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The Febrile Infant

Pedro Rino, MD[1,2,*]
Eugenia Hernández, MD[1]

Address
[1]Hospital de Pediatría "Prof. Dr. Juan P. Garrahan", Buenos Aires, Argentina
[*,2]Universidad de Buenos Aires, Unidad Emergencias, Hospital de Pediatría "Prof. Dr. Juan P. Garrahan, Combate de los Pozos, 1881, Ciudad Autónoma de Buenos Aires, Argentina
Email: pedrorino@hotmail.com

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Abstract

Purpose of review Fever is a common complaint between children under 36 months of age. While most of febrile children are affected from viral infections, some infants can suffer from a serious bacterial infection (SBI). This article focuses on the child with fever without source (FWS) and the available diagnostic tools to estimate SBI risk and avoid unnecessary complementary tests and treatments, as well as their use in routine clinical practice in a Latin American country.

Recent findings The combination of medical history, physical examination, and complementary tests continues to being very important to take decisions on febrile infant. Procalcitonin, C-reactive protein, and absolute neutrophil count are the most relevant complementary tests to help us perform actions on infants with FWS with good clinical appearance and without risk factors.

Summary The evaluation and disposition of febrile infants is highly variable, particularly among infants between 29 and 60 days of age. If a child has bad appearance or the bacterial source of fever is definite, treatment needs to be started immediately. However, if febrile infant has FWS, has a good clinical appearance, and does not have risk factors in medical history, the complementary tests can be necessary to identify febrile infants with low SBI risk. The evaluation of SBI risk, and mainly of invasive bacterial infection—bacteremia and meningitis—, will continue to change according to new scientific researches; training and experience of physicians and availability of auxiliary tests; and, of course, sociocultural background. This is particularly important in low-resource settings; therefore, in children 1 to 2 months of age, it is preferable to establish a safer strategy to assess SBI risk and hospitalization should be considered.

Introduction

Fever is one of the most frequent complaints in children under 3 years old in emergency department [1–4]. Parents and physicians can be concerned as it can be a serious problem that requires urgent evaluation, complementary tests and treatment. Fever may be associated with serious bacterial infections (SBI). Most of febrile children looks good and suffers from self-limited viral infections; others have bad appearance and suffer from a serious disease; and, finally, a small percentage has an occult SBI.

After asking about health history and physical examination, 1 in 5 of patients has fever without source (FWS) [5]. Within this percentage, a small group could suffer from an occult SBI such as urinary tract infection (UTI), pneumonia, occult bacteremia (OB) or, more rarely, bacterial meningitis.

Since the implementation of conjugate vaccines against *Haemophilus influenzae* type B (HibCV) and *Streptococcus pneumoniae* (PCV) the incidence of SBI has decreased. The impact has been greater, the incidence of bacteremia was not only reduced among vaccinated children but the unvaccinated population also benefited through the protection phenomenon known as "herd effect" [2, 4, 6]. But immunization coverage varies around the world. In 2017, in Argentina, there was 92% of infants younger than 1-year old who had 3 doses of HibCV [7] and 78% of PCV [8]; in Latin America, the percentage was 81% of PCV [8].

In high-resource settings, most infants with FWS who looks good and has normal complementary tests can be followed as outpatients, but this is more difficult in low-resource settings. In developing countries, such as Argentina and other Latin American countries, there is a high percentage of population that has low educational level and poor immediate access to health system. FWS, especially in younger children, should be addressed even more carefully in this sociocultural background.

Fever

In Argentina and other countries of Latin America, temperature is measured with a thermometer in axillary region. Non-rectal measurements would underestimate the fever register, although it is accepted that in the case of temperature ≥ 38 °C (100.4 °F) in a non-rectal measurement the diagnosis of fever should be recognized. Hyperpyrexia may be associated with a higher rate of SBI. Before the implementation of the PCV, the relation between SBI due to *Streptococcus pneumoniae* (especially in young children) and higher body temperature was described [2, 9–15]. We must also consider that hypothermia can be as important as fever during the evaluation of a child with a bad appearance since it can be associated with sepsis.

Approach to febrile child under 36 months of age

Whatever age or risk factors, the child with sepsis requires an intensive approach that include diagnostic test, antibiotic treatment, and hospitalization. If the patient has bad appearance or the physical examination is abnormal, this should be enough to initiate actions that can be adapted to medical history and complementary tests. On the other side, risk factors in medical history between well appearance patients (e.g., immunocompromised or recent surgery), often, by themselves, can define the beginning of medical actions. But in case of febrile child with good appearance and history without risk factors, the auxiliary tests could be necessary to define SBI risk. Then, we could do an evaluation in steps to determine the risk of suffering SBI. This approach must be dynamic, since according to the child's appearance, we will sometimes take

immediate actions after the physical examination while at other times we will ask about the medical history or wait for the results of complementary exams to define actions to follow.

If the first step (appearance and physical examination) is abnormal, it may be necessary to take diagnostic and therapeutic actions immediately. If it is normal, the second step (clinical history and risk factors) can by itself determine diagnostic and therapeutic actions. Finally, when first and second steps are normal, the third one (complementary tests) may be essential to determine SBI risk.

First step: Appearance and physical examination

Some signs and symptoms will guide us to determine severity and cause of illness. Tachypnea or bradypnea, tachycardia, cyanosis, dehydration, mottled skin, petechiae, poor peripheral perfusion, decreased muscle tone, lethargy, irritability, lack of eye contact, and poor interaction with parents should make us suspect of a serious infectious disease [11, 12, 16–23]. Children who look bad have a higher SBI risk than children who have good appearance. Similarly, febrile children who have obvious viral source (e.g., rhinitis, non-petechial rash, non-dysenteric diarrhea) have lower SBI risk than those with FWS [2, 10].

Second step: History

History of fever, over-all health during fever-free time, pregnancy history, history of birth, previous diseases, receiving drugs as antibiotics, antipyretics or other medication, recently received vaccine, recent contact with infected people, immunizations, trips and signs, or symptoms are very relevant to guide clinical suspicion [2, 10, 12, 24].

Sometimes, isolated presence of some risk factors (e.g., immunocompromised) in child with fever can define diagnostic and therapeutic actions since it increases SBI risk [2, 9, 25].

Third step: Complementary tests

There are several tests to approach the diagnosis of SBI. None of them is 100% effective and sensitive, so a combination of them is needed for the diagnostic assessment.

White blood cell count

Most studies agree that white blood cell count (WBCC) ≤ 5000 or ≥ 15,000/mm^3, absolute neutrophil count (ANC) ≥ 10,000/mm^3, band neutrophil count (BNC) ≥ 1500/mm^3 and BNC/ANC index ≥ 0.2 are associated with highest SBI risk. These last three values of neutrophils have higher sensitivity than the total WBCC. WBCC and ANC were predictors to determine the risk for SBI previous the introduction of PCV [2, 10, 12, 16, 17, 26–28, 29••]. Recently, ANC ≤ 4090/mm^3 was associated with lower risk for SBI [30••].

C-reactive protein

Sensitivity and specificity vary according to the cut points used [31–33]. It can also rise in some viral infections. It increases about 12 h after the onset of fever. C-reactive protein (CRP) > 20 mg/L can be associate to bacterial infection.

Procalcitonine

It is best marker to differentiate between bacterial, viral and noninfectious causes of inflammation. It rises more rapidly than CRP and is more sensitive and specific as predictors of SBI than WBCC, ANC, and CRP. It increases rapidly and intensely in bacterial infection, correlating magnitude of ascent with severity of infection. Value < 0.5 ng/mL is normal [31, 33, 34, 35••, 36, 37], and some researchers consider a value < 0.3 ng/mL and less to improve sensitivity to define low SBI risk in younger children [30••, 35••, 37]. Neither procalcitonine (PCT), CRP, WBC, nor ANC is an absolute determinant by itself to define SBI risk.

Urine tests and culture

Diagnosis of UTI is made through urine culture but its result is not obtained immediately so it requires faster tests that approach the diagnosis. Detection of leukocytes ≥ 10/high-power field, bacteriuria, leukocyte esterase, and nitrites is good as these screening tests predict UTI [2, 10]. Although in our country it is common to use a technique of a medium jet after meticulous genital hygiene, the urethrovesical catheterization and suprapubic puncture are the methods of choice for urine culture, particularly in younger children [12, 17, 27, 38, 39].

Blood cultures

It is a gold standard for diagnosis of bacteremia. Blood cultures with contaminating microorganisms are even more frequent than those that develop true pathogenic organisms, which increase the probability of unnecessary complementary tests, antibiotic therapy, and hospitalizations [2, 10].

Lumbar puncture

To make the diagnosis of meningitis, a sample of cerebrospinal fluid (CSF) must be obtained, usually by lumbar puncture (LP). Absolute and differential count of white blood cells, red blood cells, Gram stain and glucose (in relation to the glycaemia value), and protein determinations should be performed. Occasionally other CSF tests may be necessary (e.g., latex agglutination in case of patients receiving antibiotics that inhibit microbial development). CSF culture and glucose determination can be modified if the patient received previous antibiotic therapy but not so quickly the cells.

Stools tests and culture

In case of diarrhea, stools tests can be performed. The presence of leukocytes ≥ 5/high-power field is considered abnormal [2, 10, 12].

Chest x-ray

If there are respiratory symptoms or signs (cough, cyanosis, tachypnea, rales, etc.), it should be performed [10, 12, 16, 27, 40]. WBCC > 20,000/

mm^3 can be a predictor of pneumonia in children without respiratory semiology. Also, chest x-ray should be performed in presence of high hyperthermia and several days elapsed of cough or fever [10, 27, 41].

Age-specific consideration

The immaturity of the immune system and the few signs and symptoms that the infant shows lead a greater SBI risk when the child is younger. Therefore, in order to assess febrile children, they are divided into three age groups: 0 to 28 days, 29 to 90 days, and 3 to 36 months. There is a current tendency to modify the last two groups to 29 to 60 days and 2 to 24 months.

Younger than 1 month

The risk of having a SBI is 12 to 28% in this group [2, 6, 10, 42–44]. The most frequent presentation is UTI, followed by bacteremia (2 to 3%) and meningitis [2, 4, 6, 10, 16, 42, 44]. Appearance and physical examination may be normal and auxiliary tests do not have adequate sensitivity among infants younger than 28 days, so they should be admitted and blood, CFS, and urine cultures are needed. Studies in neonates who tried to reproduce the criteria of low risk to suffer SBI reported a low but not tolerable percentage of SBI in groups of children considered to be at low risk [2, 9, 10, 16, 42–47]. The delay in diagnosis and treatment can increase morbidity and mortality.

Despite the presence of suggestive signs or even positive tests for viral infection, complementary tests and antibiotic treatment for a possible SBI should not be delayed. [2, 10, 48, 49•].

In conclusion, all infants of this age group should be hospitalized, since it is not possible to know who is having serious invasive disease [6, 9, 10, 16, 50].

Since *Streptococcus* group B begun to search in pregnant women and intrapartum treatment have been performed, its incidence in early sepsis decreased [45, 51]. *Escherichia coli* is the most common germ today, especially in UTI. Other bacteria are *Staphylococcus* spp., *Streptococcus* spp., and Gram-negative; *Listeria monocytogenes* and *Streptococcus pneumoniae* are rare.

Antibiotic therapy can include intravenous ampicillin 100 mg/kg/day (200 to 400 mg/kg/day in meningitis) associated with gentamicin 5–7.5 mg/kg/day. Another therapeutic option is intravenous ampicillin and cefotaxime 150 mg/kg/day (300 mg/kg/day in meningitis) [52]. Ampicillin has activity against *Listeria monocytogenes* as well as on *Streptococcus* group B, *Enterococcus faecalis* and some *Escherichia coli*; gentamicin or cefotaxime on the resistant *Escherichia coli* [53–55]. Ceftriaxone is generally not used in this age group because it competes with bilirubin for albumin binding sites and causes hyperbilirubinemia.

If the patient presents history of previous hospitalization, intravenous vancomycin 40 mg/kg/day (60 mg/kg/day in meningitis) associated with amikacin 15 mg/kg/day due to hospital-acquired infections (*Staphylococcus* spp., *Pseudomonas* spp., etc.) is recommended.

Herpes simplex virus infection should be suspected if there are risk factors (skin vesicles, scalp during fetal monitoring, premature rupture of membranes, seizures, lethargy, pleocytosis in the CSF, etc.); it is recommended to prescribe intravenous acyclovir 60 mg/kg/day [4, 6, 9, 45].

Currently, since the decrease of bacterial infections after the second and third week of life, some authors propose only observation, no antibiotics, in children older than 21 days without risk factors in history and with normal physical examination and normal auxiliary tests [29].

The suggested approach to febrile infant younger than 1 month of age is shown in Fig. 1.

One to three months

Also, in this age group, physical examination may be insufficient even for invasive bacterial infections (IBI), such as meningitis and bacteremia. About 5 to 10% of infants under 3 months of age with FWS has SBI, and between 0.5 and 2% of these children are affected by bacterial meningitis [56]. In the last decades, the way we approach febrile infants of this age group has been changed.

The identification of viral infection decreases but does not eliminate SBI risk [2, 4, 6, 10, 48, 57–60]. The most frequent coinfection with the viral infection is UTI [6, 48].

Of course, in this group, UTI is also the most frequent SBI [4, 6, 9, 22] and it is diagnosed in 4–16% of infants under 3 months of age with FWS. There is evidence that supports ambulatory approach of children older than 2 months with UTI, with good general condition and assured follow-up, without performing blood cultures or lumbar puncture [2, 10, 56, 61–63].

In spite of this, it is known that this age group also has a higher bacteremia risk and bacterial meningitis although infant has good appearance [6]. Since bacterial meningitis is less frequent, the utility of LP is discussed [6, 29••, 64–66, 67•, 68••, 69••, 70]. Although it has been recognized that abnormal, low, or high WBCC increases risk of bacteremia and meningitis [2, 10, 71], neither the clinical examination nor WBCC alone is absolutely reliable to rule out IBI in this age group. Therefore, LP should be strongly considered, especially if antibiotic is prescribed [6, 71]. In febrile infant between 30 and 90 days of age, it is described that the abnormal urine test has a high negative predictive value for meningitis, so the LP would not be routinely necessary if it also has low SBI risk according to clinical criteria and auxiliary tests [29••].

Between infants who meet criteria of low SBI risk, ambulatory management could be considered. Empiric antibiotic treatment in this group should be avoided, especially if blood cultures and LP were not performed, so as not to impair evaluation during follow-up.

Especially in this age group, the evaluation of risk of SBI and IBI will continue to change according to the progress of scientific research and the availability of auxiliary tests ranging from C-reactive protein to procalcitonin through panels to quickly find out viral or bacterial microorganism.

Sociocultural aspects of the patient's environment are very important factors to decide the way of follow-up. So, today, we cannot establish a single recommendation for febrile infant 1 to 3 months.

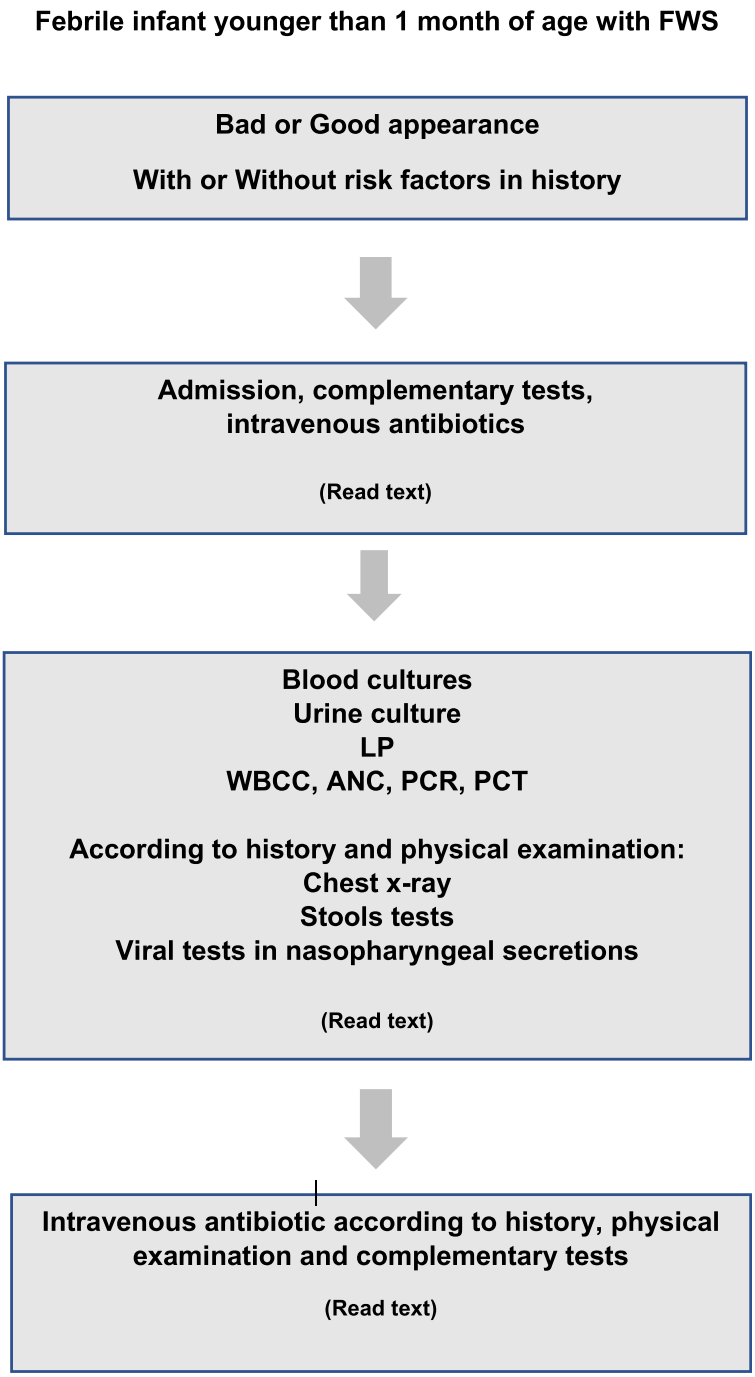

Fig. 1. Febrile infant younger than 1 month of age with FWS.

At present, there is a clear tendency to treat febrile infants between 2 and 3 months of age as those who belong to the age group of 3 to 36 months [6].

Patients who do not meet the low risk criteria for SBI could receive intravenous ceftriaxone 50 mg/kg/day (100 mg/kg/day in meningitis), and it could be

associated with ampicillin 200–300 mg/kg/day if suspected infection by *Listeria monocytogenes* and vancomycin 60 mg/kg/day for resistant Gram-positive cocci or *Enterococcus* spp.

The suggested approach to febrile infant 1 to 3 months of age is shown in Fig. 2.

Three to thirty-six months

There are less difficulties to evaluate a child of this age, since they generally interact better with the surrounding environment. Although good appearance does not completely rule out an SBI, it is unlikely to occur [2, 6, 10, 72, 73]. The prevalence of occult bacteremia (OB) among this group is between 0.5 and 2% [9, 74]. The use of clinical observation scales can be more useful in this group but the problem lies in the difficulty of detecting occult SBI.

In this group, a body temperature of ≥ 39 °C is used as the cutoff line to initiate a more extensive evaluation because increases OB risk due to pneumococcus and UTI [2, 9–11, 16, 43, 75–77].

Urinary infection

It is the most common cause of occult SBI [9, 13, 16, 22, 78–81]. Fever is usually the only sign of UTI in young children. It is described that approximately 5% of febrile children < 12 months suffer from UTI, more frequent in women and with higher temperatures [6, 10, 34].

Sometimes, UTI can still occur along with other infections such as diarrhea or rhinitis or a febrile post-vaccinal syndrome. In younger children, the urine test may be normal, so a sample should always be taken for urine culture. The most frequent bacteria are *Escherichia coli*, *Klebsiella* spp., and *Proteus* spp.

In Latin America, where the circumcision is not usual in most of population, it would be convenient to rule out UTI in all febrile children < 2 years who present at least two of the following risk factors: age < 12 months, duration of fever ≥ 24 h, temperature ≥ 39 °C (102.2 ° F), no other probable infectious source, and history of UTI or known uropathy [2, 6, 10, 22].

Initial antibiotic treatment will depend on antibiotic sensitivity of the most frequent pathogens; in Argentina, it can start with oral cephalexin 50–100 mg/kg/day or trimethoprim-sulfamethoxazole 6–12 mg/kg/day or amoxicillin-clavulanic acid 40 mg/kg/day. Duration of treatment will be 7 to 14 days. Children < 2–3-month old, bad appearance or oral intolerance, or due to sociocultural factors that do not allow ambulatory follow-up, will be admitted [82].

Occult bacteremia

It is the presence of pathogenic bacterium in blood cultures taken from a child in which a bacterial infection is not suspected from medical history, physical examination, and some complementary tests. Implementation of immunizations has changed etiology of bacteremia [2, 4, 6, 9]. In pre PCV era, bacteremia by *Streptococcus pneumoniae* was the most frequent, between 6 and 24 months of age [2, 10, 83, 84]; higher hyperthermia; WBC ≥ 15,000/mm^3; and ANC ≥ 10,000/mm^3 are associated with a higher risk of

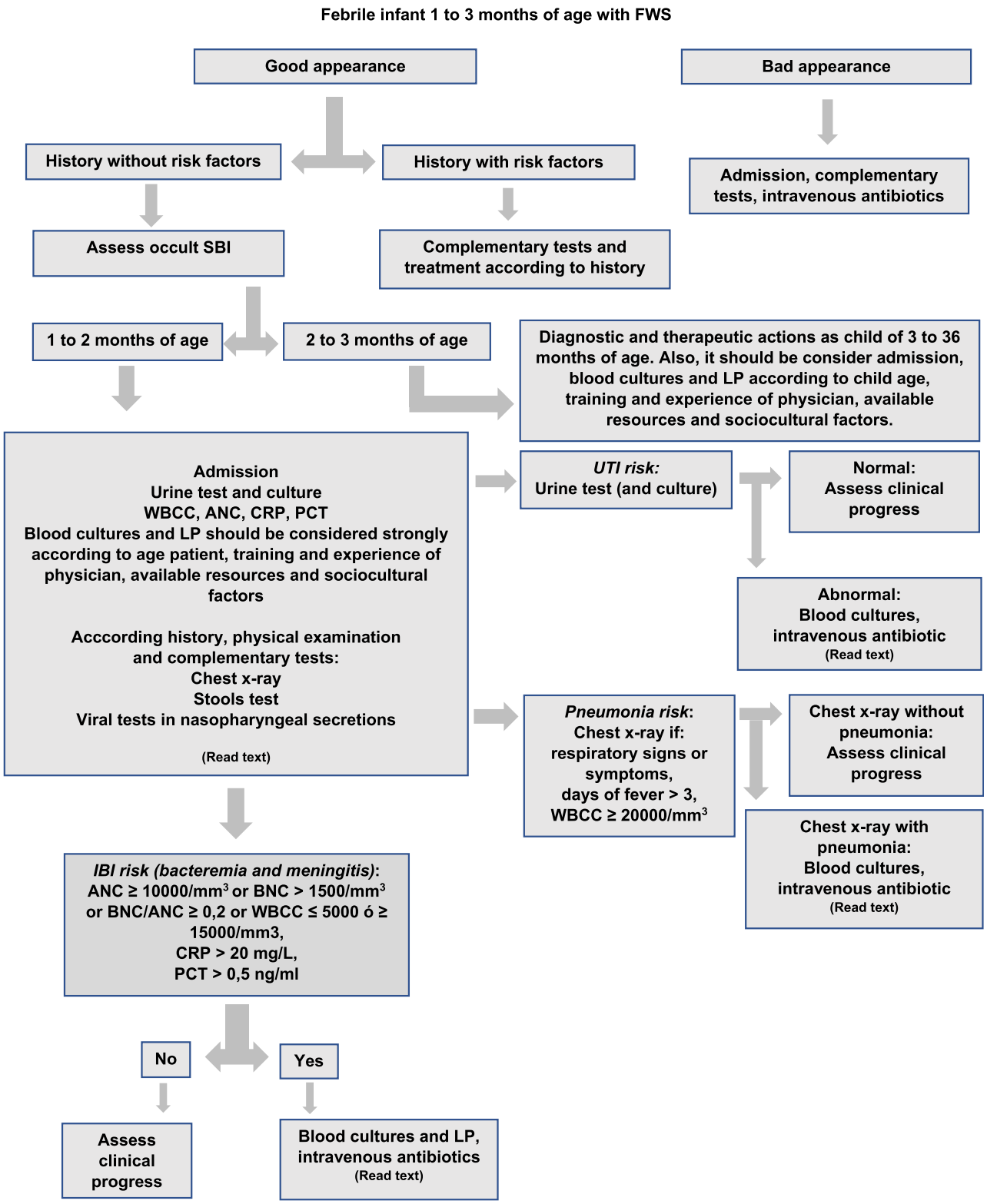

Fig. 2. Febrile infant 1 to 3 months of age with FWS.

OB [43, 83, 84]. The second most common cause of bacteremia has been *Escherichia coli* and that it is usually associated with UTI [4, 6, 55, 71, 85]. *Salmonella* spp. causes between 4 and 8% of the OB, and occurs most frequently with temperatures ≥ 39 °C (102.2 ° F) and suffering from diarrhea [6, 16, 83–85]. *Streptococcus pyogenes*, *Enterococcus* spp., *Neisseria meningitidis*, *Haemophilus influenzae* no type B, *Escherichia coli*, *Moraxella Catarrhalis*, *Salmonella* spp., and *Staphylococcus aureus* arise as more frequent causes of OB [4, 16, 55, 74, 85–87]. Although infections by *Neisseria meningitidis* are less frequent causes of bacteremia, patients look usually bad and it is associated with high rates of morbidity and mortality; also, blood cultures should be performed and intravenous antibiotics should be administered to febrile children with risk factors for meningococcal infection (contacts with patients with meningococcal disease, outbreaks of meningococcal disease, and fever and petechiae below the nipple region) [6, 9, 88].
In countries where HibCV and PCV are mandatory and there is good vaccine coverage in the population, according to the association between UTI and bacteremia due to *Escherichia coli*, the low relative frequency of bacteremia due to other germs and the limited value of the usual complementary tests to predict non-pneumococcal bacteremia, the empirical diagnostic, and therapeutic actions to be taken in febrile children who received ≥ 2 doses of anti-Hib and anti-pneumococcal conjugate vaccines are questioned [6].
If a febrile infant has abnormal blood complementary tests or risk factors, blood cultures and initiate intravenous antibiotic (ceftriaxone 50 mg/kg/day) should be performed; optionally, it can be admitted and be observed without antibiotics.
All febrile children who underwent blood cultures will be cited in 24 h for clinical control and blood culture reading. If the patient presents bacteremia due to *Streptococcus pneumoniae* but at the time of control the child has good appearance and no fever can be managed as outpatient after receiving intravenous antibiotic, while if persistently, febrile child should be hospitalized, blood cultures be repeated, and LP be performed. Patients with bacteremia by *Neisseria meningitidis* and *Haemophilus influenzae* type B should be hospitalized to perform LP and intravenous antibiotic therapy. And hospitalization, repeat blood cultures, perform LP, and intravenous antibiotic therapy in bacteremia by Salmonella spp. and *Escherichia coli* should be considered [2, 10].

Occult pneumonia

The most frequent etiology of pneumonia at this age is viruses, then *Streptococcus pneumoniae*, and *Chlamydia trachomatis*. *Mycoplasma pneumoniae* and *Staphylococcus aureus* are uncommon in this age group but are arising more commonly as causes of pneumonia. Like pneumococcal bacteremia and meningitis, pneumonia also became less frequent because of immunizations. It is usual for bacterial respiratory infections to be preceded by viral infections of the respiratory tract. But, in fact, neither signs, symptoms, blood tests, nor radiological findings can reliably distinguish between bacterial and non-bacterial etiology. There is consensus in Argentina to treat pneumonia of probable bacterial etiology in children > 3–6 months with

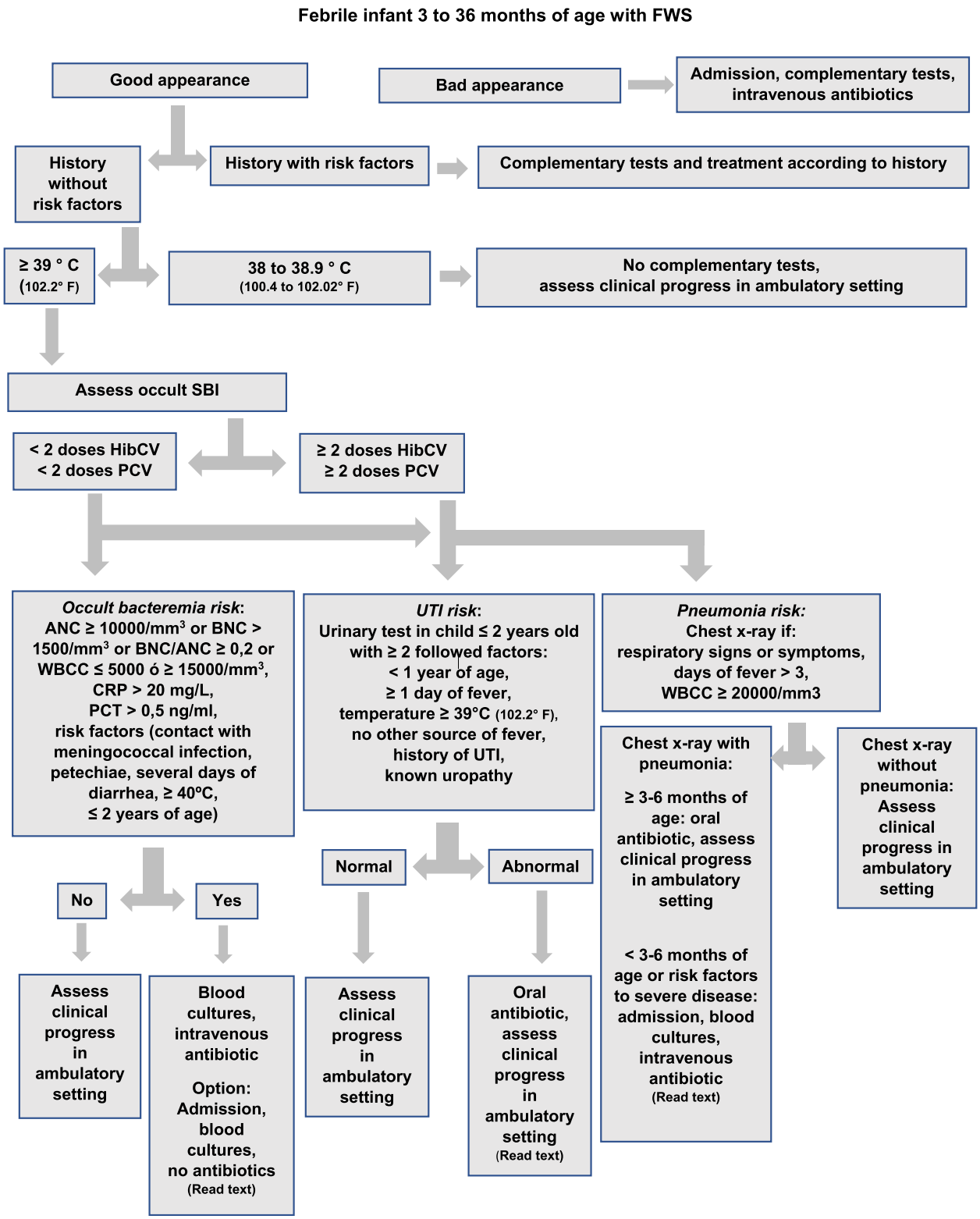

Fig. 3. Febrile infant 3 to 36 months of age with FWS.

good general condition like outpatients with oral amoxicillin 80–100 mg/kg/day for 10 days. Children younger than 3–6 months or with risk factors to severe pneumonia need to be admitted. Azithromycin or other macrolides can be used when there is suspicion of the infection by *Chlamydia trachomatis* or *Mycoplasma pneumoniae*. Children younger than 3–6 months with bad appearance, moderate-to-severe respiratory distress, hypoxemia, complicated pneumonia, suspicion or confirmation of a more virulent etiology (e.g., *Staphylococcus aureus*), difficulty feeding or oral intolerance, lack of response to antibiotic treatment in 48–72 h, rapid progression of the disease in 48–72 h, or other risk factors for severe disease should be admitted. Treatment can include ampicillin 200 mg/kg/day (or ceftriaxone 80 mg/kg/day or cefotaxime 100 mg/kg/day). Clindamycin 30 mg/kg/day or vancomycin 40–60 mg/kg/day is added for suspected community-acquired methicillin-resistant *Staphylococcus aureus* infection. Sociocultural factors are causes of admission too [6, 89–91].

Meningitis

Although meningitis is a severe and invasive infection, is not recommended routinely perform During evaluation of a febrile child between 3 and 36 months of age who presents a normal neurological examination because bacterial meningitis decreased markedly since implementation of the HibCV and PCV, LP will be performed in individual cases based on history and physical examination. Ceftriaxone 100 mg/kg/day if the child has meningitis is recommended. The suggested approach to febrile infant 3 to 36 months of age is shown in Fig. 3.

Conclusions

The challenge in febrile infant continues to identify and treat SBI, optimize the use of diagnostic tools, rationalize the use of antibiotics and hospitalizations, and minimize iatrogenic complications.

No history nor finding of the physical examination or complementary tests in children under 3-year old with FWS are enough to predict 100% for SBI risk. However, the combination of low risk background, good appearance, and normal value of complementary tests can identify most febrile children of this age with low risk for SBI.

New researches are taking other pathways to better identify the risk for SBI; it is proposed that analysis of host expression patterns in response to infections may provide an alternative diagnostic approach [92••].

The evaluation of SBI risk, and mainly of IBI—bacteremia and meningitis—, will continue to change according to the progress of scientific research; environment in which the patient is assisted; training and experience of the physicians and availability of auxiliary tests; and, of course, sociocultural background of the patient's environment.

At present, there is a clear tendency to approach febrile infants between 2 and 3 months of age as those who belong to the age group of 3 to 36 months (according age of patient, experience of attending physician, available resources, and sociocultural factors).

On the other hand, since characteristics of population and conformation of the health system in Argentina and other Latin American countries, here it seems preferable to approach a strategy of greater security to assess the SBI risk (i.e., admit, observe, and strongly consider lumbar puncture) in children between 1 and 2 months. However, it is likely that individually, the institutions modify their care protocols according to their own characteristics and that of the population they attend, in order to reduce the variation in care.

Compliance with Ethical Standards

Conflict of Interest

Pedro Rino declares that he has no conflict of interest.
Eugenia Hernández declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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They compared RNA biosignatures with routine complementary tests and Yale Observation Scale to distinguish bacterial infections in infants younger than 2 months of age.

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