American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: **Fever without Source — Child**

Variant 1: **Infant or child age 1 month to 36 months with no respiratory signs or symptoms.**

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	2		☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 2: **Infant or child age 1 to 36 months with respiratory signs or symptoms, or fever ≥39° centigrade and WBC count ≥20,000/mm^3.**

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	9		☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

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

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	6	Little supporting data, but neonates are at relatively greater risk for SBI and occult infection.	☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually 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	6	Little supporting data, but this is a 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.	☢
FDG-PET/CT skull base to mid thigh	2	Mixed data, but in the child with persistent fever and a negative thorough workup it might provide useful information.	☢ ☢ ☢ ☢ ☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Clinical Condition: **Fever without Source — Child**

Variant 5: **Child with fever and neutropenia.**

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	6	Little supporting data, but this is a simple and low-radiation examination to exclude significant parenchymal consolidation and adenopathy.	☢
CT sinuses chest abdomen with contrast	6	Evaluation of the chest and sinuses has a greater yield for detecting occult infection than does evaluation of the abdomen. Low yield in the absence of localizing findings on physical examination. However, in bone marrow transplant patients and others at particular risk for bacterial and fungal infection, CT of the chest has been shown to provide clinically useful information even in the absence of respiratory symptoms. Further, in patients who do not respond to broad-spectrum antibiotics and remain neutropenic, CT of the chest and abdomen is useful to evaluate for disseminated fungal infection.	☢☢☢☢
CT sinuses chest abdomen without contrast	3	Only if there is a strong contraindication to the administration of contrast media.	☢☢☢☢
CT sinuses chest abdomen without and with contrast	2	Additional information gained does not justify additional radiation exposure.	☢☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

FEVER WITHOUT SOURCE — CHILD

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Summary of Literature Review

Introduction/Background

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 [1,2]. 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 [2-8]. Most FWS is caused by infections [2-4,7-9]. While this is mostly 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 [10,11]. 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* (*H. flu*) and *Streptococcus pneumoniae* (*S. pneumonia*), the incidence of SBI has dropped significantly [2,3,7,12,13]. However, the need to identify those FWS patients with potential SBI remains [2,4,8,14-19].

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 3 weeks or more without an apparent etiology [20], although some recent authors have liberalized the definition of FUO to fevers lasting more than 1 week and undiagnosed despite outpatient evaluation [4,21-23]. The majority of children with FUO have infectious causes, although inflammatory, neoplastic, and autoimmune conditions are also in the differential [4,21,22,24-26]. The distinction between FWS and FUO is more than just academic, as the clinical and imaging approaches to these conditions may differ.

Fever without Source

The cause of fever in the pediatric patient can often be determined from the history, physical examination, and laboratory tests [4,6-8,27,28]. Prior medical conditions, medications, foreign travel, and immunization history are all important in directing subsequent investigations [2,3,12,13,29,30]. Twenty percent of cases, however, will have no apparent source and thus are defined as having FWS [6]. The approach to a febrile child is generally divided into the infant younger than 3 months and the older infant and child between 3-36 months of age [6,7,28]. Many authors place infants younger than 1 month 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 the protection afforded by the *H. flu* and *S. pneumonia* vaccines [2,4,7]. For purposes of this discussion regarding the contribution of imaging in the evaluation of these patients, children will be grouped into neonates younger than 1 month, and older infants and children 1-36 months of age.

Traditionally, febrile infants younger than 1 to 3 months of age are often hospitalized with the goal to prevent any SBI that might not be immediately apparent but could prove clinically devastating if there were diagnostic or treatment delay. While there is adherence to guidelines varies, in general the cerebral spinal fluid is examined (especially in neonates younger than 1 month of age), 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 [2,4,8,31,32]. Hospitalization for all febrile infants in the first several months of life has been shown to be an expensive

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management strategy and can incur significant iatrogenic complications. Infants in this category traditionally 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 [6-9,14,22,28,33,34]. 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 [6,35,36]. In general these guidelines rely upon the degree and duration of fever, urinalysis, white blood cell (WBC) count, and lumbar puncture in younger patients.

Some studies have also examined the utility of C-reactive protein (CRP) and pulse oximetry oxygen saturation [14,28], and more recent studies have included evaluation of procalcitonin and rapid viral testing. Procalcitonin is a biomarker of bacterial and fungal infection, and rises within 6 to 24 hours after the onset of fever, much sooner than CRP increases [17]. Although its exact role in routine use is not fully established, distinguishing between children who have a potential SBI and those with a less concerning febrile illness could prove important [11]. Similarly, rapid viral testing is being used to separate those children with fevers caused by simple viral infections from those with potentially more SBI [10,15,18]. At least one paper has reported a significantly lower risk of SBI in patients with documented bronchiolitis [16]. The goal of all of these investigations is to decrease the amount of additional ancillary testing (including usually low-yield imaging studies) and unnecessary prophylactic antibiotic administration without missing any cases of occult SBI. 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.

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 [2,6-9,19,25,32,37]. (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, intercostal retractions, and nasal flaring are also predictive of pneumonia in the pediatric population [14,38,39]. Other traditional clinical factors that may be predictive of pneumonia in children of all ages, such as degree of fever, WBC, and pulse oximetry have been studied [9,39-42], as well as newer biomarkers such as CRP, procalcitonin, and rapid viral testing as discussed above.

Baraff [2,43] 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 [44] 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 [45], 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 [6] summarizing the work of other authors [38,41,46] reports that occult pneumonia is seen in only 3% of infants without respiratory findings on physical examination. Given that the risk of SBI in febrile infants and children has dropped in the era of pneumococcal vaccination, and that most FWS cases will be related to urinary tract or viral infections, some authors recommend obtaining urinalysis first and considering chest imaging only if this is negative [2,4,15].

Bramson et al [47] combined data of three investigations and subjected them to a statistical meta-analysis by using methods described in recent medical literature [48,49]. 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 [50]. Bramson et al [47] 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* and *H. influenza* 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. Similarly, another recent article by Baraff suggests that even in infants younger than 3 months, chest radiographs are probably only warranted when there is a high fever or the presence of respiratory symptoms [2].

Patterson et al [51] retrospectively studied 105 infants who had fever. Of the 37 patients who had no respiratory symptoms or signs, only one had chest radiograph showing a focal parenchymal airspace disease. 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 airspace diseases treatable by antibiotics for infants younger than age 2 is necessary only in those who have clinical evidence of lower respiratory illness. Heulitt et al [49] 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 airspace diseases evident on their chest radiographs.

In a recent study by Mahabee-Gittens et al [39] of 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 ≤96%, and nasal flaring in children younger than 12 months. 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 younger than 1 month, 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 [7]. A chest radiograph in a septic-appearing neonate with FWS may disclose an occult thoracic source of the fever [7-9,52]. 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 [42] found that 26% of children with fever ≥39° centigrade and a WBC count ≥20,000/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% [53]. This led Baraff [6] 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 with fever ≥39° centigrade and a WBC count ≥20,000/mm^3 [54]. Similar recommendations have been made by the British Thoracic Society for children younger than 5 years [55]. Other authors have included this scenario in their recommendations, although their evidence is generally not listed [6-9]. Rutman et al [3] reported that since the institution of pneumococcal vaccination, the incidence of radiographically evident pneumonia has dropped by 20% to 39%. In their study of children younger than 5 years with fever >39° centigrade, WBC >20,000, and respiratory symptoms, pneumonia was present in 18% of 355 children, making chest radiography a reasonable study under those circumstances. Brook [9] also recommends obtaining a chest radiograph in all patients younger than 36 months with an oxygen saturation <95%, although there is no supporting evidence given, nor are there data as to the diagnostic yield of such radiographs.

Fever of Unknown Origin

Occult infection is the usual cause of FUO in adults and children, and is less commonly due to rheumatologic, autoimmune, neoplastic, or other inflammatory conditions [4,21,25,56,57]. Some children never have a specific diagnosis reached [4,25,58]. 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 at some point in their evaluation; 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 [24] 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, the exact nature of which depends upon local disease prevalence [4,21,24,25,59]. Advanced imaging plays a relatively minor role [4] especially early in the evaluation of FUO, 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 [27].

Steele et al [60] 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 concluded that in children with FUO without localizing signs or symptoms, special imaging studies rarely lead to a diagnosis. Lopez Rodriguez et al [61] 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 [62] 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 [58] 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% [63]. This same group subsequently showed that indium-111 granulocyte scintigraphy performed better than positron emission tomography with the tracer 2-[18]-fluoro-2-deoxy-D-glucose (FDG-PET) imaging, with the latter hampered by a much greater rate of false positive results [64]. However, Sturm et al [65] studied 11 children with biliary cirrhosis and FUO with FDG-PET prior to liver transplantation and imaging findings with histopathology from the explanted livers; there were five true positive and six true negative results, indicating that FDG-PET was clinical useful in the this small select group of patients.

The combination of CT with scintigraphy improves the diagnostic performance of scintigraphic techniques. Dumarey et al [66] evaluated 21 adult patients with FDG-PET. 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. The importance of a reliable negative result was recently addressed by Simons et al [67]. In their study of 28 adults and 5 children FDG-PET had a negative predictive value of 79% and an overall accuracy of 91%. In the subset of nine patients with true FUO, all had a positive diagnosis after FDG-PET imaging. Bar-Shalom et al [68] evaluated 47 adult patients, 13 of whom had FUO, comparing the results of SPECT with low-dose correlative CT imaging with those of planar images obtained from gallium and indium WBC imaging. They found improved detection and localization in 36% of gallium scans and 63% of indium WBC scans. Ferda et al [69] recently reported that carefully performed whole-body FDG-PET with CT with contrast provided clarifying diagnostic information in 92% of mostly adult patients. Sheng et al [70] in a study of 48 adults found that FDG-PET/CT found positive results in 12 of 15 patients eventually proven to have infectious disease, and all 12 patients with malignancy. The negative overall negative predictive value was only 50%, but the positive predictive value was 80%. In a meta-analysis of FDG-PET and FDG-PET/CT performed by Dong et al [71] nine studies involving 388 patients met inclusion criteria. In the eventual detection of a source for FUO, The pooled sensitivity and specificity of FDG-PET were 83% and 58%, respectively, and for FDG-PET/CT were 98% and 86%, respectively. Although FDG-PET/CT performed better than FDG-PET alone, this difference was not statistically significant.

In a study of 69 children with FUO, Jasper et al [72] reported that a final diagnosis was reached in only 54% of cases, consistent with reported literature rates of 33% to 88%. In all cases in their study, FDG-PET alone or FDG-PET with low-dose CT scan correlation was considered helpful in 43%, with FDG-PET with CT helpful in 53%, and FDG-PET alone in 40%. Among those children in whom a diagnosis was eventually reached, FDG-PET with CT was considered helpful in 77% [72].

The Neutropenic Child

A child with cancer or immunodeficiency who is neutropenic and febrile causes great concern. In neutropenic patients a significant fever is usually defined as a single oral temperature of ≥38.3° centigrade or two measurements of ≥38.0° centigrade at least 1 hour apart [73]. Neutropenia is an absolute neutrophil count (ANC) of <500, or <1,000 with the expectation of rapid decrease [73]. Such children are more susceptible to the common infections facing all children; gram-positive organisms are responsible for 70% of SBI in these patients, but gram-negative organisms are responsible for most SBI related fatalities [73]. These patients are also at risk for viral and other atypical infections, and invasive fungal infections are a particular concern for high-risk patients with persistent febrile neutropenia [73]. 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 [74] 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. However, given the complexity and medical fragility of these patients, even with the low yield of chest radiography in the absence of symptoms, chest radiography may provide reassurance to the treating physician and provide a baseline for the future [73,75].

These children often undergo advanced imaging, but there is little evidence-based data about which studies are most efficacious. Archibald et al [76] 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. In their 2002 guidelines (not pediatric specific), the Infectious Diseases Society of America noted that one-half of febrile neutropenic patients with normal chest radiographs will have evidence of pneumonia on chest CT [77].

A specific exception to this finding may be children who have undergone bone marrow transplantation (BMT) or who have acute myelogenous leukemia [73]. Children frequently have fevers after BMT, and a specific source is often lacking. In 1991, Barloon et al [78] in a study of 33 adult BMT patients reported that CT found clinically significant disease that was unsuspected by chest radiographs and that CT findings improved patient management. A more recent study of 188 chest CT studies in 112 adult BMT patients with fever but normal chest radiographs [79] 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 [79] 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

- Infants and children with FWS should have prompt evaluations, even though the incidence of SBI is low. 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 that in the previously healthy child with FWS, a chest radiograph should be obtained when there is clinical evidence of a respiratory illness, and for those with fever ≥39° centigrade, WBC count ≥20,000 mm^3, and oxygen saturation ≤95%.
- Neonates younger than 1 month with FWS are a high-risk group, and chest radiography should be considered, regardless of respiratory symptoms.
- Imaging studies in children with nonlocalizing FUO have a low yield.
- There are promising data on the use of FDG-PET or FDG-PET/CT in evaluating adults with FUO, but the data regarding their use in pediatric patients are more limited.
- In children with neutropenia and persistent fever despite the administration of antibiotics, CT with contrast of the chest and abdomen should be considered to evaluate for disseminated fungal 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. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults (see Table below). 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*	**Adult Effective Dose Estimate Range**	**Pediatric Effective Dose Estimate Range**
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢ ☢	0.1-1 mSv	0.03-0.3 mSv
☢ ☢ ☢	1-10 mSv	0.3-3 mSv
☢ ☢ ☢ ☢	10-30 mSv	3-10 mSv
☢ ☢ ☢ ☢ ☢	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies".		

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Procedure Information
- Evidence Table

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