

Fever without source: evaluation of a guideline

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Abstract

Objective: To evaluate the applicability of a standardized guideline for children up to 36 months of age with fever without source (FWS).

Methods: Prospective cohort study involving children with FWS treated at the emergency department of Hospital Universitário, Universidade de São Paulo, São Paulo, Brazil, from June 2006 to May 2007. The guideline classifies the risk of serious bacterial infection (SBI) according to the presence or absence of toxemia, age, and temperature. Laboratory screening was based on risk assessment: complete blood count, blood culture, urinalysis, urine culture, and, if necessary, chest radiography, cerebrospinal fluid, and coproculture.

Results: We studied 251 children and, of these, 215 were followed up until the final diagnosis. Toxemia was found in 20 children, and 195 were well-appearing (30 up to 3 months old and 165 from 3 to 36 months old). Among those children from 3 to 36 months without toxemia, 95 had axillary temperature > 39 °C. In 107 (49.8%) children, there was spontaneous resolution of fever; in 88 (40.9%), benign self-limited disease was identified; and in 20 (9.3%), there was SBI. Among the cases of SBI, we identified 16 urinary tract infections, three cases of pneumonia and one occult bacteremia. Of the 215 children, 129 (60%) received no antibiotics, and 86 received antibiotics at some point (45 empirically). Empirical antibiotic treatment was maintained for an average of 72 hours.

Conclusion: The guideline was shown to be appropriate to follow up these children using simple laboratory tests that can be carried out at most health facilities. The most frequent SBI in this sample was urinary tract infection.

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Introduction

Fever is one of the most frequent complaints of pediatric patients and it accounts for approximately 25% of the emergency department visits. In general, the fever source can be identified during the initial evaluation after careful anamnesis and physical examination.¹⁻⁶

However, in approximately 20% of the cases, the pediatrician may deal with a febrile child whose main focus of infection cannot be identified based on the data provided by

the patient's clinical history and detailed clinical examination. This is called fever without source (FWS).^{1-5,7,8} FWS consists in the occurrence of fever for less than 7 days in a child whose medical history and careful physical examination do not reveal the cause of the fever.

Most children with FWS have acute self-limited infectious disease or are going through a prodromic phase of a benign infectious disease. Few children have serious bacterial

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infection (SBI). SBIs include all types of infections that result in risk of morbidity and mortality when diagnosis is delayed.^{1,3,4,6,8,9} The following infections are considered to be SBIs: occult bacteremia (OB), pneumonia, urinary tract infection (UTI), bacterial meningitis, septic arthritis, osteomyelitis, and cellulite.^{1,3,4,6-8} The pediatricians' major challenge is to differentiate the febrile processes of a benign self-limited disease from those processes that are caused by a SBI.

The first reports about febrile children, younger than 3 years old, who were well-appearing and had not clinical finding, but presented with positive blood culture (OB) came out in the 1970s. This resulted in intense research on the risk factors for the early identification of such children.^{10,11}

Studies carried out in the 1980s and 1990s have found that children aged up to 3 years who had FWS, white blood cell count (WBC) $> 15,000/\text{mm}^3$ and temperature $> 39^\circ\text{C}$ were at risk of having SBI.^{7,12-14} In 1992, Baraff & Lee¹² estimated a 13% risk of OB in patients with WBC $\geq 15,000/\text{mm}^3$.

The guideline developed by Baraff et al.⁷ and published in 1993 was based in the meta-analysis of 85 studies and on specialists' opinions. This document stratifies children according to age group and risk of SBI (low and high) using clinical and laboratory criteria. Several strategies have been designed based on this guideline with the purpose of standardizing the management of children with FWS.^{1,2,4,15-17}

At the emergency department of Hospital Universitário (Pronto-Socorro do Hospital Universitário, PSHU) of Universidade de São Paulo (USP), São Paulo, Brazil, these children are evaluated and followed up using a guideline that stratifies the risk of SBI according to the presence or absence of toxemia, age, and temperature. Such guideline, which is based on guidelines published in the literature and on the experience of our medical staff, was developed and adapted to the local context.

The controversies in the literature and the absence of national studies assessing the treatment and follow-up of the children with FWS in general hospitals are the reasons for the present study. The objective of this study is to evaluate the applicability of a standardized guideline for children up to 36 months old with FWS seen at the PSHU-USP.

Methods

A prospective study was conducted during a period of 12 months (May 25, 2006 to May 31, 2007) with children from 0 to 36 months who sought medical care at the PSHU-USP presenting with FWS. Those children seen at the PSHU-USP from Mondays to Fridays from 7 am to 7 pm were included in the study. The patients were treated according to the guideline (Figure 1) and followed up until fever resolution,

focus identification, or final results of cultures in case there was sample collection.

All children's parents signed a written informed consent after being provided with detailed information on the objectives of the study.

The exclusion criteria were:

- Presence of underlying disease that could result in immunity alterations;
- Use of antibiotic therapy during the previous week.

The present study was approved by the Research Ethics Committee of HU-USP (protocol no. 630/05 and SISNEP registration no. 0035.0.198.000-08).

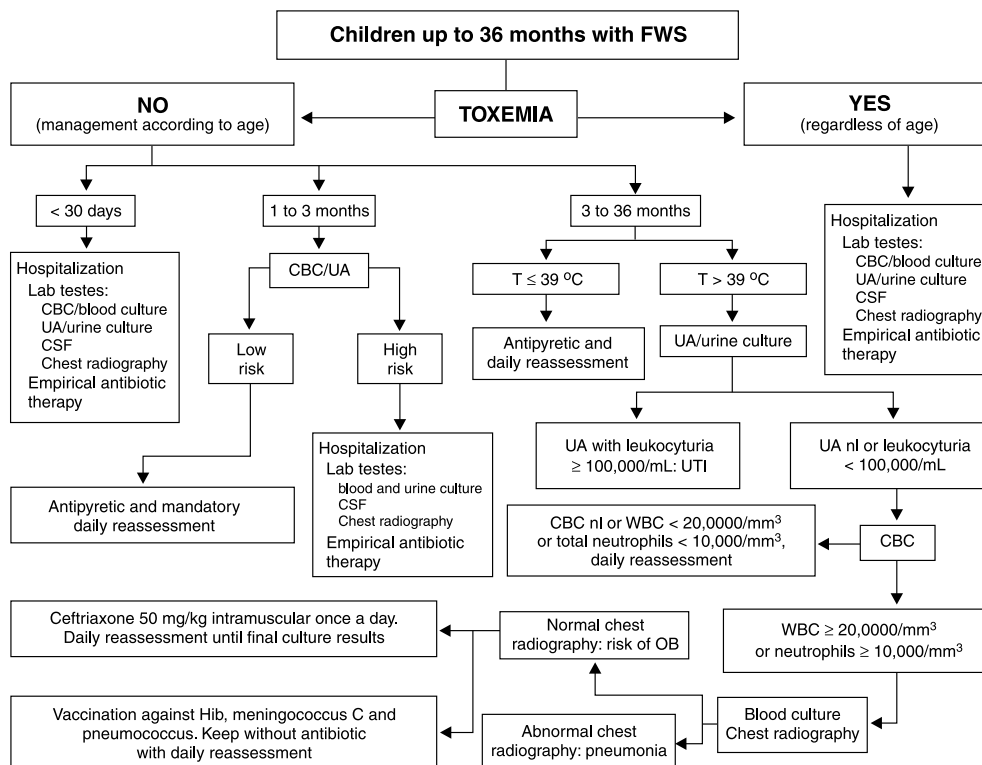
Guideline

According to the guideline, those children aged up to 36 months with FWS were initially evaluated regarding the presence of toxemia. Such evaluation was carried out when the child was not febrile, since fever may cause several different degrees of prostration. We classified children as having toxemia when they presented some degree of inability to interact with the parents or guardians, irritability, changes in the degree of consciousness, hypoactivity, hypotonia, lethargy, hyper or hypoventilation, hypotension, tachycardia, signs of poor peripheral perfusion or cyanosis.^{1,2,4,7,8,18} Those children appearing to have toxemia, regardless of their age, were carefully evaluated by means of laboratory screening, they also received broad-spectrum parenteral antibiotic and were hospitalized. Laboratory screening consisted in complete blood count (CBC), blood culture, urinalysis (UA), urine culture, and, if indicated, cerebrospinal fluid (CSF) (biochemical analysis, Gram staining and culture), chest radiography, and coproculture. All children presenting with toxemia at the initial evaluation remained in hospital for observation until the results of the tests were released.

Those children without toxemia were classified into three different age groups for FWS evaluation purpose: newborns (< 30 days of life), young infants (from 30 to 90 days), and children from 3 to 36 months of age.

Due to the higher risk of SBI, newborns with fever were hospitalized for laboratory screening and received empirical antibiotics (ampicillin and cefotaxime) until the focus of fever was identified or the final results of cultures were released.

Febrile young infants were initially evaluated with regard to the risk of SBI using the Rochester criteria (Figure 2).¹⁹ To be considered at low risk, the child must meet all these criteria. When the child does not meet only one of the criteria, the patient is considered to be at high risk of SBI. Young infants characterized as having low risk of SBI could be observed at home when the parents or guardians presented adequate sociocultural conditions: being mature, having a thermometer, a telephone and a car available,



FWS = fever without source; CBC = complete blood count; UA = urinalysis; T = axillary temperature; CSF = cerebrospinal fluid; UTI = urinary tract infection; OB = occult bacteremia; WBC = white blood cell count.

Figure 1 - Guideline

taking at most 30 minutes to reach the hospital from home, and being able to return to the hospital within 24 hours. In case these criteria were not met, the patient remained in hospital for observation during at least 24 hours. Parents were informed about the risks and benefits of each option so that they were able to participate in the decision of conducting

observation at home or in the hospital. For these children, empirical administration of intramuscular ceftriaxone was only considered when there was prior collection of CSF. When the patients were considered to be at high risk, they were hospitalized and received empirical antibiotic (ceftriaxone) until the final result of the cultures was released or until the focus of the infection was identified after collection of samples for laboratory screening.

Low risk criteria for serious bacterial infection

Clinical criteria:

- No prior illness.
- Full term birth without complications during hospital stay after delivery.
- Well-appearing infant with no evidence of bacterial infection during physical examination.
- No chronic illness.

Laboratory criteria:

- White blood cell count between 5,000 and 15,000/mm³
- Absolute neutrophil count < 1,500/mm³
- Urine white blood cell count ≤ 10 per hpf (high-power field).
- Fecal leukocytes ≤ 5 per hpf in children with diarrhea.

Figure 2 - Rochester criteria¹⁹ for assessment of bacterial infection risk in febrile young infants

Children between 3 and 36 months old without toxemia were subdivided into two groups according to the axillary temperature. After careful clinical assessment and taking into consideration the sociocultural conditions of the families, parents or guardians of children with temperature ≤ 39 °C were instructed to take their children back to the hospital every day for clinical reassessment until fever resolution or identification of the infectious focus.

The evaluation of the children with temperature > 39 °C started with urine collection using vesical catheterization or midstream sample for biochemical analysis (reagent strip, microscopy and Gram staining) and urine culture. Urine test showing leukocyturia ≥ 100,000/mL indicated need of treatment (suspicion of UTI) until the result of urine culture was released. Urine culture showing a growth

$\geq 50,000$ UFC/mL, in case of urine collected by means of catheterization, or $\geq 100,000$ UFC/mL, in case of midstream sample, was considered positive.

CBC was performed when there was normal urinalysis or leukocyturia $< 100,000$ /mL. Chest radiography was considered in children with WBC $> 20,000$ /mm³ for identification of occult pneumonia. When there was normal chest radiography with WBC $> 20,000$ /mm³ or neutrophil count $> 10,000$ /mm³, blood culture was carried out and treatment with empirical antibiotic (ceftriaxone at a single daily intramuscular dose of 50 mg/kg) was initiated due to the risk of OB.

Clinical reassessment of all patients was conducted at least every 24 hours. All children who did not return during the next 24 hours were contacted on the telephone for an assessment interview.

Blood collection and empirical antibiotic administration was optional for those children who received two or more doses of conjugated vaccines against Hib, meningococcus and pneumococcus, since the OB rate in this population is lower than 1%.^{17,21,22}

Results

Two hundred and fifty-one cases were included in the present study. Of these, 36 cases were excluded: 27 due

to loss of contact (patients did not return for assessment and/or contact on the telephone was not successful) and nine cases were withdrawn from the study (due to parents' request, because the samples were not collected or the antibiotic treatment was discontinued based on parents' decision). The characteristics of the sample and the children's clinical evolution are shown in Table 1.

Of the 215 children included in the present study, 20 had toxemia at the initial evaluation. The final diagnoses of this group and those of the group of children without toxemia are listed in Table 2. We found 20 children with SBI (9.3%): 16 with UTI, three with pneumonia, and one with OB caused by *Streptococcus pneumoniae*. Based on the assistant physician's decision, CSF was collected from five children, and bacterial meningitis was not identified in any of them.

The remaining children (195), who did not have toxemia, presented the following distribution in terms of age: eight newborns, 22 young infants, and 165 children from 3 to 36 months. Young infants were classified according to the Rochester criteria;¹⁹ five of them were classified as being at high risk of SBI and 17 were at low risk.

Of the 165 children from 3 to 36 months of age without toxemia, 68 (41.2%) had axillary temperature ≤ 39 °C and 97 (58.8%) had temperature > 39 °C. The later underwent laboratory screening.

Table 1 - Characteristics of the sample and children's clinical evolution according to stratification into age groups

| Variables | General (n = 215) n (%) | < 30 days (n = 9) n (%) | 1-3 months (n = 23) n (%) | 3-36 months (n = 183) n (%) |
|---|-------------------------------|-------------------------------|---------------------------------|-----------------------------------|
| Female | 111 (51.6) | 5 (55.6) | 15 (65.2) | 91 (49.7) |
| White | 148 (69.3) | 7 (77.8) | 12 (52.7) | 129 (70.5) |
| Hib vaccination | 98.6% | 100% | 100% | 98.4% |
| Temperature > 39 °C | 110 (51.2) | 0 | 2 (8.7) | 108 (59) |
| Toxemia | 20 (9.3) | 0 | 1 (4.3) | 19 (10.4) |
| With SBI | 2 | 0 | 0 | 2 |
| Final diagnoses | | | | |
| Spontaneous resolution | 107 (48.9) | 8 (88.9) | 16 (69.6) | 83 (45.4) |
| Self-limited disease or probable viral etiology | 88 (40.9) | 0 | 6 (26.1%) | 82 (44.8) |
| SBI | 20 (9.3) | 1 (11.1) | 1 (4.3) | 18 (9.8) |
| Antibiotic use | | | | |
| No antibiotic | 129 (60) | 2 (22.2) | 17 (73.9) | 110 (60.1) |
| Empirical | 52 (24.2) | 7 (77.8) | 4 (17.4) | 41 (22.4) |
| Therapeutic | 34 (15.8) | 0 | 2 (8.7) | 32 (17.5) |
| Procedure after 1st medical evaluation | | | | |
| Patient sent back home | 179 (70.3) | 1 (11.1) | 8 (34.8) | 170 (92.9) |
| Patient hospitalized | 36 (16.7) | 8 (88.9) | 15 (65.2) | 13 (7.1) |
| Guideline discharge | | | | |
| 1st and 2nd reassessment | 151 (70.3) | 2 (22.2) | 16 (69.6) | 133 (72.7) |
| 3rd and 4th reassessment | 51 (23.7) | 1 (11.1) | 3 (13) | 47 (25.7) |
| Hospitalization > 24 hours | 13 (6) | 6 (66.7) | 4 (17.4) | 3 (1.6) |

SBI = serious bacterial infection.

Table 2 - Final diagnoses established during the follow-up of the children from 0 to 36 months old with FWS

| Final diagnoses | Toxemia | | Total, n (%) |
|----------------------------|------------|-----------|--------------|
| | Yes, n (%) | No, n (%) | |
| Resolved FWS | 10 (50) | 97 (49.7) | 107 (49.8) |
| Viral nasopharyngitis | 3 (15) | 26 (13.3) | 29 (13.5) |
| Exanthema subitum | 2 (10) | 15 (7.7) | 17 (7.9) |
| Urinary tract infection | 1(5) | 15 (7.7) | 16 (7.4) |
| Acute otitis media | 2 (10) | 14 (7.2) | 16 (7.4) |
| Acute diarrhea | 0 | 9 (4.6) | 9 (4.2) |
| Herpangina | 0 | 7 (3.6) | 7 (3.3) |
| Sinusitis | 0 | 3 (1.6) | 3 (1.4) |
| Pneumonia | 0 | 3 (1.6) | 3 (1.4) |
| Lymph monocytic meningitis | 1(5) | 2 (1.0) | 3 (1.4) |
| Tonsillitis | 0 | 2 (1.0) | 2 (0.9) |
| Bronchiolitis | 0 | 1 (0.5) | 1 (0.5) |
| Occult bacteremia | 1 (5) | 0 | 1 (0.5) |
| Hand-foot-mouth syndrome | 0 | 1 (0.5) | 1 (0.5) |
| Total | 20 (100) | 195 (100) | 215 (100) |

FWS = fever without source.

Samples for UA and urine culture were collected from 95 children. Among them, 10 patients had UA with presence of more than 100,000 white blood cells/mL, thus suggesting suspicion of UTI, and treatment was initiated. All these children had positive urine culture. The 85 children with normal UA or leukocyturia < 100,000/mL underwent CBC and blood culture. Of these, 54 presented CBC with total number of WBC < 20,000/mm³ and total neutrophils < 10,000/mm³. These patients were instructed to return to the hospital every day until fever resolution and/or identification of the infectious focus and until the final result of the cultures was released. The 31 remaining children had CBC showing WBC > 20,000/mm³ or total neutrophils > 10,000/mm³. Chest radiography was performed in 23 children, and one child had occult pneumonia.

Of the 215 children investigated, 86 were treated with antibiotic therapy: 34 (15.81%) received therapeutic treatment and 52 (24.2%) received empirical treatment, and seven children were treated with empirical antibiotic therapy even though this was not in agreement with the guideline (clinical decision). The mean time of empirical antibiotic therapy was 72 hours. The presence of SBI was evidenced in seven (15.56%) of the 45 children who received empirical antibiotic in agreement with the guideline. There were not any cases of SBI in the children who were not treated with antibiotic. Therefore, of the 215 children studied, 86 received antibiotic at some point of the treatment, and 129 (60%) did not receive antibiotic therapy.

Discussion

In the present study, we presented a guideline for evaluation and follow-up of children up to 36 months old with FWS.

Since the publication of the guideline by Baraff et al.,⁷ several strategies have been developed aimed at delivering medical care and following up children with FWS.^{1,2,4,15-17} Currently, the studies have been discussing the changes that took place after the introduction of the conjugated vaccine against pneumococcus in 2001. The articles have compared the SBI rates, mainly considering the invasive diseases caused by pneumococcus, which is called the pre- and post-vaccination era.^{5,17,21-23} Significant reductions in the invasive infections with *Streptococcus pneumoniae* have been found and, as a consequence, interventions in children with FWS who were appropriately vaccinated against Hib and pneumococcus have become based on observation.^{8,15} Nevertheless, this is not what happens in Brazil. In our country, Hib vaccination is included in the official vaccination calendar, but vaccination against pneumococcus is not. Therefore, the evaluation and follow-up of children up to 36 months with FWS must be more detailed, and laboratory tests are still very useful for the decision-making process.

Most studies have not presented the final diagnoses in detail, except for cases of SBI and paying special attention to OB. Thus, it is difficult to compare our general results with

the literature. Galetto-Lacour et al.²⁴ conducted a study with 124 children up to 36 months old with FWS and identified 23% of cases of SBI, 10% of focal bacterial infection, and 67% of probable viral infection. Gervais et al.⁴ reported on a study involving the follow-up of febrile children aged up to 2 years that demonstrated the presence of 20.2% of children with FWS; of these, 17.3% had SBI. In our sample, most children had spontaneous fever resolution (49.8%). The presence of self-limited benign disease or probable viral etiology was found in 40.9%. SBI was identified in 9.3% of the children.

UTI is the most common bacterial infection in children with FWS, mainly in girls. The general prevalence of UTI ranges from 2 to 5% in febrile children younger than 2 years old.²⁰ In this age group, fever is often the only symptom of UTI.^{8,9,15,20} In our sample, UTI was the most frequent SBI.

In the children younger than 3 months old, several pathophysiologic, epidemiologic and etiologic aspects are different from those presented by children older than this age group.^{1,2,9,25} SBIs are more common in this age group, mainly in newborns. Some studies have shown the occurrence of SBI in approximately 10% of the febrile infants from 1 to 2 months old and in up to 13% of the newborns.^{9,25} Therefore, this age group keeps being managed in a more aggressive manner with the purpose of identifying possible SBIs as soon as possible. Our sample is small for this age group (nine newborns and 23 young infants).

Mukai et al.²⁶ carried out a prospective study with 82 febrile infants younger than 2 months old seen at the PSHU-USP. These children remained in the emergence department for observation during at least 24 hours with the purpose of being evaluated, undergoing laboratory screening, and initiating treatment. After this period, 65 children were discharged and could go home, and, of these, three had to be hospitalized later. The authors concluded that the period of 24 hours for observation associated with laboratory screening was enough for the evaluation and indication of outpatient follow-up for these infants. In our study, we recommend outpatient assessment with daily returns to our emergency department after clinical observation from 12 to 24 hours for those young infants considered as being at low risk of SBI.

Children from 3 to 36 months old without toxemia make up the most controversial group in terms of the most appropriate management. According to Baraff¹⁵ and the American College of Emergency Physicians Clinical Policy Committee,⁸ children with FWS from 3 to 36 months without UTI and who did not receive conjugated vaccine against pneumococcus, or who received incomplete immunization (two doses or less), must follow this guideline: CBC for the children with temperature > 39 °C with initiation of empiric antibiotic therapy when the total number of white blood cells

is > 15,000/mm³ and chest radiography when the number of white blood cells is > 20,000/mm³. In our sample, only two children were vaccinated against pneumococcus.

In our study, we used the total number of white blood cells > 20,000/mm³ or the total number of neutrophils > 10,000/mm³ as the cutoff point for taking the decision about the use of empiric antibiotic therapy.^{18,27} This choice was intended at increasing the specificity for identifying SBI and reducing the use of empiric antibiotic therapy. Nevertheless, there was need of clinical follow-up. Empirical antibiotic therapy is another very controversial aspect of these strategies. Initiation of empirical antibiotic therapy may reduce the occurrence of SBIs and their complications.^{12,13,28-30} However, excessive use of antibiotics may have an impact on the increase in the rates of bacterial resistance.

One of the limitations of our study was the loss of follow-up of 36 children (14.34%). For most cases (27), the reason was the fact that we could not contact the patients, which is understandable in a population like this. The remaining nine children were excluded from the sample as a result of their family's decision or because they did not adhere to the guideline. They were followed up until spontaneous fever resolution, but their results were not included in our sample.

Conclusions

Fifteen years after the publication of the strategy proposed by Baraff et al.,⁷ countless deployments regarding the identification of OB and SBI generated changes in the medical management of children with FWS. Diagnosis and follow-up of these children continue to be discussed and undergo constant updates due to the results of countless studies, optimization of laboratory techniques, use of new SBI markers, studies on the fast identification of virus and control of viral diseases, as well as production of new vaccines.

Nevertheless, no combination of laboratory tests and clinical assessment has been able to identify all patients with SBI during the initial evaluation. There is not a strategy showing the sensitivity and specificity levels expected by physicians. Reassessment and instruction of children's guardians to return for medical assessment when the child presents with any sign of worsening are essential aspects. Any guideline regarding the medical care of febrile children must be used as an supplementary resource, instead of replacing clinical assessment. However, these guidelines will continue to be useful.

Regardless of the progresses reached, the secret of the evaluation of children with FWS lays in the clinical capacity of the medical team to identify and follow up those children at risk of SBI associated with the interaction with the family.

Finally, this guideline proved to be appropriate for the follow-up of children with FWS up to 36 months old who underwent simple laboratory tests that can be performed at most health care facilities. All children with SBI were identified in the initial evaluation or during follow-up.

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References

- Trotta EA, Gilio AE. Febre aguda sem sinais de localização em crianças menores de 36 meses de idade. *J Pediatr (Rio J)*. 1999;75: s214-s22.
- Baraff LJ. Management of fever without source in infants and children. *Ann Emerg Med*. 2000;36:602-14.
- Singer JI, Vest J, Prints A. Occult bacteremia and septicemia in the febrile child younger than two years. *Emerg Med Clin North Am*. 1995;13:381-416.
- Gervais A, Cafisch M, Suter S. *Pédiatrie au Quotidien: Prise en charge des enfants fébriles sans signes localisateurs d'un foyer infectieux*. *Arch Pédiatr*. 2001;8:324-30.
- Akintemi OB, Roberts KB. Evaluation and management of the febrile child in the conjugated vaccine era. *Adv Pediatr*. 2006;53:255-78.
- Mahajan P, Stanley R. Fever in the toddler-aged child: old concerns replaced with new ones. *Clin Pediatr Emerg Med*. 2008;9:221-7.
- Baraff LJ, Bass JW, Fleisher GR, Klein JO, McCracken GH, Powell KR, et al. Practice guideline for the management of infants and children with fever without source 0-36 months of age. *Pediatrics*. 1993;92:1-12.
- American College of Emergency Physicians Clinical Policies Committee; American College of Emergency Physicians Clinical Policies Subcommittee on Pediatric Fever. Clinical policy for children younger than three years presenting to the emergency department with fever. *Ann Emerg Med*. 2003;42:530-45.
- Avner JR, Baker D. Management of fever in infants children. *Emerg Med Clin North Am*. 2002;20:49-67.
- McGowan JE Jr, Bratton L, Klein JO, Finland M. Bacteremia in febrile children seen in a "walk-in" pediatric clinic. *N Engl J Med*. 1973;288:1309-12.
- Teele DW, Pelton SI, Grant MJ, Herskowitz J, Rosen DJ, Allen CE, et al. Bacteremia in febrile children under 2 years of age: results of cultures of blood of 600 consecutive febrile children seen in a "walk-in" pediatric clinic. *J Pediatr*. 1975;87:227-30.
- Baraff LJ, Lee SI. Fever without source: management of children 3 to 36 months of age. *Pediatr Infect Dis J*. 1992;11:146-51.
- Bass JW, Steele RW, Wittler RR, Weisse ME, Bell V, Heisser AH, et al. Antimicrobial treatment of occult bacteremia: a multicenter cooperative study. *Pediatr Infect Dis J*. 1993;12:466-73.
- Fleisher GR, Rosenberg N, Vinci R, Steinberg J, Powell K, Christy C, et al. Intramuscular versus oral antibiotic therapy for the prevention of meningitis and other bacterial sequelae in young, febrile children at risk for occult bacteremia. *J Pediatr*. 1994;24:504-12.
- Baraff LJ. Editorial: Clinical policy for children younger than three years presenting to the emergency department with fever. *Ann Emerg Med*. 2003;42:546-9.
- Belfer RA, Gittelman MA, Muniz AE. Management of febrile infants and children by pediatric emergency medicine and emergency medicine: comparison with practice guidelines. *Pediatr Emerg Care*. 2001;17:83-7.
- Klein JO. Management of the febrile child without a focus in the era of universal pneumococcal immunization. *Pediatr Infect Dis J*. 2002;21:584-8.
- Kuppermann N. Occult bacteremia in young febrile children. *Pediatr Clin North Am*. 1999;46:1073-109.
- Dagan R, Powell KR, Hall CB, Menegus MA. Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis. *J Pediatr*. 1985;107:855-60.
- Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. *Pediatrics*. 1999;103:843-52.
- Lee GM, Fleisher GR, Harper MB. Management of febrile children in the age of the conjugate pneumococcal vaccine: a cost-effectiveness analysis. *Pediatrics*. 2001;108:835-44.
- Herz AM, Greenhow TL, Alcantara J, Hansen J, Baxter RP, Black SB, et al. Changing epidemiology of outpatient bacteremia in 3- to 36-month-old children after the introduction of the heptavalent-conjugated pneumococcal vaccine. *Pediatr Infect Dis J*. 2006;25:293-300.
- Kuppermann N. The evaluation of young febrile children for occult bacteremia: time to reevaluate our approach? *Arch Pediatr Adolesc Med*. 2002;156:855-7.
- Lacour AG, Gervais A, Zamora SA, Vadas L, Lombard PR, Dayer JM, et al. Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as indicators of serious bacterial infections in children with fever without localising signs. *Eur J Pediatr*. 2001;160:95-100.
- Baker MD, Avner JR. The febrile infant: What 's new? *Clin Pediatr Emerg Med*. 2008;9:213-20.
- Mukai LS, Ejzenberg B, Lotufo JP, Barbante LF, Yamashita CA, Vieira SE, et al. Febre no lactente jovem atendido em serviço de emergência: Aspectos diagnósticos e terapêuticos. *J Pediatr (Rio J)*. 1995;71:322-30.
- Kuppermann N, Fleisher GR, Jaffe DM. Predictors of occult pneumococcal bacteremia in young febrile children. *Ann Emerg Med*. 1998;31:679-87.
- Baraff LJ, Oslund S, Prather M. Effect of antibiotic therapy and etiologic microorganism on the risk of bacterial meningitis in children with occult bacteremia. *Pediatrics*. 1993;92:140-3.
- Harper MB, Bachur R, Fleisher GR. Effect of antibiotic therapy on the outcome of outpatients with unsuspected bacteremia. *Pediatr Infect Dis J*. 1995;14:760-7.
- Bulloch B, Craig WR, Klassen TP. The use of antibiotics to prevent serious sequelae in children at risk for occult bacteremia: a meta-analysis. *Acad Emerg Med*. 1997;4:679-83.

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