

American College of Radiology ACR Appropriateness Criteria®

Clinical Condition: Fever without Source—Child

Variant 1: Infant or child more than 1-month of age with no respiratory signs or symptoms.

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	2		Min
Rating Scale: 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

Variant 2: Infant or child more than 1-month of age with respiratory signs or symptoms, or fever $\geq 39^{\circ}$ centigrade and WBC count $\geq 20,000/\text{mm}^3$.

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	9		Min
Rating Scale: 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

Variant 3: Neonate less than 1-month of age (with or without respiratory symptoms).

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	6	Little supporting data, but neonates at relatively greater risk for SBI and occult infection.	Min
Rating Scale: 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

Variant 4: Infant or child more than 1-month of age with fever of unknown origin (FUO).

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	5	Little supporting data, but simple and low-radiation examination to exclude significant parenchymal consolidation and adenopathy. Part of many published clinical algorithms. In general, imaging does not play a role in patients with FUO, and there is insufficient evidence to endorse the use of other imaging modalities.	Min
Rating Scale: 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

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Clinical Condition: Fever without Source—Child

Variant 5: Child with neutropenia.

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	6	Little supporting data, but simple and low-radiation exam to exclude significant parenchymal consolidation and adenopathy.	Min
CT area of interest with contrast	5	Low yield in the absence of localizing findings on physical exam. However, in bone marrow transplant patients, CT of the chest has been shown to provide clinically useful information even in the absence of respiratory symptoms.	NS
Rating Scale: 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

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FEVER WITHOUT SOURCE—CHILD

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Summary of Literature Review

The febrile pediatric patient, especially an infant, represents a dilemma for the primary care physician. The definition of fever is generally regarded as a rectal temperature of 38° centigrade or higher [1]. Oral temperatures are less reliable in infants and young children, although they are the usual method of measuring temperature in older children and adults. Fever without source (FWS) is an acute febrile illness in which the origin of the fever is not apparent after initial careful history and examination [2-5]. Most causes of FWS are due to infections [4-6]. While most of these are self-limited and of little clinical concern, the burden on clinicians is to decide which children actually have a serious bacterial infection (SBI) that requires antibiotic treatment and even hospitalization. In children, the usual sources/causes of SBI are urinary tract infection, pneumonia, blood stream infection, and meningitis. With the advent of vaccines for the most common pathogenic serotypes of hemophilus influenza and streptococcus pneumoniae, the incidence of SBI has dropped significantly [4,7]. However, the need to identify those FWS patients with potential SBI remains [8].

Although the terms are sometimes used interchangeably, FWS is different from fever of unknown origin (FUO). Strictly defined, FUO refers to a fever of >38.3° centigrade lasting three weeks or more without an apparent etiology [9], although some recent authors have liberalized the definition of FUO to fevers lasting more than one week and undiagnosed despite outpatient evaluation [10-12]. The majority of children with FUO have infectious causes, although inflammatory and neoplastic conditions are also in the differential [10,11,13-15]. The distinction between FWS and FUO is more than just academic, as the clinical and imaging approaches to these conditions may differ.

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Fever without Source

The cause of fever in the pediatric patient can often be determined from the history, physical examination, and laboratory tests [3-5,16,17]. Prior medical conditions, medications, foreign travel, and immunization history are all important in directing subsequent investigations [7,18,19]. Twenty percent of cases, however, will have no apparent source and thus are defined as having FWS [3]. The approach to a febrile child is generally divided into the infant less than 3 months of age, and the older infant and child between 3-36 months of age [3,4,17]. Many authors place infants less than 1 month of age into a special category deserving more aggressive evaluation, as these children have more immature immune systems, are more difficult to evaluate, and do not have protection from the H flu and S pneumonia vaccines [4]. For purposes of this discussion, children will be grouped into neonates less than 1 month of age, and older infants and children 1-36 months of age.

Traditionally, febrile infants younger than 1 to 3 months of age are often hospitalized. The cerebral spinal fluid is examined, the blood and urine are cultured for pathogens, and empiric antibiotics are given. In addition, a chest radiograph has been part of most protocols and practices [20]. Hospitalization for all febrile infants in the first several months of life has been shown to be an expensive management strategy and can incur significant iatrogenic complications. The infants in this category have somewhere between 3%-10% incidence of what would be designated as a SBI. Various clinical protocols have been published to assist clinicians in evaluating the child with FWS [3-6,8,11,17,21,22]. By determining the most effective and least invasive testing, these guidelines seek to identify the child with SBI who requires aggressive management, while allowing low-risk children to avoid unnecessary intervention [3,23,24]. In general these guidelines rely upon the degree and duration of fever, urinalysis, white blood cell (WBC) count, and lumbar puncture in younger patients. Physical examination findings such as respiratory distress, poor peripheral perfusion, and a "toxic" appearance are also important in deciding on further diagnostic testing and treatment. Some studies have also examined the utility of C-reactive protein and pulse oximetry oxygen saturation [8,17].

The only radiologic study discussed in studies of the acute evaluation of children with FWS is the chest radiograph. For infants and young children who have fever and chest symptoms, most investigators feel that chest radiographs are indicated and useful [3-6,25]. (However, one could argue that a child with signs of respiratory infection does not truly fit the definition of FWS.) The presence of rales is the single best clinical indicator of pneumonia in infants and children. Tachypnea, intercostals retractions,

and nasal flaring are also predictive findings for pneumonia in the pediatric population [8,26,27]. Other clinical factors that may be predictive of pneumonia in children of all ages, such as degree of fever, WBC count, and pulse oximetry, have been studied [6,27-30].

Baraff [31] recommends that in patients 3-36 months of age with fever, chest radiographs be obtained only when there are clinical manifestations of chest disease or when the patient appears toxic. Baraff et al [32] reported a 3.3% incidence of positive chest radiographs based on collected reviews of infants and children from birth to 36 months of age with fever and no respiratory symptoms or signs. McCarthy [33], summarizing a number of clinical series dealing with acute episodes of fever in infants, also believes that chest radiographs should be obtained only when there are clinical indications. A later study by Baraff [3] summarizing the work of other authors [26,29,34] reports that occult pneumonia is seen in only 3% of infants without respiratory findings on physical exam.

Bramson et al [35] combined data of three investigations and subjected them to a statistical meta-analysis by using methods described in recent medical literature [36,37]. The larger number of patients in the combined study allowed more valid conclusions concerning the accepted practice of performing chest radiographs in febrile infants as part of the sepsis workup. These three series had 671 infants. In 361 infants with no clinical evidence of pulmonary disease on history and physical examination, all had normal chest radiographs. A finding of only hyperinflation on a chest radiograph was interpreted as normal because it was felt that the infants would likely have a viral illness or reactive airway disease and would not usually be receiving antibiotics, unlike older children and adults [38]. Bramson et al [35] indicated that a chest radiograph in a patient with no pulmonary symptoms or signs would be positive <1.2% of the time. In the current era of S pneumoniae vaccine use, this rate might fall even further. In the same series, nearly one-third of 256 infants with clinical manifestations of pulmonary disease had a positive chest radiograph; therefore, in symptomatic, febrile infants, a chest radiograph can help identify significant pulmonary disease and should be obtained.

Patterson et al [39] retrospectively studied 105 infants who had fever. Of the 37 patients who had no respiratory symptoms or signs, there was one chest radiograph that showed a focal parenchymal infiltrate. Hyperinflation and peribronchial thickening were not classified as abnormal. In a prospective study the same authors included 121 infants who were free of signs of lower respiratory tract symptoms and signs but who had fever. None had chest radiographs that showed an abnormality. These data suggest that obtaining chest radiographs to look for parenchymal infiltrates treatable by antibiotics for infants less than 2 years old is necessary only in those who have

clinical evidence of lower respiratory illness. Heulitt et al [37] concluded that in febrile infants younger than 3 months of age, a chest radiograph should be obtained only when signs of respiratory disease are present. In this series the incidence of pneumonia in infants without respiratory manifestations was 6%, and all those infants did well, having only mild infiltrates on their chest radiographs.

In a recent study by Mahabee-Gittens et al [27] 510 children 2-59 months of age presenting with symptoms of lower respiratory infection had chest radiographs, with 8.6% showing pneumonia. Clinical variables found to correlate with positive radiographic findings included age >12 months, respiratory rate >50, oxygen saturation $\leq 96\%$, and nasal flaring in children <12 months of age. Combinations of these clinical variables produced likelihood ratios of radiographic pneumonia from 3.6 to 11.0.

In spite of the often low diagnostic yield, most authors suggest that in young infants, particularly neonates less than 1 month of age, a chest radiograph should be obtained. These infants are relatively immunocompromised compared with older infants and children, and the consequences of a missed SBI or occult infection are felt to be greater [4]. A chest radiograph in a septic appearing neonate with FWS may disclose an occult thoracic source of the fever [4-6,40]. In addition, a chest radiograph will help exclude congenital or acquired cardiac disease in a child who is febrile and ill.

There are data, however, indicating that in certain circumstances chest radiography may be warranted even in the absence of clinical respiratory symptoms. Bachur et al [30] found that 26% of children with fever $\geq 39^\circ$ centigrade and a WBC count $\geq 20,000/\text{mm}^3$ had pneumonia on chest radiographs. The use of polyvalent S pneumoniae vaccine has been shown to reduce pneumonia with radiographic consolidation by 73% [41]. This led Baraff [3] to suggest that a chest radiograph should be obtained in patients with high fever and elevated WBC count who have not received the pneumococcal vaccine, regardless of respiratory findings. The American College of Emergency Physicians states that a chest radiograph should be considered in patients older than 3 months of age with fever $\geq 39^\circ$ centigrade and a WBC count $\geq 20,000/\text{mm}^3$ [42]. Similar recommendations have been made by the British Thoracic Society for children less than 5 years of age [43]. Other authors have included this scenario in their recommendations, although the evidence that this is based on is generally not listed [3-6]. Brook [6] also recommends obtaining a chest radiograph in all patients under 36 months of age with an oxygen saturation of <95%, although there is no supporting evidence given, nor are there data as to the diagnostic yield of such radiographs.

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Fever of Unknown Origin

Occult infection is the usual cause of FUO in adults and children, and is less commonly due to neoplasia or other inflammatory conditions [10,14,44,45]. Some children never have a specific diagnosis reached [14,46]. While many studies describe the clinical course of such patients, few of them examine the utility of diagnostic imaging modalities in these difficult patients. Most patients undergo chest radiography; while the results of those studies are rarely discussed, presumably they were normal or the patients in these studies would not still carry the diagnosis of FUO. Cifti et al [13] reported that chest radiography was positive in 15 of 89 pediatric patients. The clinical evaluation relies on careful physical examination and laboratory and serologic testing [10,13,14,47]. Advanced imaging plays a relatively minor role and has been shown to have mixed utility. How often noninvasive testing has provided a diagnosis in FUO cases is difficult to determine, but in adults it has been reported to help in perhaps one quarter [16].

Steele et al [48] evaluated 109 children with FUO, many of whom had advanced imaging performed. The positive rates of various imaging tests were: ultrasound (US) eight of 43 patients, abdominal computed tomography (CT) three of 14, Indium scan five of 11, and gallium scan one of four. They conclude that in children with FUO without localizing signs or symptoms, special imaging studies rarely lead to a diagnosis. Lopez Rodriguez et al [49] reported better results in a study of 24 adult patients, finding that thoracoabdominal CT contributed useful information in 10 of 24 cases; US provided help in only two of 24.

Habib et al [50] evaluated 102 adult patients with FUO who underwent, gallium 67 planar and single photon emission computed tomography (SPECT) scanning and found that in only two patients did the study contribute significant diagnostic information. Buonomo and Treves [46] evaluated 30 children with gallium scanning. In children with generalized fever and no localizing features the positive rate was only one of 25. In those children with localized complaints, the gallium scan showed an occult source of infection in three of five that had been missed by other imaging methods.

In a study of 31 adult patients, indium-111 granulocyte scintigraphy showed a sensitivity of 75% and a specificity of 83%, but had a high negative predictive value of 90% [51]. This same group subsequently showed that indium-111 granulocyte scintigraphy performed better than 2-[18]-fluoro-2-deoxy-D-glucose (FDG) imaging, with the latter hampered by a much greater rate of false positive results [52]. Sturm et al [53] studied 11 children with biliary cirrhosis and FUO with FDG-PET prior to liver transplantation and evaluated imaging findings with histopathology from the explanted livers; there were five

true positive and six true negative results indicating clinical usefulness in the this small select group of patients.

The combination of CT with scintigraphy improves the diagnostic performance of scintigraphic techniques. Dumarey et al [54] evaluated 21 adult patients with FDG-PET/CT. The accuracy of diagnosis varied depending on the interpretation algorithm used, but an examination without an observable lesion had essentially a 100% negative predictive value for bacterial infection. In the subset of nine patients with true FUO, all had a positive diagnosis after FDG-PET/CT imaging. Bar-Shalom et al [55] evaluated 47 adult patients, 13 of whom had FUO, examining the impact of SPECT/CT imaging to planar images obtained from gallium and indium WBC imaging, and found improved detection and localization in 36% of gallium scans and 63% of indium WBC scans.

The Neutropenic Child

A child with cancer or immunodeficiency who is neutropenic and febrile causes great concern. Such children are more susceptible to the common infections facing all children, but are also at risk for viral, invasive fungal and other atypical infections. Because of the heightened clinical concern, a chest radiograph is usually obtained in addition to other assessments, including cultures of the blood and urine. The practice of routinely including a chest radiograph has been challenged in a study by Korones et al [56] who evaluated 54 children with cancer who were hospitalized for hundreds of episodes of fever and neutropenia. They found an incidence of radiographic pneumonia of only 3%-6%. The children without respiratory findings had no evidence of pneumonia on chest radiographs, and children who did not have chest radiographs showed no significant outcome differences from those who did.

These children often undergo advanced imaging, but there is little evidence-based data about which studies are most efficacious. Archibald et al [57] evaluated the performance of CT in 83 neutropenic cancer patients who had 109 instances of fever lasting 4 days or more. Rates of positive CT findings varied by body region: head and neck 8%, sinus 41%, chest 49%, abdomen 19%. Findings on sinus and chest CT led to changes in therapy in 24% and 30% of cases, respectively. However, they added that "CT was rarely abnormal in the absence of localizing signs or symptoms," and that in the absence of symptoms CT findings rarely lead to therapeutic changes.

A specific exception to this may be children who have undergone bone marrow transplantation (BMT). Children frequently have fevers after BMT, and a specific source is often lacking. In 1991, Barloon et al [58] in a study of 33 adult BMT patients reported that CT found clinically significant disease that was unsuspected by chest radiographs and that CT positively impacted patient

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management. A more recent study of 188 chest CT studies in 112 adult BMT patients with fever but normal chest radiographs [59] showed CT findings suggestive of pneumonia in 60%. While many of these patients eventually had radiographic or laboratory confirmation of infection, those patients identified with CT were able to start empiric therapy an average of 5 days earlier. While Heusell et al [59] did not prove a benefit in survival, earlier institution of appropriate therapy is felt to be clearly beneficial. Also important was the finding that BMT patients with normal chest CT scans were very unlikely to have an occult infection (negative predictive value of 97%), and that a normal chest radiograph did not exclude the possibility of chest infection in BMT patients.

Summary

The incidence of SBI is low but does require prompt evaluations in infants and children with FWS. Clinical pathways provide guidelines for the physician but are not a substitute for overall clinical judgment in the decision about which febrile infants and children would benefit from chest radiographs. Most data support the opinion that chest radiographs in the previously healthy child with FWS should be obtained only when there is clinical evidence of a respiratory illness. There are also good data to support obtaining chest radiographs in those with fever $\geq 39^{\circ}$ centigrade, WBC count $\geq 20,000$ mm³, and oxygen saturation $\leq 95\%$. While there are little supporting data, most guidelines suggest that chest radiography be considered in neonates less than 1 month of age with FWS. In the acute setting, there is no evidence to support additional radiologic testing in the child with FWS.

The evaluation of a child with FUO still primarily relies on the physical examination and laboratory testing. Studies have shown value in cross-sectional imaging and scintigraphic studies in those patients with localizing signs or symptoms. As with children with FWS, advanced imaging in children with nonlocalizing FUO has a low yield. Data supporting additional imaging are largely lacking, which is not to say that such imaging is inappropriate, but rather that it lacks good documentation of its value is lacking.

Although the neutropenic febrile child arouses heightened concern for occult disease and SBI, what little evidence is available suggests that the same parameters guiding evaluation of FWS and FUO apply: imaging without localizing signs or symptoms is unlikely to alter the therapeutic course. A possible exception to this generalization is in children who have had BMT and in whom chest CT may disclose unsuspected infectious disease.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because

there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document.

Relative Radiation Level Designations	
Relative Radiation Level*	Effective Dose Estimate Range
None	0
Minimal	< 0.1 mSv
Low	0.1-1 mSv
Medium	1-10 mSv
High	10-100 mSv

*RRL assignments are not included for some examinations. The RRL assignments for the NS (not specified) exams cannot be made because the RRL depends on the region of the body exposed to ionizing radiation, and the body part will vary as a function of the clinical situation.

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