

Fever without a source in children younger than 36 months.

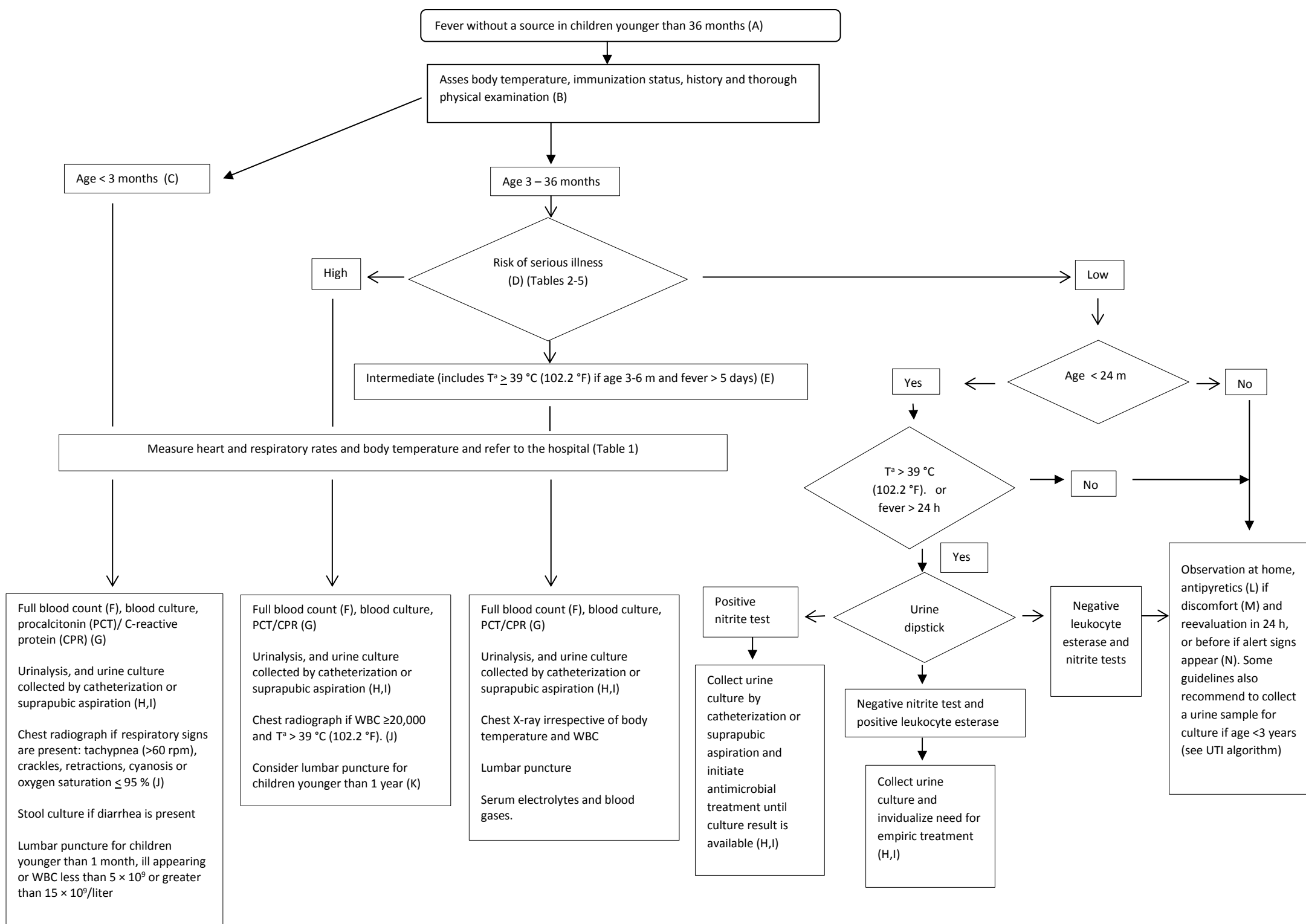
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(A) Fever is commonly defined as a rectal temperature $>38^{\circ}\text{C}$ (100.4°F), which usually corresponds to an axillary temperature of 37.5°C (99.5°F). Tympanic thermometers offer a quick but less reliable reading, with an average temperature of 0.3°C above the rectal one. Forehead chemical thermometers are unreliable and should not be used¹.

(B) It is often called fever without a source (FWS) when the history and physical examination cannot identify a specific source in an acutely ill, nontoxic-appearing child between 3 months and 3 years of age, with fever of less than 7 days duration. The presence of isolated pharyngeal or tympanic hyperemia or mild rhinorrhea does not exclude the criterion of FWS³.

(C) Age is the first factor to consider in a child with fever. The probability of presenting a serious bacterial infection is greater in children younger than 3 months (2-3 %) and especially in children under 1 month (1 in 8)³. The risk decreases between 3 and 36 months and from that age it is very uncommon for a serious bacterial infection to manifest without focal symptoms. All children with fever without a focus and toxic aspect or age <3 months should be referred to hospital for urinalysis, blood count, blood culture, C-reactive protein (CRP) and according to results, assess chest X-ray and lumbar puncture.

(D) There are several clinical scales to assess the risk of a serious bacterial infection. However they are not easily available, they need time to be assessed and also children frequently present with a fever of few hours of evolution and little disruption of general state despite having an underlying bacterial infection, so they do not replace the "clinical eye" and the parents' impression must always be taken into account.

The most used scales in children under 3 months are the YIOS (Young Infant Observation Scale) scale (Table 2) and the Rochester criteria, which include the-of laboratory tests to identify infants younger than 3 months with low risk of bacterial infection (Table 3).

The Yale observational scale (YOS) is used for children aged 3 months to 3 years (Table 4). Patients with a score ≤ 10 have only a 3% probability of serious bacterial infection; between 10 and 15 it rises to 26% and with a score ≥ 16 , 92% of patients have a serious illness.

The National Institute for Clinical Excellence (NICE)¹ proposes a clinical practice guide with a traffic light system to identify the risk of serious illness in children under five years with fever (Tables 5 and 6). Children with fever and any of the symptoms or signs in the red column should be recognized as being at high risk. Similarly, children with fever and any of the symptoms or signs in the amber column and none in the red column should be recognized as being at intermediate risk. Children with symptoms and signs in the green column and none in the amber or red columns are at low risk. Children with any "red" feature should be referred urgently to hospital

To detect signs of a potentially serious infection, the mnemonic rule ABCD may be used: "A": decreased alert or activity, "B" ("breath"): signs of respiratory distress, such as nasal flaring and tachypnea, "C" (circulation or color): tachycardia, pallor, poor perfusion, petechiae, "D":

(decrease in urine output or dehydration)⁴. The presence of any of these signs indicates the need for immediate referral to a hospital emergency department. The risk of occult bacteremia and severe bacterial infection correlates inversely with age (increased risk at lower age) and is influenced by general condition and, in a lesser extent, the magnitude of fever. Response to antipyretics does not correlate with severity of infection (strength of recommendation: A).

(E) Severe bacterial infections such as urinary tract infection (UTI) and occult bacteremia are more frequent with temperatures above 39 °C (102.2 °F). Thus, in children over 3 months a high grade fever is considered a risk factor. However, many viral infections also occur at temperatures between 39 °C and 40 °C. Temperature greater than 40 °C (104.0 °F) and especially 40.5 °C (104.9 °F) is more typical of bacterial infections.

(F) White blood cell count (WBC) is generally not very useful for detecting or ruling out a serious bacterial infection. It has different characteristics depending on whether the infection is due to a Gram positive (pneumococcus) or a Gram negative pathogen (salmonella or meningococcus). In the last case there may be no leukocytosis but leftward deviation. WBC greater than 15,000 or less than 5,000/mm³ or an absolute neutrophil count (ANC) above 10,000/mm³ are considered risk factors for occult bacteremia. A total leukocyte count above 20,000/mm³ suggests an increased risk of occult pneumonia¹.

(G) Elevations in levels of inflammatory mediators (i.e. C-reactive protein [CRP] and procalcitonin [PCT]) may be better markers of severe bacterial infection (SBI) than white blood cell count (WBC) and absolute neutrophil count (ANC) in children at significant risk for bacterial infection. A CRP level > 150 mg/l is useful as a marker of bacterial infection, but CRP concentrations generally do not increase until 12 hours after the onset of fever. CRP values <20 mg/l are typical of viral infections

PCT levels rise in response to bacterial infections more rapidly than those of CRP (3 h). PCT levels are usually < 1 ng/ml in viral infections whereas a value ≥ 20 ng/ml is indicative of SBI. Some data suggest that PCT levels may be more sensitive and specific markers for severe invasive bacterial infection in infants and children than WBC, ANC, and CRP. However, those trials included febrile children with urinary tract infection (UTI) or other focal symptoms of infection, so their value in the diagnosis of children with fever without a source (FWS) and good general condition is still unknown.

(H) Urine dipstick is very useful in the outpatient setting to guide the need to collect a urine culture and assess the indication of an empirical treatment until its result.

Urinary nitrite can indirectly reflect the presence of bacteriuria, because dietary nitrates are converted to nitrites in the presence of the most Gram-negative enteric bacteria in urine. This conversion requires urine to remain in the bladder for at least 4 hours, which often does not occur in infants, who empty their bladders frequently. Nitrite test has a high specificity (i.e. there are few false-positive results) but a low sensitivity, so it's helpful when the result is positive but has a little value when negative in ruling out urinary tract infection (UTI)

The presence of leukocyte esterase in the urine dipstick is a surrogate marker for pyuria. The overall sensitivity of leukocyte esterase test ranges from 85-95 % but specificity of the test is not as good, and therefore false-positive results are common. The absence of pyuria in children with true UTI is rare⁶, and leukocyte esterase is also negative in asymptomatic bacteriuria.

The probability of UTI with dipstick negative for leukocytes and nitrites is 2-6%, raises to 40-65% with positive nitrites or leukocytes and to 75-90 % with both positive nitrites and leukocytes. Therefore, for non-toxic, febrile children >3 months, dipstick urinalysis is an appropriate screening test⁴. However, some guidelines recommend to perform urine culture with sterile technique in children without sphincter control (see UTI pathway). With dipstick positive for nitrites, UTI is very reliable and it would be indicated to start an empiric antibiotic after collecting an appropriate urine sample for culture. If negative for nitrites and positive for leukocytes, a urine culture should be collected and individualize the decision between initiating antibiotic treatment or waiting for results (see UTI pathway).

(I) Urinary tract infection (UTI) is the most common serious bacterial infection in children with fever without focus (FWS). The overall prevalence of UTI in febrile infants between 2 months and 2 years with FWS is 3-7%. In the first 6 months of life it is more prevalent in males, frequently associated with structural abnormalities of the urinary tract and from this age on it's more prevalent in girls. Risk factors of UTI are $T^a > 39^\circ\text{C}$ and previous UTI.

It is necessary to ensure that a urine specimen for both culture and urinalysis is obtained before if it is decided to start antimicrobial therapy. The specimen needs to be obtained through catheterization or suprapubic aspiration (SPA)⁶, because the diagnosis of UTI cannot be reliably established through an urine culture collected in a bag because it has a high percentage of false positives (30%). So, a "positive" culture result from a specimen collected in a bag cannot be used to document an UTI, although it is valid to discard it if negative. It could be an acceptable technique if immediate antimicrobial therapy is not required.

Urine obtained through catheterization for culture has a sensitivity and specificity similar to that obtained through SPA¹ and is less painful.

(J) Most children with fever and pneumonia have some signs on physical examination: usually tachypnea, abnormal auscultation, low pulse oximetry, retractions, or nasal flaring, suggesting respiratory tract disease. The absence of cough or respiratory signs (tachypnea, retractions, nasal flaring, pulse oximetry <95% or abnormal auscultation) makes the diagnosis of occult pneumonia very unlikely³. Chest x-ray is indicated in infants under 3 months of age only if respiratory signs are present (Recommendation: B). There is insufficient evidence to determine when an Rx should be performed in children older than 3 years, but a chest x-ray should be considered in highly febrile children (temperature $>39^\circ\text{C}$ [$>102.2^\circ\text{F}$]) with leukocytosis (WBC count $>20,000/\text{mm}^3$) (Recommendation C) because of the strong association between leukocytosis and pneumonia^{1,8}. The lack of signs or symptoms of lower respiratory tract infection obviates the need for a chest x-ray in children with $T^a < 39^\circ\text{C}$ ($>102.2^\circ\text{F}$) with no features of serious illness.^{1,9}

(K) Around 15% of cases of invasive meningococcal disease may present as fever without focus (FWS), basically in children aged 3 months to 3 years. There are no clinical nor analytical predictive factors of meningococcal bacteremia in the febrile child. Left shift with band cells > 10% is characteristic of meningococcal bacteremia, but it has a very low positive predictive value.

Lumbar puncture is indicated in infants younger than 1 month, all infants aged 1–3 months who appear unwell or with a white blood cell count (WBC) less than 5×10^9 /liter or greater than 15×10^9 /liter, children with “red” features (NICE’s traffic light scale of all ages and also should be considered for children younger than 1 year who have 1 or more “amber” features.¹

Physical examination may lead to suspicion of meningitis in patients older than 3 months and therefore lumbar puncture is not systematically indicated in this age group³

(L) Paracetamol is given at doses of 10-15 mg / kg / dose every 4-6 h (max 75 mg / kg / day or 90 mg / kg / day for less than 3 consecutive days). The onset of action occurs at 30-60 minutes, with peak at 3-4 h, duration of 4-6 h and a reduction of the temperature of 1-2 °C. Ibuprofen, at 10 mg / kg / dose every 6 hours, has a similar onset, peak and temperature reductions, but a somewhat longer effect (6-8 h). Magnesium metamizole at doses of 10 mg / kg / dose every 6 hours orally or rectally or at 0.05 - 0.1 ml / kg / dose i.v. has also an antipyretic effect but presents the potential risk of agranulocytosis, and therefore is less commonly used.

Paracetamol and ibuprofen have a similar safety profile and antipyretic efficacy, perhaps with a somewhat longer duration of antipyretic effect for ibuprofen. Although hepatotoxicity with acetaminophen at recommended doses has been rarely reported, hepatotoxicity is most commonly seen in the setting of an acute overdose. In addition, there is significant concern over the possibility of acetaminophen-related hepatitis in the setting of a chronic overdose. The most commonly reported scenarios are those of children receiving multiple supratherapeutic doses (i.e. > 15mg/kg per dose) or frequent administration of appropriate single doses at intervals of less than 4 hours, which have resulted in doses of more than 90 mg/kg per day for several days. Ibuprofen can potentially cause gastritis, although no data suggest that this is a common occurrence when used on an acute basis, such as during a febrile illness¹⁰. Ibuprofen does not seem to worsen asthma symptoms¹⁰.

A special mention should be made of the possibility of nephrotoxicity after the administration of an adequate dose of non-steroidal anti-inflammatory drugs (NSAID) ¹¹. In children with dehydration, prostaglandin synthesis is an important mechanism for maintaining an adequate renal flow, which could be interfered by the use of ibuprofen or other NSAIDs. However, the actual incidence of renal failure secondary to the use of ibuprofen over a short period of time is not known. Children at highest risk of ibuprofen-related renal toxicity are those with dehydration, cardiovascular disease, underlying nephropathy, or concomitant use of other nephrotoxic drugs. Another potential group at risk are infants younger than 6 months because of the possibility of differences in ibuprofen pharmacokinetics and developmental differences in renal function¹⁰.

(M) The mere presence of fever does not always require treatment. Fever may produce child's discomfort and increase insensible fluid losses, but with the exception of children with chronic or those critically ill who may not tolerate the increase in fever-induced metabolic demand, there is no evidence that the reduction of fever could reduce the morbimortality of the process. There is also no evidence that antipyretic therapy decreases the recurrence of febrile seizures. Therefore, the main goal of treating a febrile child should be to improve the child's overall comfort rather than to achieve normothermia¹⁰.

Adequate hydration should be ensured and avoid excessive draping to prevent dehydration. Application of alcohol, which can cause intoxication by inhalation, and cold water baths, which could even raise the central temperature by provoking skin vasoconstriction, are formally contraindicated. According to a limited number of studies, bath with warm water associated with antipyretic could contribute to reduction of temperature, but this effect is transient and is associated with discomfort. For all of the above, the use of physical measures to treat fever is not recommended.^{12,13}

Alternation or combination of antipyretic drugs is a widespread practice, even favored or allowed by doctors. However, there is little evidence on the benefit of combined treatment compared with the use of each drug alone. In addition, there are doubts about the safety of this practice, since Ibuprofen blocks renal prostaglandins and inhibits the production of glutathione (essential for the excretion of the toxic metabolite of paracetamol), and can lead to dosage errors and promote "feverfobia". Therefore, this practice is not recommended.^{4,12,14}

(N) Prescription of oral antibiotics to children with fever without apparent source is discouraged. However, with suspected meningococcal disease it is recommended to give parenteral antibiotics to children at the earliest opportunity (either benzylpenicillin or a third-generation cephalosporin).^{1,12}

TABLES**Table 1. Heart and respiratory rates for age**

Tachycardia		Tachypnea	
Age	Heart rate (bpm)	Age	Respiratory rate (breaths/minute)
< 12 months	>160	0-5 months	> 60
12-24 months	>150	6-12 months	> 50
2-5 years	>140	> 12 months	> 40

Table 2. YIOS Scale (Young Infant Observation Scale)

Observation item	Normal [1 point]	Moderate impairment [3 points]	Severe impairment [5 points]
Affect	Smiles and/or not irritable	Irritable, consolable	Irritable, not consolable
Respiratory status / effort	No impairment, vigorous	Mild - moderate respiratory compromise (tachypnea > 60 rpm, retractions or grunting)	Respiratory distress with inadequate effort (apnea, respiratory failure)
Peripheral perfusion	Pink, warm extremities	Mottled, cool extremities	Pale, shock
YIOS <7: low risk serious bacterial infection. YIOS ≥7 : high risk serious bacterial infection			

Table 3. Rochester Criteria for Febrile Infant 0 to 60 days

1. Well appearing infant

2. Previously healthy:

- Full term birth
- No prior hospitalizations
- Not hospitalized longer than mother after delivery
- No prior antibiotics
- No Hyperbilirubinemia
- No chronic or underlying illness

3. No skeletal, soft tissue, skin or ear infections

4. Lab findings:

- White Blood Cell Count normal (5000 to 15,000/mm³)
- Band Neutrophils < 1,500/mm³
- If diarrhea is present, Fecal Leukocytes <5 WBC/hpf
- Urine White Blood Cells <10 WBC/hpf

(Reassuring if all criteria are present)

Table 4. Yale Scale for Febrile Child 3 to 36 months

Observation item	Normal [1 point]	Moderate impairment [3 points]	Severe impairment [5 points]
Quality of Cry	Strong or No cry	Whimper or Sob	Weak cry, Moan, or high pitched cry
Reaction to parents	Brief Cry or Content	Cries off and on	Persistent cry
State variation	Awakens quickly	Difficult to awaken	No arousal or falls asleep
Color	Normal, pink	Acrocyanosis	Pale, Cyanotic, or Mottled
Hydration	Eyes, skin, and mucus membranes moist	Mouth slightly dry	Mucus Membranes dry, eyes sunken
Social Response	Alert or Smiles	Alert or brief smile	No smile, anxious, or dull
<p>Interpretation:</p> <p>Score = 10: Incidence serious illness: 2.7%</p> <p>Score = 11-15: Incidence serious illness: 26%</p> <p>Score >16 : Incidence serious illness: 92.3%</p>			

Table 5. Traffic light system for identifying risk of serious illness. NICE 2013

	Green - low risk	Amber - Intermediate risk	Red - high risk
Color	Normal color of skin, lips or tongue	Pallor reported by parent/carer	Pale/mottled/ashen/blue
Activity	<p>Responds normally to social cues</p> <p>Content/smiles</p> <p>Stays awake or awakens quickly</p> <p>Strong normal cry/not crying</p>	<p>Not responding normally to social cues</p> <p>No smile</p> <p>Wakes only with prolonged stimulation</p> <p>Decreased activity</p>	<p>No response to social cues</p> <p>Appears ill to a healthcare professional</p> <p>Does not wake or if roused does not stay awake</p> <p>Weak, high-pitched or continuous cry</p>
Respiratory		<p>Nasal flaring</p> <p>Tachypnoea:</p> <p>RR > 50 breaths/minute, age 6–12 months</p> <p>RR > 40 breaths/minute, age > 12 months</p> <p>Oxygen saturation ≤ 95% in air</p> <p>Crackles in the chest</p>	<p>Grunting</p> <p>Tachypnoea: RR > 60 breaths/minute</p> <p>Moderate or severe chest indrawing</p>
Circulation and hydration	<p>Normal skin and eyes</p> <p>Moist mucous membranes</p>	<p>Tachycardia:</p> <p>> 160 beats/minute, age < 1 year</p> <p>> 150 beats/minute, age 1–2 years</p> <p>> 140 beats/minute, age 2–5 years</p>	<p>Reduced skin turgor</p>

		<p>CRT \geq 3 seconds</p> <p>Dry mucous membranes</p> <p>Poor feeding in infants</p> <p>Reduced urine output</p> <p>Reduced skin turgor</p>	
<p>Other</p>	<p>None of the amber or red symptoms or signs</p>	<p>Age 3–6 months, temperature \geq 39°C</p> <p>Fever for \geq 5 days</p> <p>Rigors</p> <p>Swelling of a limb or joint</p> <p>Non-weight bearing limb/not using an extremity</p>	<p>Age < 3 months, temperature \geq 38°C</p> <p>Non-blanching rash</p> <p>Bulging fontanelle</p> <p>Neck stiffness</p> <p>Status epilepticus</p> <p>Focal neurological signs</p> <p>Focal seizures</p>

CRT capillary refill time; RR respiratory rate

Table 6. Management of children with fever without apparent source (NICE)

Green - low risk	Amber - Intermediate risk	Red - high risk
<p>Urine testing for urinary tract infection</p> <p>Do not routinely perform blood tests and chest X-rays in children with fever who have no features of serious illness</p>	<p>Urine testing for urinary tract infection</p> <p>Blood tests: full blood count, blood culture, C-reactive protein</p> <p>Chest X-ray in a child with a fever greater than 39°C and WBC greater than 20×10^9/litre</p> <p>Lumbar puncture should be considered for children younger than 1year</p>	<p>Urine testing for urinary tract infection</p> <p>Blood tests: full blood count, blood culture, C-reactive protein</p> <p>Consider (guided by the clinical assessment):</p> <ul style="list-style-type: none"> - Lumbar puncture in children of all ages (if not contraindicated) - Chest X-ray irrespective of body temperature and WBC - Serum electrolytes and blood gas <p>Give parenteral antibiotics to:</p> <ul style="list-style-type: none"> -infants younger than 1month with fever - All infants aged 1–3months with fever who appear unwell - Infants aged 1–3months with WBC less than 5×10^9/litre or greater than 15×10^9/litre.

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