inhibition of COX-1 and COX-2 through peroxidase metabolism, blocking prostaglandin synthesis and cyclooxygenase activity [10].

The present cross-sectional survey was intended to gather expert perspectives regarding the prescription practice and clinical use of paracetamol, as well as experiences and observations related to pediatric febrile illness in routine clinical settings.

2. MATERIALS AND METHODS

We carried out a cross sectional, questionnaire based study among pediatricians in the major Indian cities from June 2023 to December 2023

2.1 Questionnaire

The questionnaire booklet titled FACT (Fever Management and Care in Paediatrics: Role of Paracetamol and combinations) study was sent to the pediatricians who were interested to participate in this study. The FACT study questionnaire comprised 30 multiple choice questions addressing current feedback, clinical observations, and specialists' experiences pertaining to prescription practices and clinical use of paracetamol, along with experiences and observations related to pediatric febrile illness in routine clinical settings. Reliability as determined by a split-half test (coefficient alpha) was adequate but should be improved in future versions of the questionnaire. A study of criterion validity was undertaken to test the questionnaire and to develop methods of testing the validity of measures of Physicians Perspectives. However, the extraneous variable in this includes the clinicians experience, usage of the newer drugs etc. The two criteria used were the doctors' perspectives from the clinical practice and the assessment of an external assessor and statistician.

2.2 Participants

An invitation was sent to leading pediatricians in managing pediatric febrile illness in the month of March 2023 for participation in this Indian survey. About 341 pediatricians from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Clinicians had the option to skip any questions they did not want to answer. They were instructed to complete the survey individually, without consulting their coworkers.

2.3 Statistical Methods

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to provide a clear insight into their distribution. The frequency of occurrence and corresponding percentage were used to represent the distribution of each variable. Graphs and pie charts were created using Microsoft Excel 2013 (version 16.0.13901.20400) to visualize the distribution of categorical variables.

3. RESULTS

The survey sought the expert opinion of 341 clinicians, and the majority reported (72.43%) upper respiratory tract infection as the most common cause of pediatric acute febrile illness in routine settings. Majority of the clinicians (50.73%) reported encountering 40-50% of pediatric patients with fever in their outpatient clinics. According to 66% of the clinicians, seizures were the most commonly reported complication. Nearly half of the respondents (53.08%) reported oral measurement as the most common method for measuring body temperature. Approximately 67% of the clinicians reported digital thermometers as the primary device used for accurate fever measurement in pediatric patients.

Majority of the clinicians prescribed paracetamol (49.56%) as the most commonly used antipyretic for children, followed by a combination of paracetamol and mefenamic acid (42.82%) (Fig. 1). According to 71% of clinicians, viral infections were the leading cause of fever cases in pediatric clinical practice (Table 1). Approximately 44% of clinicians stated that paracetamol was the most commonly recommended management intervention for patients with high-grade fever. Majority of clinicians (60.41%) reported that less than 1% of their patient's experience hepatotoxicity as a complication of paracetamol toxicity, and 63% indicated that they do not prescribe N-acetyl cysteine as an antidote for paracetamol toxicity.

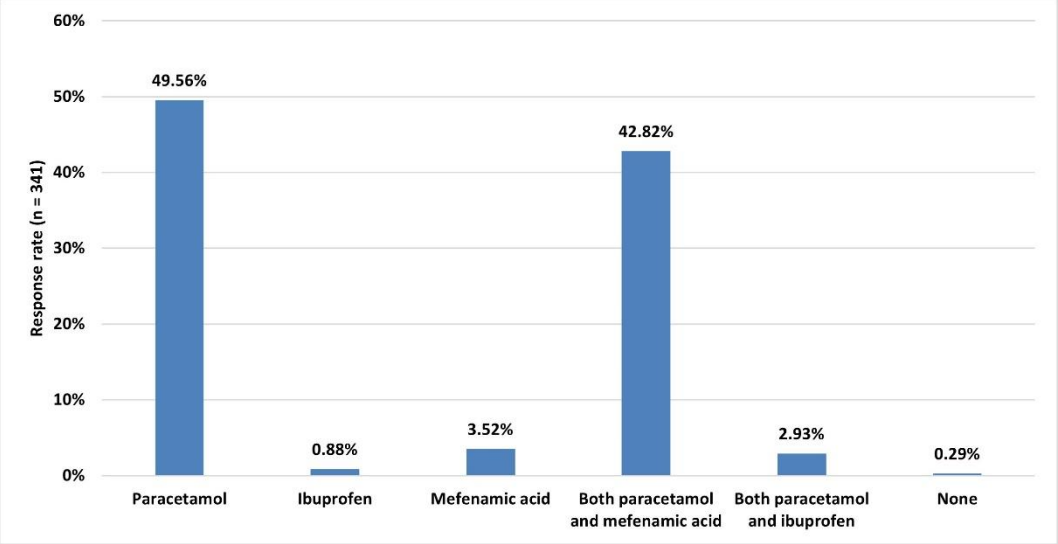

Fig. 1: Distribution of response to most commonly prescribed antipyretics in children

Table 1: Distribution of response to the most common cause of fever cases in pediatric clinical practice

Common cause of fever	(n = 341)
Bacterial infections	81 (23.75%)
Viral infections	242 (70.97%)
Protozoal and fungal infections	1 (0.29%)
Post-vaccination	5 (1.47%)
All of the above	11 (3.23%)
Malignancy	1 (0.29%)

A significant number of clinicians (39.59%) reported that less than 10% of patients experiencing complications with ibuprofen were switched to paracetamol in clinical practice. Approximately 52% of the experts stated that the percentage of patients with low-grade fever who do not respond to treatment with paracetamol is <5%. Approximately 37% of clinicians reported prescribing antibiotics along with paracetamol in 25-50% of pediatric cases, while 34.9% prescribed in 10-25% of cases. A significant proportion of clinicians (45.16%) stated experiencing fever persistence for more than 3 days in 26-50% of pediatric cases.

Approximately 72% of the respondents recommended a dose of 15 mg/kg of paracetamol for pediatric patients with low-grade fever less than 101°F (Table 2). A significant proportion of clinicians (32.26%) recommended the addition of NSAIDs in pediatric patients with more than 102°F. Around 48% of the respondents preferred a combination of paracetamol and mefenamic acid for high-grade fever (Fig. 2). With regard to the proportion of patients belonging to the age group of 8-12 years visiting the clinic, around 35% of the clinicians reported it as 20-30%.

Table 2: Distribution of response to the recommended dose of paracetamol for low-grade fever (<101°F) in pediatric patients

Dose	(n = 341)
10 mg/kg	84 (24.63%)
15 mg/kg	245 (71.85%)
Prefer combination with NSAIDs	11 (3.23%)
None	1 (0.29%)

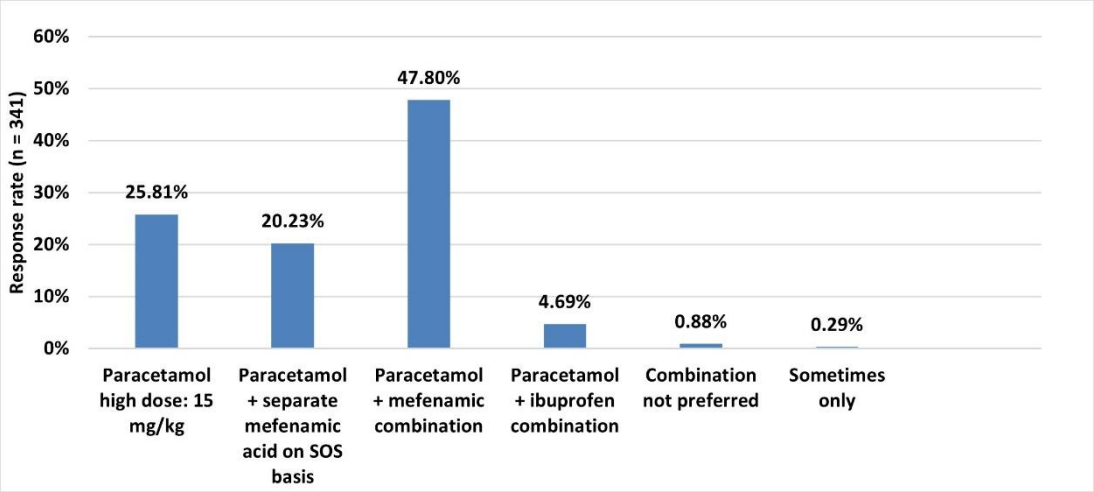

Fig. 2: **Distribution of response to treatment preference in high-grade fever conditions**
(SOS- if necessary)

Majority (55.72%) of the pediatricians indicated that 100 ml dosage form of paracetamol 250 mg/5 ml was necessary for children weighing above 20 kg for complete therapy. A large proportion (68.04%) of clinicians reported that <25% of pediatric patients visiting the clinic were obese. Approximately 40% of clinicians indicated a preference for the paracetamol + mefenamic acid combination for managing <25% of their patients, while 39% preferred the combination for 26-50% of their patients. Around 64% of the respondents indicated that they prefer the paracetamol + mefenamic acid fixed-dose combination over others for treating fever in pediatric patients (Fig. 3).

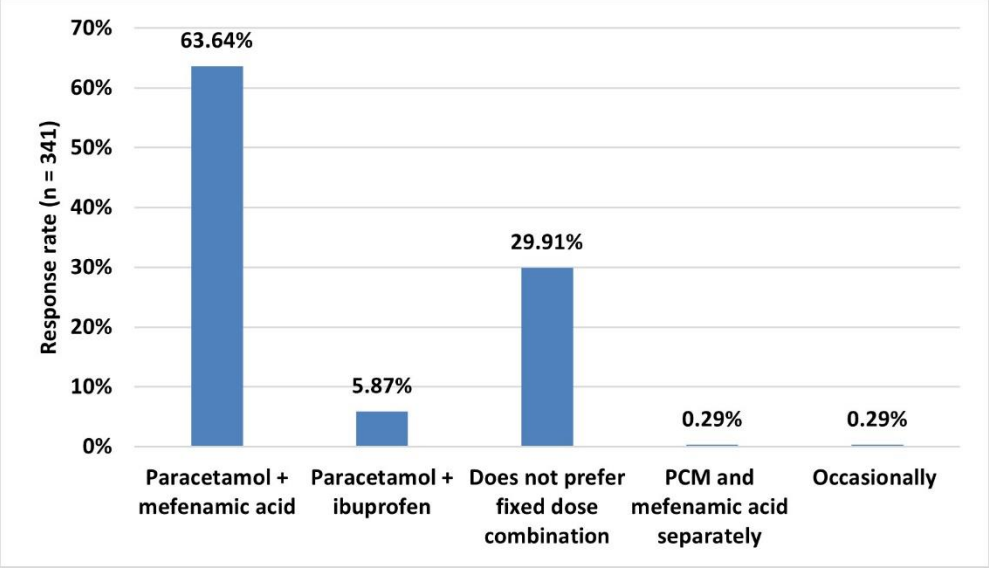

Fig. 3: Distribution of response to preference for fixed-dose combination for treating fever in pediatric patients
(PCM- Paracetamol)

Majority (66.57%) of the respondents reported that they found the paracetamol suspension (to be satisfactory. Approximately 32% of the experts recommended prescribing tablet forms of paracetamol for pediatric patients aged over 12 years (Table 3). According to 36% of clinicians, half-dosage paracetamol 650 was frequently prescribed to pediatric patients based on body weight.

Table 3: Distribution of response to age of pediatric patients recommended with tablet forms of paracetamol

Age of pediatric patients	**(n = 341)**
>8 years	78 (22.87%)
>10 years	81 (23.75%)
>12 years	112 (32.84%)
>15 years	46 (13.49%)
Do not recommend tablet dosage forms to children	22 (6.45%)

Around 57% of pediatricians reported the flavor of paracetamol suspension as excellent. According to 31% and 32% of the clinicians, strawberry (31.09%) and mango (32.55%) were the most preferred flavors of paracetamol syrup among pediatric patients in clinical practice, respectively. Majority of the clinicians rated the packaging of paracetamol suspension as excellent. Most experts preferred using handwritten papers for educating parents on paracetamol syrup dosing and administration (81.52%).

4. DISCUSSION

The cross-sectional survey provides valuable insights into current clinical practices and preferences surrounding the use of paracetamol in pediatric fever management. Majority of the clinicians identified upper respiratory tract infections as the primary cause of pediatric acute febrile illness, with viral infections recognized as the leading cause of fever cases. The survey findings underscore the importance of differentiating viral infections from other causes to guide appropriate treatment decisions.

Respiratory tract infections are responsible for approximately 3.9 million deaths annually among pediatric subjects globally [11]. India ranks among the 15 countries with the highest burden of total pneumonia episodes and associated childhood mortality. In India alone, about 400,000 children under the age of five succumb to acute respiratory infections each year. Studies indicate that 13–16% of all child deaths occur among pediatric hospital admissions due to acute respiratory infections [12,13]. A systematic review by Mathew et al. noted that acute respiratory infections contribute to approximately one-fourth of global annual deaths in children under five years old, highlighting its profound impact on public health in India [14]. In accordance with the current survey findings on viral infections, a hospital-based observational study conducted by Yadav et al. involving 90 children noted that the most frequent cause of fever accompanied by a rash was viral, accounting for 51.1% of cases. Among the viruses identified, measles was the predominant pathogen, representing 15.55% of cases, followed by Chikungunya at 14.44% [15].

The increased preference noted in the current survey for oral temperature measurement and digital thermometers for fever assessment underscores the importance of adopting standardized techniques in clinical practice. Although oral measurement was the most commonly used technique for assessing body temperature, it was considered unreliable for measuring core body temperature due to its susceptibility to environmental influences and bias from factors like smoking or consumption of hot or cold beverages before measurement. Furthermore, risks of mouth-to-mouth cross-infection or oral mucosa laceration may occur. Additionally, variations in temperature readings can arise depending on the specific location where the thermometer's bulb is placed within the oral cavity [16]. A Danish study by Jensen et al. concluded the precision of oral electronic thermometers as unsatisfactory, and the use of this device cannot be recommended for daily clinical practice. The researchers compared oral electronic thermometer with a mercury thermometer used rectally in daily clinical practice. On average, rectal temperatures were 0.7°C higher than oral temperatures. In 27% of cases, the difference between rectal and oral measurements exceeded 1°C [17].

Paracetamol was identified as the most commonly preferred antipyretic, with a significant proportion of clinicians also opting for a combination of paracetamol and mefenamic acid. This suggests a preferred regimen for managing fever in pediatric patients, particularly in outpatient settings. Similar to the current study findings, an observational cross-sectional survey conducted by Kamel et al. in Jeddah, Saudi Arabia, found paracetamol to be the most common antipyretic used by caregivers (54%) to manage fever in the pediatric age group [18]. Furthermore, a double-blind randomized placebo-controlled trial conducted by Hema et al. demonstrated that paracetamol effectively reduces fever and provides early symptomatic relief in febrile children without prolonging fever duration or causing significant adverse effects. The study showed comparable fever clearance time ($P = 0.23$), a significantly faster rate of temperature reduction ($P < 0.001$), and a greater percentage reduction in temperature ($P < 0.001$) within the first four hours' post-administration. Paracetamol also resulted in a higher proportion of afebrile children after 4 hours ($P < 0.001$) and significantly better symptomatic improvement at 6 hours ($P < 0.001$), with no observed serious clinical or biochemical adverse effects [19].

The survey respondents reported low incidence of hepatotoxicity due to paracetamol and the majority indicated that they do not prescribe N-acetyl cysteine as an antidote for paracetamol toxicity. In India, instances of paracetamol toxicity in children were considered rare and infrequently reported [20]. Prolonged administration of supratherapeutic doses of paracetamol (>90 mg/kg/day) to a sick child of <2 years of age for >1 day poses a significant risk of hepatotoxicity. In cases of acute ingestion, hepatotoxicity was associated with a higher dose of 150 mg/kg. A case series by Shivbalan et al. highlighted the significance of initiating N-acetyl cysteine at the earliest, as outcomes have been better when administered before severe liver injury. With regard to N-acetylcysteine administration, it was unnecessary if both paracetamol levels (<20 µg/mL) and transaminase levels are normal. However, if there was a delay in obtaining these values, initiating N-acetyl cysteine was advisable and can be discontinued if subsequent results were normal. Conversely, N-acetyl cysteine was recommended if paracetamol levels exceed 20 µg/mL and ALT levels were elevated (>2 times the upper limit of normal) [21].

The preferences for specific dosage forms (e.g., 100 ml suspension for children >20 kg) and flavors of paracetamol syrups reflect considerations related to adherence and ease of administration in pediatric patients, which can impact treatment compliance and efficacy. The survey findings hold significant relevance as they assist clinicians in decision-making, optimize pediatric fever treatment strategies, enhance safety measures, and improve patient-centered care. The use of handwritten materials for educating parents on paracetamol dosing highlighted the need for effective communication strategies between clinicians and caregivers

to ensure safe and appropriate medication use in pediatric settings. Findings related to paracetamol dosing, temperature measurement, and antipyretic preferences can guide continuing medical education initiatives to enhance clinicians' knowledge and skills in pediatric fever management.

The major strengths of the study were the sample size and the use of a meticulously designed and validated questionnaire to collect expert data. However, it was essential to acknowledge that personal perspectives and preferences might have influenced the conclusions, thereby increasing the potential for bias. Consequently, it was imperative to interpret the results with these limitations in consideration. Moreover, additional research was warranted to validate and broaden the scope of the current survey findings.

4. CONCLUSION

Based on the survey findings, upper respiratory tract infections emerged as the predominant cause of pediatric acute febrile illness, with seizures reported as the most common complication. Oral temperature measurement and digital thermometers were widely utilized for fever assessment in routine settings. Paracetamol was the favored antipyretic, often prescribed alone or in combination with mefenamic acid. Viral infections were identified as the primary cause of pediatric fevers. Additionally, clinicians expressed positive perceptions regarding the flavor and packaging of paracetamol suspension.

COMPETING INTERESTS DISCLAIMER:
Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

Consent

All clinicians provided written informed consent prior to the survey.

Ethical Approval

The study was conducted after receiving approval from Bangalore Ethics, an Independent Ethics Committee which is recognized by the Indian Regulatory Authority, Drug Controller General of India.

REFERENCES

1. Darishetty G, Kompally V, Nagajyothi V V, et al. Exploring Acute Febrile Illness in Children: Clinical Characteristics and Diagnostic Challenges. Cureus. 2024;16(4):e58315.
2. Herlihy JM, D'Acremont V, Hay Burgess DC, Hamer DH. Diagnosis and Treatment of the Febrile Child. In: Black RE, Laxminarayan R, Temmerman M, Walker N, editors. Reproductive, Maternal, Newborn, and Child Health: Disease Control

Priorities, Third Edition (Volume 2), Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2016.
3. Mukanga D, Tiono AB, Anyorigiya T, Källander K, Konaté AT, Oduro AR, et al. Integrated community case management of fever in children under five using rapid diagnostic tests and respiratory rate counting: a multi-country cluster randomized trial. Am J Trop Med Hyg. 2012;87:21–9.
4. D'Acremont V, Kilowoko M, Kyungu E, Philipina S, Sangu W, Kahama-Maro J, et al. Beyond malaria--causes of fever in outpatient Tanzanian children. N Engl J Med. 2014;370:809–17.
5. National Family Health Survey (NFHS-4) 2015-16. [Internet]. [cited 2024 May 8]. Available from: https://rchiips.org/nfhs/NFHS-4Reports/India.pdf
6. Pradhan HS, Mohakud NK, Pugalia R, Satpathy SK. Costing of Febrile Illness among Under Five Children, A Study in a Tertiary Care Teaching Hospital in Odisha, India. J Glob Infect Dis. 2019;11:135–9.
7. Meremikwu MM, Oyo-Ita A. Paracetamol versus placebo or physical methods for treating fever in children. Cochrane Database Syst Rev. 2002;2002:CD003676.
8. Hoover L. AAP Reports on the Use of Antipyretics for Fever in Children. Afp. 2012;85:518–9.
9. Freo U, Ruocco C, Valerio A, Scagnol I, Nisoli E. Paracetamol: A Review of Guideline Recommendations. J Clin Med. 2021;10:3420.
10. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. Inflammopharmacology. 2013;21(3):201-32.
11. Kwiyolecha E, Groendahl B, Okamo B, Kayange N, Manyama F, Kidenya BR, et al. Patterns of viral pathogens causing upper respiratory tract infections among symptomatic children in Mwanza, Tanzania. Sci Rep. 2020;10(1):18490.
12. Jain N, Lodha R, Kabra SK. Upper respiratory tract infections. Indian J Pediatr. 2001;68(12):1135–8.
13. Vashishtha VM. Current status of tuberculosis and acute respiratory infections in India: much more needs to be done! Indian Pediatr. 2010;47(1):88–9.
14. Mathew JL, Patwari AK, Gupta P, Shah D, Gera T, Gogia S, et al. Acute respiratory infection and pneumonia in India: a systematic review of literature for advocacy and action: UNICEF-PHFI series on newborn and child health, India. Indian Pediatr. 2011;48(3):191–218.
15. Yadav A, Sarkar R, Mendiratta V, Jais M, Basu S, Sonker S. A Study of Viral Causes of Fever with Rash in Children. Indian Journal of Paediatric Dermatology. 2024;24:268–72.
16. Hymczak H, Gołąb A, Mendrala K, Plicner D, Darocha T, Podsiadło P, et al. Core Temperature Measurement—Principles of Correct Measurement, Problems, and

Complications. International Journal of Environmental Research and Public Health. 2021;18(20):10606.

17. Jensen BN, Andreasen H, Kjaergaard B, Glavind K. Should electronic mouth thermometers be used in routine everyday hospital practice? Usefulness of mouth thermometers. Ugeskr Laeger. 1989;151(39):2514–6.
18. Kamel F, Magadmi R, AbuOuf NM, Alqahtani FS, Bamousa AA, Alqutub AT, et al. Knowledge, Attitude, and Practice of Paracetamol and Ibuprofen Administration Among Caregivers of the Pediatric Age Group in Jeddah. Cureus. 2021;13(1):e12460.
19. Gupta H, Shah D, Gupta P, Sharma KK. Role of paracetamol in treatment of childhood Fever: a double-blind randomized placebo controlled trial. Indian Pediatr. 2007;44(12):903–11.
20. Whitington PF, Alonso EM, Squires RH. Acute Liver Failure. In: Diseases of the Liver and Biliary System in Children [Internet]. John Wiley & Sons, Ltd; 2008 [cited 2024 May 11]. p. 169–88. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781444300536.ch7
21. Shivbalan S, Sathiyasekeran M, Thomas K. Therapeutic misadventure with paracetamol in children. Indian J Pharmacol. 2010;42(6):412–5.
22. I Chidiebere, O. D., Uchenna, E., Stanley, O., & Bernard, E. E. (2014). Umbilical Cord Care Practices and Incidence of Febrile Illnesses in the First Month of Life among Newborns- A Population Based Study. Journal of Advances in Medicine and Medical Research, 5(11), 1422–1430. https://doi.org/10.9734/BJMMR/2015/14056
23. Mohamed, H. T. E., Alruwaili, I. K., Alenazi, M. H. F., alanazi, A. sultan and Alenezi, N. T. M. (2021) “Febrile Convulsions in Anemic Children: A Review”, Journal of Pharmaceutical Research International, 33(44A), pp. 392–399. doi: 10.9734/jpri/2021/v33i44A32630.
24. Morrison AK, Chanmugathas R, Schapira MM, Gorelick MH, Hoffmann RG, Brousseau DC. Caregiver low health literacy and nonurgent use of the pediatric emergency department for febrile illness. Academic pediatrics. 2014 Sep 1;14(5):505-9.