

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Chinnock R, Butto J, Fernando N. Hot tots: current approach to the young febrile infant. <i>Compr Ther</i> 1995; 21(3):109-114.	Review/Other	N/A	Describe clinical and laboratory process to help clinicians identify young febrile infants who can be treated as outpatients.	Careful clinical examination with screening laboratory data will result in excellent results.	4
2. Baraff LJ. Management of infants and young children with fever without source. <i>Pediatr Ann</i> 2008; 37(10):673-679.	Review/Other	N/A	Review management of infants and children with FWS. There is considerable variation in the clinical management of infants and children.	Guidelines are provided for management of FWS includes: All febrile neonates (>38.0 degrees C) should have a “full sepsis evaluation”, including lumbar puncture, and be admitted for parenteral antibiotic therapy. Nontoxic appearing infants 29-90 days of age with FWS >38.0 degrees C can be managed using low-risk laboratory and clinical criteria. Nontoxic appearing infants >90 days of age who have received Hib and PCV-7 vaccines are at low risk for OB and meningitis. Therefore, the only laboratory tests necessary in this age group with FWS >39.0 degrees C are a urinalysis and urine culture for circumcised males <6 months of age and uncircumcised males and females <24 months of age.	4
3. Rutman MS, Bachur R, Harper MB. Radiographic pneumonia in young, highly febrile children with leukocytosis before and after universal conjugate pneumococcal vaccination. <i>Pediatr Emerg Care</i> 2009; 25(1):1-7.	Observational	Patients (WBC ≥20,000/μl) 889 pre-PVC, 335 post-PVC Patients (WBC ≥25,000/μl) 376 pre-PVC, 149 post-PVC	Retrospective cohort study to evaluate the impact of universal vaccination with Prevnar (PCV) on the incidence and characteristics of occult and nonoccult radiographic pneumonia among highly febrile children with leukocytosis and no other identified source of infection.	Before universal pneumococcal vaccination, radiographic pneumonia was found in 190 (21%) of 889 (95% CI, 19-24) eligible children compared with 61 (18%) of 335 (95% CI, 14-23) eligible children after universal vaccination (P=0.27). Occult pneumonia was identified in 61 (15%) of 404 (95% CI, 12-19) pre-PCV compared with 13 (9%) of 147 (95% CI, 5-15) post-PCV (P=0.07). In children younger than 2 years, radiographic pneumonia was identified in 121 (17%) of 709 (95% CI, 14-20) pre-PCV and 26 (10%) of 254 (95% CI, 7-15) post-PCV (P=0.01). Clinicians should continue to consider chest radiography in young highly febrile children with leukocytosis and no other identified source of infection.	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
4. Tolan RW, Jr. Fever of unknown origin: a diagnostic approach to this vexing problem. <i>Clin Pediatr (Phila)</i> 2010; 49(3):207-213.	Review/Other	N/A	Review management of FUO.	Evaluation should be guided by the severity of the disease. It is useful to recognize that uncommon manifestations of common diseases are more likely than are rare diseases. Furthermore, clues to the diagnosis are frequently present in the history and physical examination but are not elicited or unappreciated (perhaps due to time constraints). Therefore, thoroughness and repetition are vitally important.	4
5. Gartner JC, Jr. Fever of unknown origin. <i>Adv Pediatr Infect Dis</i> 1992; 7:1-24.	Review/Other	N/A	To review diagnosis of FUO in pediatric patients.	Best current approaches for diagnosis of FUO are the use of older and well-established methods (history and physical examination) and the addition of newer techniques (US, CT, MRI, etc.)	4
6. Baraff LJ. Management of fever without source in infants and children. <i>Ann Emerg Med</i> 2000; 36(6):602-614.	Review/Other	N/A	To describe presenting conditions and management of children who have FWS.	20% of febrile children have FWS after history and physical examination. Of these, a small proportion may have an occult bacterial infection. Infants younger than 3 months are often managed by using low-risk criteria, such as the Rochester Criteria or Philadelphia Criteria.	4
7. Ishimine P. Fever without source in children 0 to 36 months of age. <i>Pediatr Clin North Am</i> 2006; 53(2):167-194.	Review/Other	N/A	To review the evaluation and treatment of febrile neonates (0-28 days old), young infants (1-3 months old), and older infants and toddlers (3-36 months old) in the heptavalent PCV-7 era.	There is no combination of clinical assessment and diagnostic testing that will successfully identify all patients with serious infection at the time of initial presentation. Timely reassessment is very important in this regard.	4
8. Massin MM, Montesanti J, Lepage P. Management of fever without source in young children presenting to an emergency room. <i>Acta Paediatr</i> 2006; 95(11):1446-1450.	Review/Other	376 patients	To analyze the management approach in a pediatric emergency room, and to correlate it to existing practice guidelines by reviewing all cases of FUO among patients seen in the emergency department.	Significant differences exist in the management of the young febrile child between the practices' patterns and guidelines, without influence on patient outcome.	4
9. Brook I. Unexplained fever in young children: how to manage severe bacterial infection. <i>BMJ</i> 2003; 327(7423):1094-1097.	Review/Other	N/A	To review bacterial causes, essential diagnostic tests, clinical assessment, judicious use of antibiotics, and follow up in unexplained, difficult to diagnose bacterial infection causing fever in children.	Febrile children <3 years of age without a clear source of infection have a small but important risk of sepsis and meningitis. Although risk has been reduced in countries that have vaccination programs, vigilance and thorough evaluation of each febrile child followed by proper antimicrobial treatment are indicated when appropriate.	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
10. Lacour AG, Zamora SA, Gervaix A. A score identifying serious bacterial infections in children with fever without source. <i>Pediatr Infect Dis J</i> 2008; 27(7):654-656.	Observational	202 children 54 had SBI	To develop a clinical tool to identify SBI in children with FWS. For each child, a clinical assessment, a WBC count, a urine analysis, a determination of C-reactive protein, procalcitonin, and appropriate cultures were performed.	In multivariate analysis, only procalcitonin (OR: 37.6), C-reactive protein (OR: 7.8), and urine dipstick (OR: 23.2) remained significantly associated with SBI. Sensitivity of the score for the identification of SBI was 94% and the specificity 81%. In the validation set the sensitivity of the score was 94% and the specificity 78%.	3
11. Semeraro M, Thomee C, Rolland E, et al. A predictor of unfavourable outcome in neutropenic paediatric patients presenting with fever of unknown origin. <i>Pediatr Blood Cancer</i> 2010; 54(2):284-290.	Observational	72 episodes of febrile neutropenia	Prospective study to determine whether procalcitonin is useful in predicting the outcome of FUO. The following variables were assessed: age 0.5-22 years; solid tumor diagnosis; chemotherapy-related grade-4 febrile neutropenia.	Procalcitonin values were significantly higher in episodes of unfavorable outcome (P<0.001). None of the other prediction candidates appeared to be significantly linked to the risk of unfavorable outcome. In the validation set, the best PCT cut-off was 0.12 micro/L, which was associated with a sensitivity of 80% and specificity of 64%. Procalcitonin-H0 level can predict FUO outcome. A protocol based on procalcitonin-H0 measurement, integrating clinical and bacteriological evaluation, facilitates shorter hospital stays and less antibiotic treatment. Patients with a PCT-H0 value <0.12 micro/L could benefit from an outpatient treatment starting at H48 thus reducing hospitalization costs and improving quality of life.	3
12. Gabriel ME, Aiuto L, Kohn N, Barone SR. Management of febrile children in the conjugate pneumococcal vaccine era. <i>Clin Pediatr (Phila)</i> 2004; 43(1):75-82.	Review/Other	7,500 pediatricians and 7,500 emergency department physicians	Survey conducted to evaluate physician attitudes toward the management of young febrile children since the introduction of the conjugate PCV-7.	Both pediatricians and emergency department physicians would order fewer CBC counts and blood cultures and administer less empiric ceftriaxone if a child was vaccinated with PCV-7.	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
13. Mintegi S, Benito J, Sanchez J, Azkunaga B, Iturralde I, Garcia S. Predictors of occult bacteremia in young febrile children in the era of heptavalent pneumococcal conjugated vaccine. <i>Eur J Emerg Med</i> 2009; 16(4):199-205.	Observational	1,586 children	Retrospective study. To analyze the rate of OB in infants with high FWS related to pneumococcal vaccination status and to study the yield of the CBC count to identify children with OB in the era of PCV-7.	Blood culture was positive in 15 (0.9%; pneumococcus 10, 0.6%). 1,040 of 1,586 children showed <15,000 leukocytes/mm ³ (2 pneumococcal OB, 0.19%). Of the 546 children with more than 15,000 leukocytes/mm ³ , 8 had a pneumococcal OB (PPV=1.46%, NPV=99.8%). Of the 1,586 children, 1,177 (74.2%) showed absolute neutrophil count <10,000/mm ³ (3 pneumococcal OB, 0.25%). Of those 409 with more than 10,000 neutrophil/mm ³ , 7 had a pneumococcal OB (PPV=1.71%, NPV=99.7%). Among the 429 children with at least two doses of PCV-7, one (0.23%) had a pneumococcal OB (vs 9/1090 (0.82%) with no dose or one dose of PCV-7). In the era of PCV-7, rate of pneumococcal OB is related to the pneumococcal vaccination status. The yield of the CBC is lower than in the prevaccinal era. Decisions based on CBC must be reconsidered.	4
14. Bleeker SE, Derksen-Lubsen G, Grobbee DE, Donders AR, Moons KG, Moll HA. Validating and updating a prediction rule for serious bacterial infection in patients with fever without source. <i>Acta Paediatr</i> 2007; 96(1):100-104.	Observational	381 patients	Patients ages 1-36 months presenting with FWS were prospectively enrolled to test the externally validate of a previously developed (and recently updated) rule for predicting the presence of SBI in this population.	The generalizability of the rule appeared insufficient in the new patients (n=150). In the updated rule, independent predictors from history and examination were duration of fever, vomiting, ill clinical appearance, chest-wall retractions and poor peripheral circulation [ROC area (95%CI): 0.69 (0.63-0.75)]. It seems to have utility as a first-line screening tool but additional laboratory tests (serum WBC count and C-reactive protein, and in urinalysis ≥70 white bloods) are also needed.	3
15. Antonyrajah B, Mukundan D. Fever without apparent source on clinical examination. <i>Curr Opin Pediatr</i> 2008; 20(1):96-102.	Review/Other	N/A	Review heptavalent PCV-7 and rapid tests for identification of viruses in children with FWS.	The incidence of true bacteremia has decreased to 1% since the introduction of the PCV-7 vaccine. This implies the management guidelines for fever in the under-3-year-old population need to be reviewed. In addition, better markers are required to predict SBI in this population. Further research into the understanding of the host immune response is also needed.	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
16. Bilavsky E, Shouval DS, Yarden-Bilavsky H, Fisch N, Ashkenazi S, Amir J. A prospective study of the risk for serious bacterial infections in hospitalized febrile infants with or without bronchiolitis. <i>Pediatr Infect Dis J</i> 2008; 27(3):269-270.	Review/Other	312 infants without bronchiolitis 136 infants with bronchiolitis	To assess prospectively the frequency of concurrent SBI in febrile infants ≤ 3 months of age with or without bronchiolitis.	SBI was detected in 30/312 (9.6%) infants without bronchiolitis compared with 3/136 (2.2%) infants with bronchiolitis. The risk of SBI in febrile infants is significantly lower in the presence of bronchiolitis.	4
17. Bressan S, Andreola B, Cattelan F, Zangardi T, Perilongo G, Da Dalt L. Predicting severe bacterial infections in well-appearing febrile neonates: laboratory markers accuracy and duration of fever. <i>Pediatr Infect Dis J</i> 2010; 29(3):227-232.	Observational	99 patients SBI documented in 25 neonates	Observational study to assess the diagnostic accuracy of WBC count, absolute neutrophil count, and C-reactive protein in detecting SBI in well-appearing neonates with early onset FWS and in relation to fever duration.	Areas under ROC curves were 0.78 (95% CI, 0.69-0.86) for C-reactive protein, 0.77 (95% CI, 0.67-0.85) for absolute neutrophil count and 0.59 (95% CI, 0.49-0.69) for WBC. 62 patients presented normal laboratory markers on initial determination. Of these, 58 successfully underwent repeated blood examination at >12 hours from fever onset. Five of them had an SBI. The area under curve calculated for repeated laboratory tests showed better values, respectively of 0.99 (95% CI, 0.92-1) for C-reactive protein, 0.85 (95% CI, 0.73-0.93) for absolute neutrophil count and 0.79 (95% CI, 0.66-0.88) for WBC. In well-appearing neonates with early onset FWS, laboratory markers are more accurate and reliable predictors of SBI when performed after >12 hours of fever duration. Absolute neutrophil count and especially C-reactive protein resulted better markers than the traditionally recommended WBC.	3
18. Doan Q, Enarson P, Kissoon N, Klassen TP, Johnson DW. Rapid viral diagnosis for acute febrile respiratory illness in children in the Emergency Department. <i>Cochrane Database Syst Rev</i> 2009; (4):CD006452.	Review/Other	4 total trials 3 randomized control trials and 1 quasi-randomized control trial, with 759 children in rapid viral testing and 829 in control group	Meta-analysis was performed to determine the effect of rapid viral testing in the emergency department on the rate of precautionary testing, antibiotic use and emergency department length of visit.	Rapid viral testing did not reduce antibiotic use in the emergency department significantly, neither clinically or statistically. Lower rates of chest radiography (RR 0.77, 95% CI 0.65 to 0.91) in the rapid viral testing group but no effect on length of emergency department visits, blood or urine testing in the emergency department. Authors conclude that current evidence is insufficient, although promising, to support routine rapid viral testing as a means to reduce antibiotic use in pediatric emergency departments. Results suggest that rapid viral testing may be beneficial but are not statistically significant due to lack of power. A large trial addressing these outcome measures is needed.	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
19. Machado BM, Cardoso DM, de Paulis M, Escobar AM, Gilio AE. Fever without source: evaluation of a guideline. <i>J Pediatr (Rio J)</i> 2009; 85(5):426-432.	Review/Other	251 children	To evaluate the applicability of a standardized guideline for children up to 36 months of age with FWS. Prospective cohort study of children treated at the emergency department.	Toxemia was found in 20 children, and 195 were well-appearing (30 up to 3 months old and 165 from 3 to 36 months old). Among those children from 3 to 36 months without toxemia, 95 had axillary temperature >39 degrees C. In 107 (49.8%) children, there was spontaneous resolution of fever; in 88 (40.9%), benign self-limited disease was identified; and in 20 (9.3%), there was SBI. Among the cases of SBI, there were 16 urinary tract infections, 3 cases of pneumonia and one OB. Of the 215 children, 129 (60%) received no antibiotics, and 86 received antibiotics at some point (45 empirically). Empirical antibiotic treatment was maintained for an average of 72 hours. The guideline was shown to be appropriate to follow up these children using simple laboratory tests that can be carried out at most health facilities.	4
20. Petersdorf RG, Beeson PB. Fever of unexplained origin report on 100 cases. <i>Medicine (Baltimore)</i> 1961; 40:1-30.	Review/Other	100 cases	To analyze cases of FUO.	Most patients with FUO are not suffering from unusual diseases; instead they exhibit atypical manifestations of common illnesses. Some delay in diagnosis occurred because available information was not used properly.	4
21. Cogulu O, Koturoglu G, Kurugol Z, Ozkinay F, Vardar F, Ozkinay C. Evaluation of 80 children with prolonged fever. <i>Pediatr Int</i> 2003; 45(5):564-569.	Observational	80 patients	To determine the causes of prolonged fever, value of laboratory tests, and to establish guidelines for approach to fever in children.	The causes of fever, the value of laboratory tests, and clues to establishing the causes were given. The diagnosis was established in 87.5% with infection as the most common cause.	3
22. McCarthy P. Fever without apparent source on clinical examination. <i>Curr Opin Pediatr</i> 2005; 17(1):93-110.	Review/Other	N/A	Literature review that discusses recent literature that has focused on the epidemiology, clinical and laboratory evaluation and treatment of episodes of acute illnesses associated with fever and also of prolonged episodes of fever in children.	In the review period, there was a particular emphasis on invasive disease caused by <i>S. pneumoniae</i> and the impact of vaccination with PCV, on the occurrence of SBI in febrile infants with respiratory syncytial virus, and on the broad spectrum of diagnoses in children with prolonged fever in varying geographic locales.	4
23. McCarthy PL, Bachman DT, Shapiro ED, Baron MA. Fever without apparent source on clinical examination, lower respiratory infections in children, bacterial infections, and acute gastroenteritis and diarrhea of infancy and early childhood. <i>Curr Opin Pediatr</i> 1995; 7(1):107-125.	Review/Other	N/A	Evaluation of FWS in infants and children.	Overview of various causes of fever and their evaluation and treatment.	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
24. Ciftci E, Ince E, Dogru U. Pyrexia of unknown origin in children: a review of 102 patients from Turkey. <i>Ann Trop Paediatr</i> 2003; 23(4):259-263.	Review/Other	102 patients	Retrospective review of children presenting with FUO in order to describe the patterns of underlying conditions and diagnostic modalities.	Infections, collagen vascular disorders, malignancy and miscellaneous conditions constituted 44.2%, 6.8%, 11.7% and 24.5% of cases, respectively, while 12.8% of the cases remained undiagnosed. Biopsy, aspiration, serology, bacteriology, radiology and observation of the clinical course were the most useful diagnostic procedures.	4
25. Pasic S, Minic A, Djuric P, et al. Fever of unknown origin in 185 paediatric patients: a single-centre experience. <i>Acta Paediatr</i> 2006; 95(4):463-466.	Review/Other	185 patients	Prospective study to evaluate the causes and outcome in children with FUO.	The most important infectious causes of FUO in our study were Epstein-Barr virus and visceral leishmaniasis. Kawasaki disease represented a significant cause of FUO at the beginning of our study because it was not recognized by primary-care physicians. We report myelodysplastic syndrome as another emerging cause of pediatric FUO. Repeated clinical examination and careful use of specific laboratory examinations, invasive diagnostic procedures or imaging are crucial in approaching pediatric FUO.	4
26. Hofer M, Mahlaoui N, Prieur AM. A child with a systemic febrile illness - differential diagnosis and management. <i>Best Pract Res Clin Rheumatol</i> 2006; 20(4):627-640.	Review/Other	N/A	Text that reviews the differential diagnosis of prolonged or recurrent fever, and discusses most of the inflammatory syndromes presenting with fever.	Diagnosis is based on the clinical presentation as well as a widespread panel of investigations that are necessary in order to exclude the many potential causes of fever before reaching a definite diagnosis. In particular, the physician will look for infections and malignancies before considering the disease as inflammatory.	4
27. Arnow PM, Flaherty JP. Fever of unknown origin. <i>Lancet</i> 1997; 350(9077):575-580.	Review/Other	N/A	To review the subject of FUO. Majority of patients are adults.	Reviewed the subject and made recommendations for an approach to FUO, outcomes, and discussed selected diseases. Detailed list of causes of FUO. Minimum of diagnostic evaluation.	4
28. Kourtis AP, Sullivan DT, Sathian U. Practice guidelines for the management of febrile infants less than 90 days of age at the ambulatory network of a large pediatric health care system in the United States: summary of new evidence. <i>Clin Pediatr (Phila)</i> 2004; 43(1):11-16.	Review/Other	N/A	Guideline for the management of febrile infants <90 days of age at the ambulatory network of a large pediatric health care system.	N/A	4
29. Lohr JA, Hendley JO. Prolonged fever of unknown origin: a record of experiences with 54 childhood patients. <i>Clin Pediatr (Phila)</i> 1977; 16(9):768-773.	Review/Other	54 patients	To describe FUO and its diagnostic workup in children.	Showed the value of certain lab tests and history and physical exams. Clinical symptoms and signs directed the imaging.	4

* See Last Page for Key

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. McClung HJ. Prolonged fever of unknown origin in children. <i>Am J Dis Child</i> 1972; 124(4):544-550.	Review/Other	99 patients	To review the causes of fever of children admitted to hospital over a 10 year period. The records of every child were screened for evidence of fever.	Diseases were categorized into 8 groups. No pathologic diagnosis in 41 patients. Specific diagnoses were established in 58 children. A good history and physical and selectively simple blind tests was the key to the diagnosis in a vast majority of patients.	4
31. Jones RG, Bass JW. Febrile children with no focus of infection: a survey of their management by primary care physicians. <i>Pediatr Infect Dis J</i> 1993; 12(3):179-183.	Review/Other	1,600 physicians	Mailed survey to pediatricians, family practice physicians and emergency medicine physicians regarding management of children with high fever and no focus of infection at various ages: 3 weeks; 7 weeks; 4 months; and 16 months.	Hospitalization and empiric antibiotic treatment of very young infants (<2 months of age) with high fever and no focus of infection are preferred by most of the pediatricians, family practice physicians and emergency medicine physicians surveyed. Nearly one-half of these physicians would treat 4-month-olds and a fourth would treat 16-month-olds with high fever and no focus of infection with antibiotics as outpatients.	4
32. Goldman RD, Scolnik D, Chauvin-Kimoff L, et al. Practice variations in the treatment of febrile infants among pediatric emergency physicians. <i>Pediatrics</i> 2009; 124(2):439-445.	Observational	257 patients	Prospective, concurrent, cohort study of consecutive infants who presented to 6 pediatric emergency departments in Canada. Study objective is to characterize variations in treatment decisions and to document the extent of practice variations among pediatric emergency department practitioners.	Practices in the evaluation of young infants with fever in tertiary pediatric emergency departments varied substantially. Blood and urine tests were ordered in the majority of centers, but rates of cerebrospinal fluid testing and antibiotic treatment differed across centers.	3
33. Berger RM, Berger MY, van Steensel-Moll HA, Dzoljic-Danilovic G, Derksen-Lubsen G. A predictive model to estimate the risk of serious bacterial infections in febrile infants. <i>Eur J Pediatr</i> 1996; 155(6):468-473.	Observational	138 patients	Prospective study to determine predictors of severe bacterial infections in febrile infants.	The C-reactive pattern duration of fever, “standardized clinical impression score”, history of diarrhea and focal signs of infection were the most powerful predictors of SBI.	3
34. Bonadio WA, Hagen E, Rucka J, Shallow K, Stommel P, Smith D. Efficacy of a protocol to distinguish risk of serious bacterial infection in the outpatient evaluation of febrile young infants. <i>Clin Pediatr (Phila)</i> 1993; 32(7):401-404.	Observational	534 patients	Prospectively evaluate febrile infants 4-8 weeks for symptoms and evaluate the Milwaukee Protocol. Two groups were compared: 1) Infants with uncompromised presentation who met all Milwaukee Protocol criteria received ceftriaxone 50 mg/kg and were discharged, then re-evaluated within 24 hours. 2) Infants with compromised presentation who did not meet Milwaukee Protocol criteria were hospitalized for antibiotic therapy pending culture results.	The Milwaukee Protocol criteria had a sensitivity of 96% and a 99% NPV for distinguishing SBI outcome. The Milwaukee Protocol was useful in selecting infants who are at low-risk for SBI.	3
35. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. <i>N Engl J Med</i> 1993; 329(20):1437-1441.	Observational	747 patients	Prospective study on the efficacy of managing fever in young infants.	Most febrile 1-2-month-old infants with unremarkable exams can be treated as outpatients without antibiotics.	3

* See Last Page for Key

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Jaskiewicz JA, McCarthy CA, Richardson AC, et al. Febrile infants at low risk for serious bacterial infection--an appraisal of the Rochester criteria and implications for management. Febrile Infant Collaborative Study Group. <i>Pediatrics</i> 1994; 94(3):390-396.	Observational	1,057 patients	Prospective studies to test the hypothesis that infants unlikely to have SBI can be accurately identified by low risk criteria.	NPV of low risk criteria was 98.9% (95% CI, 97.2%-99.6%) for SBI, and 99.5% (95% CI, 98.2%-99.9%) for bacteremia. Low risk criteria are useful in helping to identify infants unlikely to have SBI.	3
37. Alario AJ, McCarthy PL, Markowitz R, Kornguth P, Rosenfield N, Leventhal JM. Usefulness of chest radiographs in children with acute lower respiratory tract disease. <i>J Pediatr</i> 1987; 111(2):187-193.	Observational	102 patients	To determine how chest radiographs change management in infants with respiratory signs or symptoms.	Of the 102 children evaluated, the chest radiograph resulted in a change of the pre-x-ray diagnosis in 21% and pre-x-ray management plans in 16%. When the pattern of decision making was consistent, with the initial diagnosis and the need for a chest radiograph remaining the same throughout all phases, the chest radiograph resulted in a change of pre-x-ray diagnosis in 5 (10%) of 48 patients, compared with a change in 16 (30%) of 54 when the pattern was inconsistent (P<0.02). Similarly, when the pattern was consistent, the pre-x-ray management was modified in only 3 (6%) of 48 patients vs 13 (24%) of 54 inconsistent cases (P<0.015).	3
38. Leventhal JM. Clinical predictors of pneumonia as a guide to ordering chest roentgenograms. <i>Clin Pediatr (Phila)</i> 1982; 21(12):730-734.	Review/Other	136 patients	Prospective study. Determine consideration of signs and symptoms to serve as index for obtaining chest radiographs.	Tachypnea was best predictor of pneumonia.	4
39. Mahabee-Gittens EM, Grupp-Phelan J, Brody AS, et al. Identifying children with pneumonia in the emergency department. <i>Clin Pediatr (Phila)</i> 2005; 44(5):427-435.	Observational	510 patients	Prospective cohort study of patients 2-59 months of age presenting with symptoms of lower respiratory tract infection in order to identify risk factors predicting pneumonia within that population.	The combination of age older than 12 months, respiratory rate 50 or greater, oxygen saturation 96% or less, and in children under age 12 months, nasal flaring, can be used in determining which young children with lower respiratory tract infection symptoms have radiographic pneumonia.	3
40. Losek JD, Kishaba RG, Berens RJ, Bonadio WA, Wells RG. Indications for chest roentgenogram in the febrile young infant. <i>Pediatr Emerg Care</i> 1989; 5(3):149-152.	Review/Other	209 patients	Combined retrospective and prospective analysis of infants to identify those factors which indicate that chest radiograph is needed.	Individual clinical factors were not found to be highly predictive of pneumonia. However, infants with these 9 factors did not have pneumonia — illness in the summer months; absence of cough, dyspnea, and respiratory distress (grunting/flaring/retracting); respiratory rate <60; absence of rales and decreased breath sounds; presence of normal color; and WBC count <19,000/mm ³ .	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. Zukin DD, Hoffman JR, Cleveland RH, Kushner DC, Herman TE. Correlation of pulmonary signs and symptoms with chest radiographs in the pediatric age group. <i>Ann Emerg Med</i> 1986; 15(7):792-796.	Observational	125 patients	Prospective study to determine whether findings on clinical examination are predictive of abnormalities seen on chest radiograph.	The clinical examination can help determine the need for chest radiographs.	3
42. Bachur R, Perry H, Harper MB. Occult pneumonias: empiric chest radiographs in febrile children with leukocytosis. <i>Ann Emerg Med</i> 1999; 33(2):166-173.	Observational	278 patients and 225 chest radiographs	Prospective cohort study at a large urban hospital was conducted to determine the incidence of radiographic findings of pneumonia in highly febrile children with leukocytosis and no clinical evidence of pneumonia or other major infectious source.	Pneumonia was found in 32/79 of those patients with findings suggestive of pneumonia and in 38/146 of those without clinical evidence of pneumonia. If patients who did not have a chest radiograph are assumed to not have pneumonia, the minimum estimate of occult pneumonia was 38/199 patients. Based on the relatively high incidence of occult pneumonias, chest radiograph should be considered a routine diagnostic test in children with a temperature of 39 degrees C or greater and WBC count of 20,000/mm ³ or greater without an alternative major source of infection.	3
43. Baraff LJ. Management of infants and children 3 to 36 months of age with fever without source. <i>Pediatr Ann</i> 1993; 22(8):497-498, 501-494.	Review/Other	N/A	To present evidence and guidelines for infants and children from birth to 36 months with FWS.	No guidelines can eliminate all risk nor confine antibiotic treatment only to children likely to have OB. The optimal management strategy reduces risk to a minimum at a reasonable cost and can be used in most practice settings.	4
44. Baraff LJ, Bass JW, Fleisher GR, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Agency for Health Care Policy and Research. <i>Ann Emerg Med</i> 1993; 22(7):1198-1210.	Review/Other	N/A	To develop evidence-based practice guidelines for management of infants up to 36 months with FWS.	All toxic-appearing infants and children and all febrile infants <28 days of age should be hospitalized for parenteral antibiotic therapy. Febrile infants 28 to 90 days of age defined at low-risk by specific clinical and laboratory criteria may be managed as outpatients if close follow-up is assured. Older children with fever <39.0 degrees C without source need no laboratory tests or antibiotics. Children 3 to 36 months of age with fever of 39.0 degrees C or more and whose WBC count is 15,000/mm ³ or more should have a blood culture and be treated with antibiotics pending culture results. Urine cultures should be obtained from all boys 6 months of age or less and all girls 2 years of age or less who are treated with antibiotics.	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
45. McCarthy PL. The pediatric clinical evaluation and pneumonia. <i>Curr Opin Pediatr</i> 1996; 8(5):427-429.	Review/Other	N/A	To review the value of clinical evaluation in identifying children with acute episodes of fever who have pneumonia.	Clinical evaluation generally suffices to diagnose pneumonia.	4
46. Singal BM, Hedges JR, Radack KL. Decision rules and clinical prediction of pneumonia: evaluation of low-yield criteria. <i>Ann Emerg Med</i> 1989; 18(1):13-20.	Observational	255 adults and 78 children	Community hospital emergency department population of adults and children were evaluated prospectively for the presence of predictive clinical parameters and the physician's estimate of pneumonia prior to obtaining a chest radiograph.	Authors were unable to develop useful low-yield criteria for identifying patients who did not need chest radiograph.	3
47. Bramson RT, Meyer TL, Silbiger ML, Blickman JG, Halpern E. The futility of the chest radiograph in the febrile infant without respiratory symptoms. <i>Pediatrics</i> 1993; 92(4):524-526.	Review/Other	617 patients	To determine efficiency of chest radiograph in febrile infants.	Chest radiographs as part of sepsis workup should be eliminated unless there are clinical indications of pulmonary disease.	4
48. Crain EF, Bulas D, Bijur PE, Goldman HS. Is a chest radiograph necessary in the evaluation of every febrile infant less than 8 weeks of age? <i>Pediatrics</i> 1991; 88(4):821-824.	Observational	242 patients	To examine the relationship between respiratory signs and likelihood of having an abnormal chest radiograph in febrile infants <8 weeks of age and extent of abnormal radiographs in absence of respiratory findings.	In the absence of respiratory signs, febrile infants are unlikely to have an abnormal chest radiograph.	1
49. Heulitt MJ, Ablow RC, Santos CC, O'Shea TM, Hilfer CL. Febrile infants less than 3 months old: value of chest radiography. <i>Radiology</i> 1988; 167(1):135-137.	Observational	192 patients	To evaluate the necessity of obtaining chest radiographs in febrile infant less than 3 months old.	When chest radiography was considered the gold standard for the presence or absence of pneumonia, findings of respiratory distress on physical examination had a sensitivity of 58% and a specificity of 93% for the detection of pneumonia.	4
50. Bramson RT, Griscom NT, Cleveland RH. Interpretation of chest radiographs in infants with cough and fever. <i>Radiology</i> 2005; 236(1):22-29.	Review/Other	N/A	To review the imaging findings in the chest in infants with cough and fever.	The appearance of the chest radiograph in infection differs between infants and older children.	4
51. Patterson RJ, Bisset GS, 3rd, Kirks DR, Vanness A. Chest radiographs in the evaluation of the febrile infant. <i>AJR</i> 1990; 155(4):833-835.	Observational	226: (105 retrospective 121 prospective)	To determine usefulness of chest radiographs in infants <24 months old with fever and no obvious cause.	Chest radiographs in infants <3 months of age are of value only in those with clinical evidence of respiratory tract illness.	3
52. Singer JI, Vest J, Prints A. Occult bacteremia and septicemia in the febrile child younger than two years. <i>Emerg Med Clin North Am</i> 1995; 13(2):381-416.	Review/Other	N/A	To review literature on assessment and the preferred treatment strategies for children without a focus of infection.	No results stated.	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. <i>Pediatr Infect Dis J</i> 2000; 19(3):187-195.	Experimental	37,868 patients randomly assigned 1:1 to receive either the PCV or meningococcal type C CRM197 conjugate	Randomized double blind trial to determine the efficacy, safety and immunogenicity of the heptavalent CRM197 PCV against invasive disease caused by vaccine serotypes and to determine the effectiveness of this vaccine against clinical episodes of otitis media.	Efficacy for otitis media against visits, episodes, frequent otitis and ventilatory tube placement was 8.9, 7.0, 9.3 and 20.1% with $P<0.04$ for all. In the analysis of spontaneously draining ears, serotype-specific effectiveness was 66.7%. The heptavalent PCV is highly effective in preventing invasive disease in young children and it has a significant impact on otitis media.	3
54. Clinical policy for children younger than three years presenting to the emergency department with fever. <i>Ann Emerg Med</i> 2003; 42(4):530-545.	Review/Other	N/A	Clinical policy for children <3 years with fever. Policy is a revision of the 1993 American College of Emergency Physicians pediatric fever policy.	N/A	4
55. British Thoracic Society Guidelines for the Management of Community Acquired Pneumonia in Childhood. <i>Thorax</i> 2002; 57 Suppl 1:i1-24.	Review/Other	N/A	Guidelines for the Management of Community Acquired Pneumonia in Childhood.	N/A	4
56. Abdulsalam AM, Al-Jahdali HH, Memish ZA, Ahmad AH. Fever of unknown origin. Experience of a large tertiary care hospital in Saudi Arabia. <i>Saudi Med J</i> 2005; 26(2):352-354.	Review/Other	20 patients	To review FUO cases to define the categories of the disease in patients and to determine the clinical presentation, methods of diagnosis, and disease outcome.	Causes of FUO were infections (35%), miscellaneous (25%), neoplasms (15%), collagen vascular diseases (10%), and no definitive diagnosis (15%).	4
57. Arce-Salinas CA, Morales-Velazquez JL, Villasenor-Ovies P, Muro-Cruz D. Classical fever of unknown origin (FUO): current causes in Mexico. <i>Rev Invest Clin</i> 2005; 57(6):762-769.	Review/Other	45 patients	To review all patients admitted to a tertiary care hospital with FUO in order to describe the epidemiology of classical FUO, the time and procedures to achieve a definitive diagnosis, and to underline the variables useful in distinguishing FUO categories.	Classical FUO is an unusual presentation of frequent infectious diseases; systemic lupus erythematosus is the main cause within the inflammatory noninfectious conditions, and non-Hodgkin's lymphoma is the first cause of cancer. Some clinical and laboratory clues may be used to guide the study workup of patients with classical FUO.	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
58. Buonomo C, Treves ST. Gallium scanning in children with fever of unknown origin. <i>Pediatr Radiol</i> 1993; 23(4):307-310.	Review/Other	30 patients	To determine the role of Gallium scanning in children with FUO.	4/30 children had positive Gallium scans. Of 25 children with only systemic signs and symptoms in addition to fever, 1 had a positive scan. Of 5 children with more focal complaints, 3 had positive studies: all had localized infections which had remained occult despite imaging with other modalities. In most children with FUO, who have only systemic complaints, Gallium scanning is rarely useful. It may be very helpful, however, when there is a suspicion of localized infection, even if other imaging studies are negative.	4
59. Tsukahara M, Tsuneoka H, Iino H, Murano I, Takahashi H, Uchida M. Bartonella henselae infection as a cause of fever of unknown origin. <i>J Clin Microbiol</i> 2000; 38(5):1990-1991.	Review/Other	41 patients	Patients with a positive serologic diagnosis in questionable case of cat scratch fever were studied to determine the prevalence of systemic Bartonella henselae infection. Serological diagnosis was done using the indirect fluorescent-antibody method.	14/41 patients (34%) with positive serological diagnosis of Bartonella henselae infection had prolonged fever without apparent cause. Findings support previous reports and suggest that generalized systemic Bartonella henselae infection is not rare in healthy individuals and that children seem to be more prone to develop a prolonged fever.	4
60. Steele RW, Jones SM, Lowe BA, Glasier CM. Usefulness of scanning procedures for diagnosis of fever of unknown origin in children. <i>J Pediatr</i> 1991; 119(4):526-530.	Review/Other	109 patients	To evaluate patients for prolonged FUO. A two-phase protocol of outpatient followed by inpatient diagnostic studies was performed for most patients.	Confirmed diagnoses were achieved in just 36 of these children (33%) in the following disease categories: infectious, 24 (22%); autoimmune, 7 (6%); and neoplastic, 2 (2%). Scanning or special procedures and the number with positive results (in parentheses) were as follows: abdominal US, 43 (8); abdominal CT, 14 (3); indium scan 11 (5); gallium scanning, 4 (1), upper gastrointestinal tract series, 13 (2); technetium bone scanning 15 (2); bone marrow examination, 16 (1); and cranial CT, 7 (0).	4
61. Lopez Rodriguez M, Vazquez Munoz E, Gomez Cerezo J, et al. [Cost-effectiveness of computerized axial tomography in the diagnosis of traditional clinical picture of fever of unknown origin]. <i>Rev Clin Esp</i> 2005; 205(1):19-23.	Review/Other	24 patients	Cost-effectiveness comparing thoracoabdominal CT with abdominal echography was analyzed to define the role of thoracoabdominal CT in the first diagnostic stage.	CT pointed at diagnosis in 10/24 patients, whereas the abdominal echography contributed information in only two patients. The data from CT allowed for a definitive diagnosis in 9/10 patients. Therefore, CT is justified for initial workup of patients with FUO.	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
62. Habib GS, Masri R, Ben-Haim S. The utility of gallium scintigraphy in the evaluation of fever of unknown origin. <i>Isr Med Assoc J</i> 2004; 6(8):463-466.	Observational	102 patients	Retrospective chart review to evaluate the utility of gallium scintigraphy in the evaluation of patients with FUO in one department during the period 1995-2002.	A final diagnosis had been reached in 63 patients among whom the etiology was infectious in 54%, neoplastic in 19% and immunologic/rheumatic in 16%. 41 patients had had an abnormal gallium scintigraphy, and in only 21 patients did the gallium study results contribute to the diagnosis of the cause of FUO. Even among patients in whom the test made a contribution, it was considered crucial to the diagnosis in only two instances. Therefore, it must be concluded gallium scintigraphy has very limited utility in the evaluation of FUO.	4
63. Kjaer A, Lebech AM. Diagnostic value of (111)In-granulocyte scintigraphy in patients with fever of unknown origin. <i>J Nucl Med</i> 2002; 43(2):140-144.	Observational	31 patients	Retrospective review of patient records to assess the diagnostic value of granulocyte scintigraphy in patients fulfilling the criteria of FUO. Also studied was whether increased peripheral leukocyte count or C-reactive protein level could be used to select patients for scintigraphy to raise the diagnostic value.	Scintigrams had sensitivity of 75%, specificity of 83%, PPV of 60%, and NPV of 90%. Leukocyte counts did not differ between patients with true positive and true negative. C-reactive protein was elevated in all patients with true positive scintigrams but in only half the patients with true negative. Seems to be OK and the high NPV seems worthwhile.	3
64. Kjaer A, Lebech AM, Eigtved A, Hojgaard L. Fever of unknown origin: prospective comparison of diagnostic value of 18F-FDG PET and 111In-granulocyte scintigraphy. <i>Eur J Nucl Med Mol Imaging</i> 2004; 31(5):622-626.	Observational	19 patients	To compare prospectively the diagnostic value of FDG-PET and indium-111 granulocyte scintigraphy in patients with FUO.	The sensitivity of granulocyte scintigraphy and FDG-PET were 71% [95% CI, 37%-85%] and 50% (CI, 16%-84%), respectively. The specificity of granulocyte scintigraphy was 92% (71%-100%), which was significantly higher than that of FDG-PET, at 46% (34%-62%). PPV and NPV for granulocyte scintigraphy were both 85%. PPV and NPV for FDG-PET were 30% and 67%, respectively. (111)In-granulocyte scintigraphy has a superior diagnostic performance compared to FDG-PET for detection of a localized infectious/inflammatory or neoplastic cause of FUO.	1

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
65. Sturm E, Rings EH, Scholvinck EH, Gouw AS, Porte RJ, Pruim J. Fluorodeoxyglucose positron emission tomography contributes to management of pediatric liver transplantation candidates with fever of unknown origin. <i>Liver Transpl</i> 2006; 12(11):1698-1704.	Review/Other	11 patients	To report an experience using FDG-PET to detect the origin of infection in children with biliary cirrhosis presenting with FUO during the waiting period for liver transplantation.	In 5 children, positive intrahepatic FDG-PET signals correlated with bacterial cultures of the excised liver and/or anatomic or histologic signs of infection. In others, no abnormal hepatic FDG-PET signals were found and no infections could be detected in the liver. Transplantation in these patients was performed only after becoming afebrile. Standard imaging techniques did not reveal abnormalities compatible with infection in any of the children.	4
66. Dumarey N, Egrise D, Blocklet D, et al. Imaging infection with 18F-FDG-labeled leukocyte PET/CT: initial experience in 21 patients. <i>J Nucl Med</i> 2006; 47(4):625-632.	Observational	21 patients	Prospective study to assess the feasibility and the potential role of PET/CT with FDG-labeled autologous leukocytes in the diagnosis and localization of infectious lesions.	The best trade-off between sensitivity and specificity was obtained when a visual score of ≥ 2 was chosen to identify increased tracer uptake as infection. With this threshold, sensitivity, specificity, and accuracy were each 86% on a patient-per-patient basis and 91%, 85%, and 90% on a lesion-per-lesion basis. In this small group of patients, the absence of areas with increased WBC uptake on WBC PET/CT had a NPV of 100%. While the results are impressive, the small study size suggests that further investigation of FDG-WBC PET/CT in a larger prospective series is warranted.	2

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
67. Simons KS, Pickkers P, Bleeker-Rovers CP, Oyen WJ, van der Hoeven JG. F-18-fluorodeoxyglucose positron emission tomography combined with CT in critically ill patients with suspected infection. <i>Intensive Care Med</i> 2010; 36(3):504-511.	Observational	35 FDG-PET/CT in 33 intensive care unit patients (28 adults and 5 children)	Retrospective study to assess the value of FDG-PET combined with CT in critically ill patients suspected of having an infection.	21 FDG-PET/CT scans were true positive. Three FDG-PET/CT scans were considered false positive, in one case leading to additional diagnostic procedures (specificity 79%). Additionally, 11 true negatives were found (sensitivity 100%), leading to an overall accuracy of 91%. FDG-PET/CT scanning is of additional value in the evaluation of suspected infection in critically ill patients in whom conventional diagnostics did not lead to a diagnosis. Apart from the high accuracy, in this study it appeared that, in addition to conventional diagnostic techniques that were routinely performed, a normal FDG-PET/CT ruled out important infections requiring prolonged antibiotic therapy or drainage. Since sensitivity is lower in highly metabolic active tissues (eg, endocarditis, meningitis), the FDG-PET/CT scan is not suited to detect infections in these tissues.	2
68. Bar-Shalom R, Yefremov N, Guralnik L, et al. SPECT/CT using 67Ga and 111In-labeled leukocyte scintigraphy for diagnosis of infection. <i>J Nucl Med</i> 2006; 47(4):587-594.	Observational	82 patients 88 SPECT/CT	To assess the role of SPECT/CT as an adjunct to 67Ga or 111In-labeled WBC scintigraphy for diagnosis or localization of infection.	SPECT/CT provided additional information for infection diagnosis and localization in 39/82 patients and in 47/98 sites. It defined the extent of infection in 35 patients in 43 sites and excluded infection in four suggestive sites defined as physiologic bowel uptake on 67Ga scan. It was incorrect in two suggestive sites (1 67Ga and 1 WBC). The contribution was higher for WBC than for 67Ga ($P<0.05$) in 63% vs 36% of patients, respectively, and in 61% vs 36% of sites, respectively. Because SPECT/CT made an incremental contribution to 67Ga scan and WBC in 48% of patients with suspected infections, it should have an important role mainly with highly specific, low-background infection-seeking tracers such as WBC.	3

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
69. Ferda J, Ferdova E, Zahlava J, Matejovic M, Kreuzberg B. Fever of unknown origin: a value of (18)F-FDG-PET/CT with integrated full diagnostic isotropic CT imaging. <i>Eur J Radiol</i> 2010; 73(3):518-525.	Observational	48 patients	Retrospective study to evaluate the clinical value of FDG-PET/CT in patients with FUO and to compare PET/CT finding with the results of biopsies, immunology, microbiology or autopsy.	The cause of FUO was explained according to the PET/CT findings and followed investigations in 44/48 cases. 18 cases of microbial infections, 9 cases of autoimmune inflammations, 4 cases of noninfectious granulomatous diseases, 8 cases of malignancies and 5 cases of proved immunity disorders were found. In 46 cases, the PET/CT interpretation was correct. Only in one case, the cause was overlooked and the uptake in atherosclerotic changes of arteries was misinterpreted as vasculitis in the other. The reached sensitivity was 97% (43/44), and specificity 75% (3/4) respectively. In patients with FUO, FDG-PET/CT might enable the detection of its cause.	3
70. Sheng JF, Sheng ZK, Shen XM, et al. Diagnostic value of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with fever of unknown origin. <i>Eur J Intern Med</i> 2011; 22(1):112-116.	Observational	48 patients	To retrospectively evaluate the diagnostic value of PET/CT for patients with FUO.	Final diagnosis established for 36 patients (75%). Among them, 15 patients had infectious diseases, 12 patients had malignancies, and 9 patients had non-infectious inflammatory diseases. 32 abnormal PET/CT results correctly revealed the source of fever (true-positives). PET/CT had PPV of 80%, NPV of 50%, a sensitivity of 89%, and a specificity of 33% in patients with FUO. Study showed FDG-PET/CT is a valuable imaging tool for the identification of the etiology in patients with FUO. Results suggest that this procedure may be considered as a second-line test, especially when conventional structural imaging was normal or unable to distinguish lesions from benign and malignant.	3

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
71. Dong MJ, Zhao K, Liu ZF, Wang GL, Yang SY, Zhou GJ. A meta-analysis of the value of fluorodeoxyglucose-PET/PET-CT in the evaluation of fever of unknown origin. <i>Eur J Radiol</i> 2010.	Review/Other	9 studies with 388 patients (5 FDG-PET studies and 4 FDG-PET/CT studies)	Meta-analysis was performed to examine the overall diagnostic performance of FDG-PET and FDG-PET/CT for the detection of FUO, which cannot be identified by conventional diagnostic methods.	Pooled sensitivity and specificity of FDG-PET for the detection of FUO were 0.826 (95% CI, 0.729-0.899) and 0.578 (95% CI, 0.488-0.665), respectively, and the area under the curve was 0.810. Pooled sensitivity and specificity of FDG-PET/CT were 0.982 (95% CI, 0.936-0.998) and 0.859 (95% CI, 0.750-0.934), respectively, and the area under the curve was 0.947. Although FDG-PET studies were heterogeneous, FDG-PET appears to be a sensitive and promising diagnostic tool for the detection of the causes of FUO. FDG-PET/CT should be considered among the first diagnostic tools for patients with FUO in whom conventional diagnostics have been unsuccessful.	4
72. Jasper N, Dabritz J, Frosch M, Loeffler M, Weckesser M, Foell D. Diagnostic value of [(18)F]-FDG PET/CT in children with fever of unknown origin or unexplained signs of inflammation. <i>Eur J Nucl Med Mol Imaging</i> 2010; 37(1):136-145.	Review/Other	47 FDG-PET and 30 PET/CT scans from 69 children	Retrospective study to assess the diagnostic value of FDG-PET and PET/CT in the diagnostic workup in pediatric patients.	A diagnosis in pediatric patients with FUO or unexplained signs of inflammation could be established in 32 patients (54%). Of all scans, 63 (82%) were abnormal, and of the total number of 77 PET and PET/CT scans 35 (45%) were clinically helpful. In patients with a final diagnosis, scans were found to have contributed to the diagnosis in 73%. Combination of PET with CT seems to be superior, since the site of inflammation can be localized more accurately.	4
73. Paulus S, Dobson S. Febrile neutropenia in children with cancer. <i>Adv Exp Med Biol</i> 2009; 634:185-204.	Review/Other	N/A	Review febrile neutropenia in children with cancer.	Gram negative bacteria are still responsible for most of the mortality associated with febrile neutropenia. Piperacillin/tazobactam, cefipime, or meropenem are all effective first-choice antimicrobial monotherapy in febrile neutropenia. There is no good evidence for adding an aminoglycoside compound to the initial empiric therapy regimen. Following local microbiological data is of utmost importance in choosing the right empiric antimicrobial regimen for a particular institution. Outpatient management of a well-defined subset of low-risk patient for bacterial invasive infection with intravenous ceftriaxone or oral ciprofloxacin and daily re-evaluation is possible.	4

Fever without Source—Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
74. Korones DN, Hussong MR, Gullace MA. Routine chest radiography of children with cancer hospitalized for fever and neutropenia: is it really necessary? <i>Cancer</i> 1997; 80(6):1160-1164.	Observational	54 patients	Prospective study to determine how often chest radiographs showed pneumonia in children with fever and neutropenia and how those children without chest radiographs fared.	Not necessary to obtain chest radiographs for children hospitalized for fever and neutropenia without respiratory symptoms or signs.	3
75. Walsh TJ, Groll A, Gonzalez C, Pizzo PA. Infectious Complications in Pediatric Cancer Patients In: Pizzo PA, Poplack DG, eds. <i>Principles and Practice of Pediatric Oncology</i> . 5th ed: Lippincott Williams & Wilkins; 2005:1269-1329.	Review/Other	N/A	Book chapter.	N/A	4
76. Archibald S, Park J, Geyer JR, Hawkins DS. Computed tomography in the evaluation of febrile neutropenic pediatric oncology patients. <i>Pediatr Infect Dis J</i> 2001; 20(1):5-10.	Review/Other	83 patients	Retrospective medical record review of all pediatric cancer patients who had CT for case of febrile neutropenia that lasted >4 days in order to evaluate the diagnostic utility of CT in this population.	CT detected abnormalities frequently lead to alterations in therapy, particularly sinus and thoracic CT. Most patients with CT-detected abnormalities have symptoms or signs referable to the site of abnormality. Asymptomatic febrile neutropenic children rarely have CT findings that lead to a change in therapy.	4
77. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. <i>Clin Infect Dis</i> 2002; 34(6):730-751.	Review/Other	N/A	An update of guidelines established a decade ago and revised in 1997 by the Infectious Disease Society of America for the use of antimicrobial agents to treat neutropenic patients with unexplained fever.	Recommendations are presented in guideline.	4
78. Barloon TJ, Galvin JR, Mori M, et al. High-resolution ultrafast chest CT in the clinical management of febrile bone marrow transplant patients with normal or nonspecific chest roentgenograms. <i>Chest</i> 1991; 99(4):928-33	Observational	33 patients	Prospective study to determine if chest CT scans can provide information that will change the patient's clinical management of febrile bone marrow transplant.	In most instances noncontrast ultrafast chest CT scans can provide information that may either change a patient's clinical management or help establish the extent of pulmonary disease.	3
79. Heussel CP, Kauczor HU, Heussel GE, et al. Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high-resolution computed tomography. <i>J Clin Oncol</i> 1999; 17(3):796-805.	Observational	188 HRCT studies in 112 patients	Prospective study to obtain data on the use of HRCT for detection of pneumonia in febrile neutropenic patients with unknown focus of infection.	HRCT: sensitivity 87% (88% in transplant recipients), specificity 57% (67%), NPV 88% (97%). Patients with normal HRCT scans have a low risk of pneumonia during follow-up.	2

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
 - a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
 - b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
 - c) the study is an expert opinion or consensus document.

Abbreviations Key

CBC = Complete blood cell

CI = Confidence interval

CT = Computed tomography

FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography

FUO = Fever of unknown origin

FWS = Fever without source

HRCT = High-resolution computed tomography

MRI = Magnetic resonance imaging

NPV = Negative predictive value

OB = Occult bacteremia

OR = Odds ratio

PCV = Pneumococcal conjugate vaccine

PET = Positron emission tomography

PPV = Positive predictive value

ROC = Receiver-operator characteristic

RR = Relative risk

SBI = Serious bacterial infection

SPECT = Single-photon emission tomography

US = Ultrasound

WBC = White blood cell