FEBRILE INFANT AND SMALL CHILD, A RATIONAL SOLUTION OF THE PROBLEM.

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1. ABSTRACT

1.1 Aim:
The aim of this systematic review is an approach in the clinical management of fever in children younger than 5 years of age.

1.2 Objectives:
To summarize, identify and evaluate guidelines and articles for the clinical management of fever in children younger than 5 years old. Lastly, to determine the relative use of strategies for managing febrile children and to determine an easy way for clinicians to adhere to protocol recommendations.

1.3 Data sources: Electronic data bases were searched up to 2007-2017. We used a 10% of literature older than these dates.

1.4 Review methods: The systematic review was conducted using relevant publications in PubMed, guideline websites, Google scholar and Pediatric Journals. These searches along with textbook chapters on the febrile child in commonly accepted textbooks of pediatrics and pediatric emergency medicine were reviewed. Our research was conducted in both Spanish and English.

1.5 Results: Previous recommendations are substantially reaffirmed. This systematic review is based on NICE guidance, which was revised after careful consideration of the evidence available. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. Antipyretics should be administered with the purpose to control the child’s discomfort. Combined use of paracetamol and ibuprofen is discouraged, considering risk and benefit.

1.6 Conclusion: Most guidelines were recommended for use even if with modification, especially in the methodology, the applicability and the editorial independence domains. Our results could help
improve reporting of future guidelines, and affect the selection and use of guidelines in clinical practice.

1.7 **Key words:** Children, Children under 5 years, Fever, Febrile infant, Pediatric Fever, Serious bacterial infection.

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2. **ACKNOWLEDGEMENTS**

First and foremost my earnest thanks to Prof. Doc. Rimantas Kėvalas, for supporting this project. I am grateful for his valuable advice, constructive criticism, positive appreciation and counsel throughout the course of the investigations which led to the successful completion of the systematic research work.

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Last, but not least, the most special thanks goes to my best partner and friend, my boyfriend, Johnathan T. for his continued and unfailing love, support and understanding during the completion of this thesis.

3. **CONFLICT OF INTEREST**

The author declare that she has no competing interests.

4. **ETHICS APPROVAL AND CONSENT TO PARTICIPATE**
5. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>APP</td>
<td>American Academy of Pediatrics</td>
</tr>
<tr>
<td>ABX</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>APC</td>
<td>Antigen-presenting cell</td>
</tr>
<tr>
<td>ACEP</td>
<td>American College of Emergency Physicians</td>
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<tr>
<td>ADR</td>
<td>Adverse reaction</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CV</td>
<td>Conjugated vaccine</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CRT</td>
<td>Capillary refill time</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest X-ray</td>
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<tr>
<td>FUO</td>
<td>Fever of unknown origin</td>
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</table>
GP  General practitioner
GA  Gestational age
HIB Haemophilus influenzae type B
HR  Heart rate
HSV Herpes simplex virus
IV  Intravenous
Ig  Immunoglobulin
IgG Immunoglobulin G
IgA Immunoglobulin A
MenB Serogroup B meningococcus
NK  Natural killer
NICE National Institute of Health Excellence
PCV7 Pneumococcal conjugate vaccine- heptavalent
PCV13 Pneumococcal conjugate vaccine- tridecavalent
RR  Respiratory rate
SBI Serious bacterial infection
UA  Urine analysis
UTI Urinary tract infection
WHO World Health Organization
WBC White blood cell
YOS Yale Observation Scale
YIOS Young Infant Observation Scale
6. INTRODUCTION

Throughout the years, the field of medicine has evolved into a multifaceted study of the human body. Today with the existence of over 100 specialties, many physicians experience an unique set of encounters. Perhaps one of the most challenging and common encounters within the field of pediatrics department are patients who present concerns of “fever” to healthcare providers.

Fever is among the most common presenting complaints of children and infants and number one cause of alarm in parents “fever phobia”. Fever represents a normal physiologic response that may result from the introduction of an infectious pathogen into the organism, with a rectal temperature greater than 38°C (>100.4 °F). About 20% of febrile children have fever of unknown origin (FUO) after a complete history and physical examination. Despite advances in healthcare, infections remain the leading cause of death in children under the age of 5 years.

Over the years a lot of different approaches have been evolved in pediatric, family medicine and emergency medicine. What follows is an overview of management of fever in young children, specially taking into account different group ages: 0-3 months of age, 3-36 months of age and 3-5
Because children of different ages have important differences in the cause and outcome of fever-generating illnesses. In most cases, the illness is due to a self-limiting viral infection. Some children may appear clinically unwell or have abnormal screening investigations, meanwhile a small percentage of them will eventually be found to have a clinically undetectable serious bacterial infection (SBI), such as urinary tract infection (UTI), occult bacteremia, bacterial meningitis or pneumonia. UTI’s are the most common cause, in boys around 3-4% younger than 1 year and mainly in those who are uncircumcised, although in girls occur in 8-9% younger than two years old of age. In a child with fever, estimating the risk of SBI remains a diagnostic challenge. The young human child, even as the innate and adaptive immune systems start to mature, is at risk from many pathogenic viruses, bacteria, fungi and parasites. The immune system gradually matures during infancy and therefore the risk of SBI decreases between 3 and 36 months, and from this age onwards, is considered to be minimal.

On the other hand, the introduction of new vaccination programmes may have significantly reduced the level of admissions to hospital, such as the heptavalent pneumococcal conjugate vaccine (PCV7) in the recent years, and more recently PCV13, has led to a decrease in the prevalence of SBI, specially in occult pneumococcal bacteremia, modifying the diagnostic-therapeutic management of children under three years of age. Also the frequency of meningitis has also decreased with the use of conjugated vaccines (CV) against Haemophilus influenzae type b (HIB), Streptococcus pneumoniae, and meningococcus C. However, evidence suggests a 68% increase in the prevalence of disease caused by subtypes of bacteria not covered by vaccination programmes. The next challenges in this regard will be the expansion of vaccine coverage with conjugated pneumococcal vaccine and the universal application of the meningococcal vaccine B, already available for selected cases.

7. OBJECTIVES

The main objective of this thesis is an aged-based approach to investigations and mostly clinical management of fever in children younger than 5 years of age. Moreover, which methods of biological samples are required for the proper management of feverish children and how to classify them according their risk for a serious infection.

1. Considering different groups of age in pediatric patients:
   - Management of fever in infant 0-90 days.
   - Management of fever in children 91 days to 36 months.
   - Management of fever in children up to 5 years.
2. To define when and what investigations should be considered.

3. Which treatment is best required. Antipyretic treatment, as well as, physical measures.

4. To assess the need for further investigations or just observation of the pediatric patient.

The primary outcomes of the research were to encourage the improvement of the quality of the guidelines to reinforce the most common recommendations and to stimulate further research on discordant recommendations primarily between Lithuania, Spain, UK, and USA in order to unify medical behaviour.

8. METHODS

8.1 Search strategy:

We searched the databases of PubMed, Google Scholar, Web of knowledge, articles, Pediatric Journals, International and National Pediatric Guidelines up to 2007-2017. These searches along with textbook chapters on the febrile child in commonly accepted textbooks of pediatrics and pediatric emergency medicine were reviewed, in order to develop a comprehensive database of peer reviewed literature. Hand-search was performed after screening the retrieved articles for pertinent publications. An exhaustive research was made to assess the highest quality of those sources. Studies included were directed to the pediatric population but restricted to children under five years of age. We used the following search terms: child or children, fever or febrile, serious bacterial infection, bacteremia, and antipyretics.

8.2 Study selection:

Inclusion/exclusion criteria
Guidelines or reviews that did not focus on the management of fever were excluded. Protocols were included in the research. The scientific data collected is not older than 10 years old. Abstracts were reviewed and full-text articles and others were obtained for research that met the eligibility criteria.  

Age stratification:  
We have conducted this study based on age groups: young infants (up to three months); older infants (91 days to 36 months) and young children up to 5 years old.

8.3 Management:  
This review concentrates on the management of febrile children. We used NICE Guidelines as well as protocols such Boston, Philadelphia and Rochester. However, although these protocols have been well-validated, they are not absolute. Boston and Philadelphia protocols excluded infants under 1 month of age. Furthermore, YALE and YIOS scales were also studied. As well as Spanish protocols and clinical guidelines in feverish children.

8.4 Data extraction:  
Literature searches were performed specifically for each pediatric age group. Pertinent publications in English and Spanish were identified through online and hand-searches in the previous mentioned databases. This selection of studies, evaluation and data extraction process were selected according their level of scientific evidence. The data extracted from each study/guideline was summarized in decision trees specific to each group age.

9. RESULTS AND THEIR DISCUSSION  
Fever plays an important physiologic role in response to infection, inhibiting bacterial growth and viral replication, and enhancing the immune response. Furthermore, it is a vital symptom for diagnosis.  

Fever occurs when there is a rise in the hypothalamic set point in response to endogenously produced pyrogens. Among the broad range of conditions that cause fever are infections, malignancies, autoimmune diseases, metabolic diseases, chronic inflammatory conditions, medications (including immunizations), CNS abnormalities, and exposure to excessive environmental heat. In most settings, the majority of fevers in pediatric patients are caused by self-limiting viral infections. In a child, many infections disease either single or in combination could present with fever. Teething does not cause fever.

Regarding the use of antipyretics, it has been proved that it does not prolong illness in children. Nevertheless, since fever itself is not dangerous, antipyretic treatment should be
reserved for distressed children, aiming at improving the child’s wellbeing rather than achieving normothermia. Several studies have reported a high percentage of parents/tutors/caregivers administering antipyretics even when there is minimal or no fever, with wrong dosages or with insufficient intervals between doses.\textsuperscript{32,34,94} Moreover, the response to antipyretics cannot predict the severity of the underlying illness. The majority of feverish children have benign viral illness, but in a small, defined percentage the fever is the first sign of a more serious infection.\textsuperscript{30,44,80,98}

Fever management may differ in different group ages and in specific clinical situations.

9.1 Initial evaluation:

When evaluating a child with fever, one should elicit from the parents information about the duration of fever, how the temperature was taken, the maximum height of fever documented at home, all associated symptoms, any chronic medical conditions, any medications taken, medication allergies, fluid intake, urine output, exposures and travel, and any additional features of the illness that concern the parents.

In the office, temperature, HR, RR, BP, and CRT should be documented, as well as an oxygen saturation if the child has any increased work of breathing. A complete physical examination, including a neurologic examination, should then be performed, with particular attention paid to the child's degree of toxicity and hydration status. A well-appearing, well-hydrated child with evidence of a routine viral infection can be safely sent home with symptomatic treatment and careful return precautions.\textsuperscript{1,19,39,40,75,76} Depending on patient age, presence of underlying conditions, type of infection, and the provider's assessment of toxicity and hydration, many children with focal bacterial infections can also be treated as outpatients, with appropriate oral antibiotics as discussed below.\textsuperscript{1,3,7,5,9,10,11,12}

9.1.1 The value of risk stratification:

Many clinical prediction rules and international guidelines have been developed for the evaluation of febrile children\textsuperscript{3,9,16,30,37}. Based on clinical parameters and laboratory markers have been proposed to stratify those at low and high risk of SBI. The most commonly used clinical prediction rules include Rochester criteria\textsuperscript{53} (for infants aged 0-60 days), Philadelphia criteria\textsuperscript{55} (for infants aged 29-60), and Boston criteria( for infants aged 28-89 days)\textsuperscript{56}. These were designed to provide a set of reassuring criteria that allow safe discharging if requirements are met. Overall, risk stratification is acknowledged as not having 100% sensitivity\textsuperscript{54} but has been implemented across many clinical centres worldwide, and they still represent the basis of standard clinical management of febrile infants. (Annex A)
These protocols, when applied to 28 days or younger, will miss 3% of febrile infants with SBI. \(^{54,60,61}\) The Philadelphia and Rochester protocols also were re-evaluated in other studies and because of the percentage of missed SBI, ACEP advocates the admission of all febrile infants less than 1 month for observation and parenteral antibiotics.\(^3\)

Furthermore, observation scales are also useful in order to assess if the child appears “toxic” or “septic”.\(^{41}\) The clinical features that define toxicity include irritability, lethargy, and decreased social interaction.\(^{1,41}\) There also may be signs of compromised circulation with poor perfusion and cyanosis, and/or respiratory distress. However, young infants may have serious illness without showing signs of toxicity.

Over the years, various observational scales have been developed to differentiate children with a viral or other infection and a benign course. Firstly, the **Yale Observation Scale (YOS)** was developed by McCarthy et al.\(^{62}\) in 1982 to predict serious illness in the febrile child age <24 months. In this scale, the child is assigned a score for each of six observable characteristics. Scores vary from a minimum of 6 to a maximum of 30, and 10 is the cut-off for “serious illness”. It is simple, quick, easy to apply and cost-effective, as it is purely observational and does not contain investigational items.

<table>
<thead>
<tr>
<th>Observation item</th>
<th>Normal (Score=1)</th>
<th>Moderate Impairment (Score=3)</th>
<th>Severe Impairment (Score=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Quality of cry</td>
<td>Strong with normal tone OR</td>
<td>Whimpering OR Sobbing</td>
<td>Weak OR Moaning OR</td>
</tr>
<tr>
<td></td>
<td>Content and not crying</td>
<td></td>
<td>High pitched</td>
</tr>
<tr>
<td>2. Reaction to parent stimulation</td>
<td>Cries briefly then stops OR</td>
<td>Cries off and on</td>
<td>Continual cry OR</td>
</tr>
<tr>
<td></td>
<td>Content and not crying</td>
<td></td>
<td>Hardly responds</td>
</tr>
<tr>
<td>3. State variation</td>
<td>If awake → Stays awake OR</td>
<td>Eyes close briefly</td>
<td>Awake OR Falls to sleep OR</td>
</tr>
<tr>
<td></td>
<td>If asleep and stimulated →</td>
<td>awakes up with prolonged stimulation</td>
<td>Does not wake up</td>
</tr>
<tr>
<td>4. Color</td>
<td>Pink</td>
<td>Pale extremities OR Acrocyanosis</td>
<td>Pale OR Cyanotic OR Mottled OR Ashen</td>
</tr>
<tr>
<td>5. Hydration</td>
<td>Skin normal, eyes normal AND</td>
<td>Skin, eyes- normal AND</td>
<td>Skin doughy/tented AND</td>
</tr>
<tr>
<td></td>
<td>Mucous membranes moist</td>
<td>Mouth slightly dry</td>
<td>Dry mucous membranes AND/OR Sunken eyes</td>
</tr>
<tr>
<td>6. Response (talk, smile) to social</td>
<td>Smiles OR</td>
<td>Brief smile OR</td>
<td>No smile, Face anxious/dull/</td>
</tr>
<tr>
<td>overtures</td>
<td>Alerts (≤2 mo)</td>
<td>Alerts briefly (≤2 mo)</td>
<td>expressionless OR No alerting (≤2 mo)</td>
</tr>
</tbody>
</table>

A febrile child with an elevated YOS score (>10), however, needs further work up and referral to a center with investigational facilities to reduce further mortality and morbidity.\(^{63}\)

In addition to the McCarthy scale, the **Young Infant Observation Scale (YIOS)** was developed for use in infants <8 weeks of age.

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*If the score is >7 it is necessary to admit the child in the hospital. Septic testing and empirical antibiotics should be started immediately. Nonetheless, if the score is <7, complementary tests will be necessary.

Further models were also developed to try to improve diagnostic performance, resulting in many diverse clinical prediction rules, such as ‘Step by Step Approach’\textsuperscript{54}, NICE traffic light system\textsuperscript{1} and the Dutch College of General Practitioner Guidelines\textsuperscript{57}. Moreover, these last two guidelines were very effective in ruling out SBI\textsuperscript{58}.

The NICE guidelines\textsuperscript{4} on the febrile child established the ‘traffic light’ that divides febrile children into high, intermediate or low risk of having a serious bacterial infection and suggest recommendations on appropriate management of children in each category. Children with any ‘red’ features should be referred urgently to the care of a paediatric specialist. If any ‘amber’ features are present and no diagnosis has been reached, healthcare professionals should provide parents or carers with a ‘safety net’ or refer to specialist paediatric care for further assessment. The safety net should be one or more of the following:\textsuperscript{58}

- Providing the parent or carer with verbal and/or written information on warning symptoms and how further healthcare can be accessed:\textsuperscript{58}
- Arranging further follow-up at a specified time and place

<table>
<thead>
<tr>
<th>Observation item</th>
<th>Normal (1 point)</th>
<th>Moderate impairment (3 points)</th>
<th>Severe impairment (5 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (talk, smile) to social overtures</td>
<td>Smiles OR Alerts</td>
<td>Brief smile OR Alerts briefly</td>
<td>No smile, face anxious/dull/expressionless OR No alerting</td>
</tr>
<tr>
<td>Respiratory effort</td>
<td>Normal</td>
<td>Tachypnea &gt;60 bpm</td>
<td>Respiratory distress with inadequate effort. Apnea</td>
</tr>
</tbody>
</table>

YIOS Scale (Young Infant Observation Scale <2 months of age)\textsuperscript{64}
• Liaising with other healthcare professionals, including out-of-hours providers, to ensure direct access for the child if further assessment is required.

Children with ‘green’ features and none of the ‘amber’ or ‘red’ features can be managed at home with appropriate advice for parents and carers, always including advice on when to seek further attention from the healthcare services. NICE guidelines have been shown to significantly decrease the rate of representation in the incidence of a febrile child, but more importantly, it gives parents the information to recognise that their child’s illness has deteriorated and the need to seek further medical help. (Annex B)

Nevertheless, considering the limits of the existing clinical guidelines and prediction rules, as well as the possibility of unpredictable progression of illness, careful clinical examination, watchful waiting, prudent utilization of laboratory tests, and post-discharge guidance remain the cornerstone of safe management of febrile children.

9.1.2 Management in children younger than 3 months:

The fetal immune system develops in a sterile and protected environment and therefore lacks antigenic experience. Soon after birth, the newborn is exposed to the "hostile world" of bacteria, viruses, fungi, and parasites and must immediately defend itself. The immunologic competence of the neonate progresses rapidly in the first three months of life as the cells involved in acquired immunity mature and gain antigenic experience. During this period, the neonate mainly depends upon components of the innate or antigen-independent immune system, including phagocytes, natural killer (NK) cells, antigen-presenting cells (APCs), humoral mediators of inflammation, and complement.

The breastfed infant also receives antimicrobial components in breast milk that help prevent certain acute infections. Most of the newborn's serum immunoglobulins are derived from the transfer of maternal immunoglobulin G (IgG) across the placenta during the third trimester of pregnancy. Maternal immunoglobulins are then gradually cleared while antibodies produced by the infant simultaneously increase. Moreover, complement levels increase after birth and reach adult levels between 6 to 18 months of age.
As the child grows, the immune repertoire is also shaped by intercurrent infections and vaccinations. The development of the immune system occurs early in fetal development. 

Newborns (even premature infants) can actively distinguish self from non-self.

The immune system gradually matures during infancy. Critical early protection against many infectious diseases previously experienced by the mother is given by the passive IgG antibody transferred from the mother transplacentally and in milk. Once that fades away, young children become more vulnerable to infections, though by then better armed with the maturing innate and adaptive immune systems.
Therefore, having developed a fully effective immune response in early childhood, this matures as memory accumulates and maintains the health of the individual during critical periods of life, including child bearing. 66

Febrile 0-3 month-olds are a group in whom it is challenging to differentiate a serious bacterial infection (SBI) from a benign illness. 12,27

In children who are younger than one month old we can diagnose fever when rectal temperature is above 38°C. 10,27,33,34,35 Furthermore, it has been seen that a 12% of these children have a higher risk of suffering from a serious bacterial infection (SBI), and it is even higher (up to 20%) in neonates (≤ 28 days old)27, so, as a general rule, every newborn with fever requires hospital admission. 9,10,11,12,36

Febrile infants 28 days old or younger, because of their likelihood of serious disease, including sepsis, should always be treated conservatively. This children are at highest risk because they are predispose to infection by a different set of organisms (group B streptococcus, Escherichia coli and Listeria monocytogenes). Moreover, hospitalization and parenteral antibiotics should be strongly considered in all circumstances. 1,5 An initial diagnostic evaluation should include CBC; blood culture; urinalysis; urine culture; and Gram stain, cerebrospinal fluid protein and glucose tests, as well as culture of the cerebrospinal fluid. Consideration should also be given to the possibility of a perinatal
herpes simplex virus infection. A chest radiograph should be obtained for any infant with increased work of breathing.

Spanish Guidelines follow YIOS scale, since observation is very important in order to determine which algorithm we should adhere to. Although some reviews say that this scoring system is not an accurate risk-stratification tool among young febrile infants <8 weeks of age.

In the case the child is afebrile and well appearing, observation and recheck within the next 24h. No antibiotics are given unless full workup is performed. If patient becomes febrile, full workup and most accurate treatment is chosen. However, it can be difficult to define what the “ill-appearing” infant looks like. On the other hand, “well-appearing” infants in this age group are more challenging to manage.

Personal disposition of these will vary depending on physician’s training background and level of comfort with physical examination and diagnosis. Infants that meet low risk criteria by using any of the previous protocols, can be safely managed as outpatients, granted that reliable follow up is arranged. Short observation periods of no more of 24h are generally recommended. Hospital admission can often come at a time when infant-family bonding is just begining, and therefore should focus on maximizing family bonding by encouraging breast feeding, skin-to-skin contact, and maintaining previous routines, while minimizing unnescessarry situations.

a) Management of neonates:

Any infant in this age group with a rectal temperature of 38°C requires hospital admission. Empirical parenteral antibiotics should be administered before culture results are available. Acyclovir is added empirically for neonates with clinical risk factors such as viral exposure, rash or bloody CSF.

Management of neonates, should be as follows:

1. If there’s an specific cause, admission and specific treatment.
2. If there’s fever without a source, admission and antibiotic treatment: ampicillin 200 mg/kg/d in 4 doses i.v. (2 doses if the neonate is younger than 7 days) along with gentamycin 5mg/kg/d every 24h i.v. within 30 minutes.
3. If there’s highly suspicion of meningitis, ampicillin with cefotaxime 200-300 mg/kg/d.
4. If the mother suffered from genital herpes or there are characteristic lesions (mucocutaneous vesicles or ulcerations) in the child, add acyclovir i.v. 60 mg/kg/d in three dosages.
Fever in an otherwise healthy child does not necessarily require treatment. Although antipyretics can provide comfort, they do not change the course of an infection. In fact, fever is an integral part of the inflammatory response to infection and can help the child fight the infection. However, most clinicians use antipyretics to help alleviate discomfort and to reduce physiologic stresses in children who have cardiopulmonary disorders, neurologic disorders, or a history of febrile seizures.

b) Management of children 1-3 months old:

In children that are 1-3 months old, there is a potential risk of occult bacteremia, eventhough the majority of the infections are viral. 5 to 10% of these children will undergo SBI. The most common SBI was a diagnosed or presumed UTI (16,5%)commonly from *Escherichia coli* or *Klebsiella species.*

1. If we follow Rochester protocol, and the child meets all the criteria, this child can go home with no antibiotic coverage. But, it has to be feeding well, it has to be able to come for a
follow-up within the next 24h and it has to be easy for the parents to get to the hospital. If any of these conditions are not meet, the child must be admitted and observed.¹,¹²

2. If the child does not meet all the criteria and there’s a source for the fever, admission and specific treatment.⁷

3. If the child does not meet all the criteria and there’s fever without a source: admission, with ampicillin i.v. 200mg/kg/d in 4 doses along with gentamycin 5mg/kg/d every 24h ⁸,¹³ or cefatoxime i.v. 200mg/kg/d in 4 doses. ¹,⁸,⁹,¹₀,¹₂,¹³

When parenteral antibiotics are indicated for infants younger than 3 months of age, a third-generation cephalosporin (for example cefotaxime or ceftriaxone) should be given plus an antibiotic active against listeria (for example, ampicillin or amoxicillin).¹,⁹,¹₀,¹¹,¹₂

Complementary studies that are totally necessary are: CBC, Blood culture, UA&Urine Culture, Optional: CSF/CXR- Only if alarming signs.
*Hospitalization if: distant domicile, not possible follow up in 24h, unreliable parents, family anguish, bad social conditions, rejection of breastfeeding.

It has also been demonstrated that we have to start the antibiotic coverage for 48-72h. It has also been demonstrated that we have to start the antibiotic coverage for 48-72h. Aspirin should be avoided in children because it increases the risk of Reye syndrome.

### 9.1.3 Management in children from 3 to 36 months old:

In children 3 to 36 months, fever generally is defined by rectal temperatures ranging from ≥38.0 to 39.0°C (100.4 to 102.2°F) and fever of concern by rectal temperatures ≥39.0°C (102.2°F). Fever in this age group is incredibly common; most cases represent self-limited viral illnesses. Common causes of fever in this age group include viral upper respiratory infections, croup, bronchiolitis, stomatitis (typically caused by HSV or Coxsackievirus), gastroenteritis, roseola, and fifth disease (parvovirus B19 infection). The prevalence of occult bacteremia is between 1.5-2%, and only 0.3% will have a serious disease. To assess the general state we can follow YALE scale. Any child who appears ill or toxic, is unable to maintain oral hydration, or has inadequate follow-up after discharge should be admitted for IV hydration and/or parenteral antibiotic therapy. Choices for antibiotics depend on the organism and the regional susceptibilities. According to spanish literature in this age group we use YALE observation scale in order to assess the risk of SBI. Less than 10 points means low risk, 11-16 intermediate and beyond 16 high risk.

Also we take into account if the child is vaccinated. *H. Influenza* infections have ceased to be a problem with the generalization of the vaccine, those due to meningococcus have decreased dramatically with universal vaccination compared to serogroup C. Unfortunately, The MenB vaccine was introduced into the routine schedule later on. The vaccine is given at 2 and 4 months, with a booster at 12 months. There are no plans for a catch-up programme for older children, because the main burden of the disease is in young babies, with a peak around 5 to 6 months of age. In September 2016 Public Health England reported on new research that shows that the number of cases of meningitis and septicaemia caused by MenB infection in these babies had nearly halved over the previous year (since the MenB vaccine was introduced). But still is necessary to keep this germ as an important challenge in the evaluation of the febrile child.

Important aspects to know in order to give the appropriate management:
- Clinical aspect
- YALE score
- Urine dipstick is considered in children who are younger than 2 years old
- Evaluate if it is necessary to make complementary tests.*

In case of no complementary assessment needed, treatment will be started with Amoxicillin-Clavulanic acid and a follow up in the next 24h in the outpatient department.\cite{9,10,48,88}

If complementary assessment for some reason is needed, we need to take into account two parameters:

1. Leukocyte number
2. CRP value\cite{72}

i. If both markers are increased, the child must be admitted for observation and treatment should be started.
ii. If leukocyte count is > 15000 or CRP > 40 mg/l (just one of them), child must be admitted for observation and treatment should be started.

iii. If only one marker is altered and fever has persisted more than 24h:
* Treatment with Amoxicillin (80 mg/kg/d) and follow up in 24h

iv. If complementary tests are normal, symptomatic treatment and follow up in 24-48h.

9.1.4 Management in children from 3 to 5 years old:

At this age, fever is usually due to a localized focus, most otorhinolaryngological, but we have to always rule out sepsis and meningitis during physical examination.\textsuperscript{12,47} There is less risk of dissemination since the immune system is almost fully developed. They can be treated by GP doctors, but in case of toxicity they will have to be admitted in the hospital. Complementary tests and treatment will be done according to the suspected pathology.

![Diagram of Diagnosis and Symptoms]

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9.1.5 Clinical assessment tool for the febrile child 0-5 years:

- **Child younger than 3 months of age**
  - Observe and monitor: temperature, heart rate, respiratory rate.
  - Perform: full blood count, C-reactive protein, blood culture, urinary tract infection, chest X-ray if respiratory signs are present, stool culture if diarrhea is present.
  - Admit, perform lumbar puncture and start parenteral antibiotics (see box 2) if the child is:
    - younger than 1-month old
    - 1–3 months old appearing unwell
    - 1–3 months old and with a white blood cell count of less than 5 or greater than 15 x 10^9/litre.
    - Whenever possible, perform lumbar puncture before the administration of antibiotics.

- **Assess, look for life threatening symptoms and signs (see table 1 below Traffic Light and table 2 overleaf Symptoms and Signs)**
  - If all green features and no amber or red:
    - Perform urine test for urinary tract infection. Assess for symptoms and signs of pneumonia. Do not perform routine blood tests or chest X-ray.
    - Provide parents/carers with discharge advice and follow up by arranging an appropriate health care professional.

- **Child 3 months of age or older**
  - If any amber features and no diagnosis reached:
    - Perform (unless deemed unnecessary): urine test, full blood count, blood culture, C-reactive protein.
    - Perform chest X-ray if fever higher than 39°C and white blood cell count greater than 20 x 10^9/litre.
    - Consider lumbar puncture if child is younger than 1-year old.

- **If any red features and no diagnosis reached**
  - Consider admission according to clinical and social circumstances and treat.
    - If the child does not need admission to hospital but no diagnosis has been reached, provide a safety net for the parents/carers by using one or more of the following:
      - Provide parent/carer with written or verbal information on warning symptoms and accessing further healthcare.
      - Liaise with other professionals to ensure parent/carer has direct access to further assessment.

9.2 Antipyretic treatment for children under 5 years:

Prescription of antipyretics at a certain body temperature level is not specifically or routinely recommended by the AAP, NICE, WHO or the Italian guidelines for the management of fever in children. Generally, the use of antipyretics in children is recommended only when the fever is
associated with evident discomfort (e.g., prolonged crying, irritability, reduced activity, reduced appetite, disturbed sleep) and not for a given temperature level.

It is important to note that neither the level of fever, nor the response to antipyretics, is a predictive factor for the cause of fever.\(^{30}\)

Antipyretic agents have become an established part of managing febrile children. The use of medication to control body temperature must not detract from monitoring child’s activity and level of consciousness (as an indicator of worsening illness) and paying attention to adequate hydration.\(^{1,80,98}\)

When the following situations occur, it is proposed that antipyretic treatment should begin:

- All necessary means must be used to prevent the child from reaching temperatures considered harmful: 41ºC in general pediatric population and 40ºC in infants under three months of age.
- Any temperature higher than 40ºC (39.5ºC in children under three months) is mandatory to be treated.
- Antipyretic treatment will be given to children younger than 7 years old with a previous history of seizures.
- In infectious processes is preferable to treat fever when it is higher than 38ºC.
- If temperature is below 38ºC we can avoid the use of antipyretics, although it does not interfere with the course of the infection.\(^{48}\)

Paracetamol and ibuprofen are the only antipyretic drugs recommended for use in children.\(^{14,5,28,80,98}\) Both are considered safe when used appropriately, and adverse events are rare. The most serious ADR are hepatic injury for acetaminophen, and acute kidney injury and gastrointestinal bleeding for ibuprofen.\(^{15,95}\) However, recent epidemiologic studies have found an association between the use of acetaminophen and the prevalence of asthma in children and adults; so some clinicians suggest that children with asthma or a strong family history of asthma should avoid using acetaminophen.\(^{19}\) It is totally contraindicated in known cases of paracetamol- or NSAID-induced asthma.\(^{5,44,80}\)

Response to antipyretics cannot predict the severity of the underlying disease, since children with bacterial or viral infections have a similar response to antipyretics.\(^{16}\)
Paracetamol and ibuprofen should not routinely be given alternately to children with fever. The National Institute for Health and Care Excellence update guidance of May 2013 does not recommend the combination of both drugs. However, use of the alternative drug may be considered if the child does not respond to the first agent or in the case of persistent or recurrent distress. Moreover, alternating use of antipyretics may encourage fever phobia.

Compared with ibuprofen, paracetamol can be used in infants under 3 months of age as well as in cases of dehydration. Mefemanic acid is registered for use from 6 months of age and may be an alternative NSAID to Ibuprofen in children with fever. The recommended dose is 6.5 mg/kg of body weight, not more than 3 times daily.

<table>
<thead>
<tr>
<th>Dose of antipyretic medication for children older than 3 months of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dose (mg/kg)</td>
</tr>
<tr>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Paracetamol</td>
</tr>
</tbody>
</table>

*Do not exceed this dose within a 24-h period.

9.3 Physical methods to reduce child’s body temperature.

Physical methods of reducing fever are recommended in cases of hyperthermia. Some physical methods may be uncomfortable for the child and do not reset the “central thermostat” that determines the body temperature.

1) **General measures:**
   a) For the child who has a high fever it is beneficial to stay in a thermal environment of about 20-22°C.
   b) Adequate care of the state of hydration and caloric intake.
   c) Children with fever should not be underdressed or over-wrapped.
2) **Physical measures:**

   a) Giving sponge baths with lukewarm water (32.2-35°C), it is completely unnecessary and unpleasant for the child, and it will be only produce a temporary relief, that is why their use is discouraged in many other articles.

   b) Do not use cold water, ice, or rubbing alcohol, which will lower the child's body temperature too quickly. The alcohol bath is risky because it can cause hypoglycemia.

3) **Other considerations:**

Parents need to consider:

- Hydration
- Feeding
- When to attend nursery or school
- How long will the fever last
- Appearance of non-blanching rash.

Fluid intake is very important and parents should be advised that fluids containing sugar are preferable to plain water as the child’s calorie intake is likely to be reduced and hypoglycaemia can occur in infants, especially if there are ongoing losses such as vomiting or diarrhoea.

Children with fever may not feel hungry, and it is not necessary to force them to eat. However, fluids such as milk (cow's or breast), formula, and water should be offered frequently. Older children may eat flavored gelatin, soup, or frozen popsicles. If the child is unwilling or unable to drink fluids for more than a few hours, the parent should consult the child's health care provider.

Parents should be informed of signs of dehydration to look out for, including: sunken fontanel, dry mouth, sunken eyes, absence of tears and poor overall appearance.
10. CONCLUSION:

Caring for the febrile young infant is often challenging, as the fear of not properly treating a serious illness can often lead to unnecessary testing, antibiotics and hospitalization. This review will lead to more appropriate management of children with fever in both primary and secondary care. The epidemiologic features of SBI have changed significantly in the past 20 years with the introduction and widespread use of vaccines against *Hib* and *S pneumoniae*. Management strategies must continue to evolve to identify the few children with SBI.

Furthermore, the management of fever in children depends on the knowledge of the inherent risks of SBI. For toxic-appearing children, this risk is high and requires investigation, admission, broad-spectrum antibiotic coverage and intensive medical support.

Well-appearing children with an apparent source of fever are treated with specific therapy according to the source. Despite some differences, most guidelines advocate a comprehensive evaluation of the very young febrile infant (28 days and younger) and less conservative approach for older infants.

Moreover, parents and healthcare providers need to be reassured when the risk of serious illness is low, and the child should be managed appropriately at home with antipyretic medication if indicated to make the child more comfortable. Clear instructions to advise parents and caregivers about when to seek further care for their child will help to reduce the morbidity associated with childhood illnesses.

Thus to summarize, most febrile children have a benign, self-limiting cause; ‘Red-flags’ help in early identification of children at high risk for a serious bacterial infection, so that early referral can be planned; Empirical broad spectrum parenteral antibiotics are indicated in febrile neonates and children with red-flags; Adequate follow-up must be ensured in those managed on an ambulatory basis.
11. REFERENCES


25. M. Deborah, Consolini, MD "Fever in Infants and Children." (Merck's Manual-online)


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http://dx.doi.org/10.1098/rspb.2014.3085


68. de Martino M, Chiarugi A. <<Recent advances in pediatric use of oral paracetamol in fever and pain management.>> Pain Ther 2015;4:149-68.


90. Aroson PL, Thurm C, Alpern ER et al. <<Variation in care of the febrile young infant <90 days in US pediatric emergency departments.>> *Pediatrics* 2014; 134: 667–77. 31


12. ANNEXES

Annex A:

Most common low-risk criteria for management of febrile young infant

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Rochester Criteria (0-60 days of age)</th>
<th>Philadelphia Criteria - (29-56 days of age)</th>
<th>Boston Criteria (28-89 days of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination</td>
<td>• Full-term</td>
<td>• Well appearing</td>
<td>• No antibiotics within preceding 48 h</td>
</tr>
<tr>
<td></td>
<td>• Normal prenatal and postnatal histories</td>
<td>• No focal infection</td>
<td>• No immunizations within proceeding 48 h</td>
</tr>
<tr>
<td></td>
<td>• No postnatal antibiotics</td>
<td></td>
<td>• Well appearing</td>
</tr>
<tr>
<td></td>
<td>• Well appearing</td>
<td></td>
<td>• No focal infection</td>
</tr>
<tr>
<td></td>
<td>• No focal infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory parameters (defines low risk)</td>
<td>• WBC: 5000-15,000/mm³</td>
<td>• WBC: &lt; 15,000/mm³</td>
<td>• WBC: &lt; 20,000/mm³</td>
</tr>
<tr>
<td></td>
<td>• Absolute band count: &lt; 15000/mm³</td>
<td>• Band: total neutrophil (LT) ratio &lt; 0.2</td>
<td>• UA: &lt; 10 WBC/HPF</td>
</tr>
<tr>
<td></td>
<td>• UA: ≤ 10 WBC/HPF</td>
<td>• UA: &lt; 10 WBC/HPF</td>
<td>• CSF: ≤ 10 WBC/mm³</td>
</tr>
<tr>
<td></td>
<td>• Stool: ≤ 5 WBC/HPF on smear*</td>
<td>• Urine: Gram stain negative</td>
<td>• Chest radiograph: no infiltrate*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CSF: Gram stain negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chest: clear</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stool: no blood, few or no WBCs on smear*</td>
<td></td>
</tr>
<tr>
<td>Treatment for high-risk patients</td>
<td>Hospitalize + empiric antibiotics</td>
<td>Hospitalize + empiric antibiotics</td>
<td>Hospitalize + empiric antibiotics</td>
</tr>
<tr>
<td>Treatment for low-risk patients</td>
<td>• Home</td>
<td>• Home, if patient lives within 30 min of the hospital</td>
<td>• Home, if caregiver available by telephone</td>
</tr>
<tr>
<td></td>
<td>• 24-h follow-up required</td>
<td>• 24-h follow-up required</td>
<td>• Empiric IM ceftriaxone 50 mg/kg</td>
</tr>
<tr>
<td></td>
<td>• No empiric antibiotics</td>
<td>• No empiric antibiotics</td>
<td>• Return for 24-h follow-up for second dose of IM/IV ceftriaxone</td>
</tr>
<tr>
<td>Performance of low-risk criteria</td>
<td>NPV: 99.9% (97.2-99.6)</td>
<td>NPV: 100% (99–100)</td>
<td>NPV: 94.6% (92.2-95.4)</td>
</tr>
</tbody>
</table>

*Obtained based on symptoms

Abbreviations: CSF, cerebrospinal fluid; HPF, high-power field; IM, intramuscular; IV, intravenous; NPV, negative predictive value; UA, urinalysis; WBC, white blood cell.

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### Traffic light system for identifying risk of serious illness

<table>
<thead>
<tr>
<th>Colour (of skin, lips or tongue)</th>
<th>Green – low risk</th>
<th>Amber – intermediate risk</th>
<th>Red – high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Normal colour</td>
<td></td>
<td>• Pallor reported by parent/carer</td>
<td>• Pale/mottled/ashen/blue</td>
</tr>
<tr>
<td>Activity</td>
<td></td>
<td>• Not responding normally to social cues</td>
<td></td>
</tr>
<tr>
<td>• Responds normally to social cues</td>
<td></td>
<td>• No smile</td>
<td></td>
</tr>
<tr>
<td>• Content/smiles</td>
<td></td>
<td>• Wakes only with prolonged stimulation</td>
<td></td>
</tr>
<tr>
<td>• Stays awake or awakens quickly</td>
<td></td>
<td>• Decreased activity</td>
<td></td>
</tr>
<tr>
<td>• Strong normal cry/not crying</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Respiratory                    |                  |                            |
|• Nasal flaring                  |                  | • Grunting                 |
|• Tachypnoea: RR > 50 breaths/minute, age 6–12 months | | • Tachypnoea: RR > 80 breaths/minute |
|• Tachypnoea: RR > 40 breaths/minute, age > 12 months | | • Moderate or severe chest indrawing |
|• Oxygen saturation ≤ 95% in air | |                           |
|• Crackles in the chest          |                  |                           |

| Circulation and hydration       |                  |                            |
|• Normal skin and eyes           |                  | • Reduced skin turgor      |
|• Moist mucous membranes         |                  |                           |
|• Tachycardia:                   |                  |                           |
|• > 160 beats/minute, age < 12 months | |                           |
|• > 150 beats/minute, age 12–24 months | |                           |
|• > 140 beats/minute, age 2–5 years | |                           |
|• CRT ≥ 3 seconds                |                  |                           |
|• Dry mucous membranes           |                  |                           |
|• Poor feeding in infants        |                  |                           |
|• Reduced urine output           |                  |                           |

| Other                           |                  | • Age < 3 months, temperature ≥ 38°C |
|• None of the amber or red symptoms or signs | | • Non-blanching rash |
|• Temperature ≥ 39°C            |                  | • Bulging fontanelle        |
|• Fever for ≥ 5 days            |                  | • Neck stiffness            |
|• Rigors                        |                  | • Status epilepticus        |
|• Swelling of a limb or joint   |                  | • Focal neurological signs  |
|• Non-weight bearing limb/not using an extremity | | • Focal seizures |

CRT, capillary refill time; RR, respiratory rate

*Some vaccinations have been found to induce fever in children aged under 3 months

This traffic light table should be used in conjunction with the recommendations in the NICE guideline on Feverish illness in children. See [http://guidance.nice.org.uk/CG180](http://guidance.nice.org.uk/CG180)