

Fever without Source—Child
EVIDENCE TABLE

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Strength of Evidence |
|--|------------|---|--|---|-------------------------|
| 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. | 12 | 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. Gartner JC, Jr. Fever of unknown origin. <i>Adv Pediatr Infect Dis</i> 1992; 7:1-24. | 12 | N/A | To review diagnosis fever of unknown origin (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 |
| 3. Baraff LJ. Management of fever without source in infants and children. <i>Ann Emerg Med</i> 2000; 36(6):602-614. | 13 | N/A | To describe presenting conditions and management of children who have fever without source (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 |
| 4. Ishimine P. Fever without source in children 0 to 36 months of age. <i>Pediatr Clin North Am</i> 2006; 53(2):167-194. | 12 | 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 pneumococcal conjugate vaccine (PCV7) 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 |
| 5. 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. | 13 | 376 | 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 (ED). | Significant differences exist in the management of the young febrile child between the practices' patterns and guidelines, without influence on patient outcome. | 3 |
| 6. Brook I. Unexplained fever in young children: how to manage severe bacterial infection. <i>BMJ</i> 2003; 327(7423):1094-1097. | 12 | 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 |
| 7. 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. | 15 | 7,500 pediatricians and 7,500 ED 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 ED physicians would order fewer complete blood cell (CBC) counts and blood cultures and administer less empiric ceftriaxone if a child was vaccinated with PCV7. | 3 |

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| 8. 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. | 9 | 381 | 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 serious bacterial infections 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 white blood cell count and C-reactive protein, and in urinalysis ≥ 70 white bloods) are also needed. | 2 |
| 9. Petersdorf RG, Beeson PB. Fever of unexplained origin report on 100 cases. <i>Medicine (Baltimore)</i> 1961; 40:1-30. | 13 | 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. | 2 |
| 10. 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. | 13 | 80 | 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 |
| 11. McCarthy P. Fever without apparent source on clinical examination. <i>Curr Opin Pediatr</i> 2005; 17(1):93-110. | 12 | 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 conjugated pneumococcal vaccine, on the occurrence of serious bacterial infection in febrile infants with respiratory syncytial virus, and on the broad spectrum of diagnoses in children with prolonged fever in varying geographic locales. | 4 |
| 12. 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. | 12 | N/A | Evaluation of FWS in infants and children. | Overview of various causes of fever and their evaluation and treatment. | 4 |

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| 13. 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. | 13 | 102 | 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. | 3 |
| 14. 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. | 13 | 185 | 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. | 2 |
| 15. 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. | 12 | 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 |
| 16. Arnow PM, Flaherty JP. Fever of unknown origin. <i>Lancet</i> 1997; 350(9077):575-580. | 12 | 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 |
| 17. 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. | 15 | 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 | 3 |
| 18. 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. | 13 | 54 | 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. | 3 |

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| 19. McClung HJ. Prolonged fever of unknown origin in children. <i>Am J Dis Child</i> 1972; 124(4):544-550. | 13 | 99 | 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. | 3 |
| 20. 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. | 15 | 1,600 physicians | Mailed survey to pediatricians, family practice physicians (FPP) and emergency medicine physicians (EMP) 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, FPP and EMP 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. | 3 |
| 21. 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. | 3a | 138 | 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 serious bacterial infection. | 2 |
| 22. 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. | 3b | 534 | Prospectively evaluate febrile infants 4-8 weeks for symptoms and evaluate the Milwaukee Protocol (MP). Two groups were compared: 1) Infants with uncompromised presentation (UP) who met all MP criteria received ceftriaxone 50 mg/kg and were discharged, then reevaluated within 24 hours. 2) Infants with compromised presentation (CP) who did not meet MP criteria were hospitalized for antibiotic therapy pending culture results. | The MP criteria had a sensitivity of 96% and a 99% NPV for distinguishing SBI outcome. The MP was useful in selecting infants who are at low risk for serious bacterial infection. | 2 |
| 23. 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. | 2 | 747 | 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. | 2 |
| 24. 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. | 1 | 1,057 | Prospective studies to test the hypothesis that infants unlikely to have serious bacterial infections can be accurately identified by low risk criteria. | NPV of low risk criteria was 98.9% (95% CI, 97.2% to 99.6%) for serious bacterial infections, and 99.5% (95% CI, 98.2% to 99.9%) for bacteremia. Low risk criteria are useful in helping to identify infants unlikely to have serious bacterial infection. | 1 |

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| 25. 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. | 10 | 102 | 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 five (10%) of 48 patients, compared with a change in 16 (30%) of 54 when the pattern was inconsistent (P less than 0.02). Similarly, when the pattern was consistent, the pre-x-ray management was modified in only three (6%) of 48 patients vs 13 (24%) of 54 inconsistent cases (P less than 0.015). | 2 |
| 26. Leventhal JM. Clinical predictors of pneumonia as a guide to ordering chest roentgenograms. <i>Clin Pediatr (Phila)</i> 1982; 21(12):730-734. | 13 | 136 | Prospective study. Determine consideration of signs and symptoms to serve as index for obtaining chest radiographs. | Tachypnea was best predictor of pneumonia. | 2 |
| 27. 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. | 13 | 510 | 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. | 2 |
| 28. 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. | 13 | 209 | 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 less than 60; absence of rales and decreased breath sounds; presence of normal color; and white blood cell count less than 19,000/mm ³ . | 2 |
| 29. 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. | 13 | 125 | 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. | 2 |

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| 30. 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. | 10 | 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. | 1 |
| 31. 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. | 15 | 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 occult bacteremia. The optimal management strategy reduces risk to a minimum at a reasonable cost and can be used in most practice settings. | 3 |
| 32. 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. | 15 | N/A | To develop evidence-based practice guidelines for management of infants up to 36 months with FWS. | <ul style="list-style-type: none"> 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 C without source need no laboratory tests or antibiotics. Children 3 to 36 months of age with fever of 39.0 C or more and whose WBC count is 15,000/mm³ 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. | 2 |
| 33. McCarthy PL. The pediatric clinical evaluation and pneumonia. <i>Curr Opin Pediatr</i> 1996; 8(5):427-429. | 12 | 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 |

* See Last Page for Key

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| 34. 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. | 13 | 255 adults and 78 children | Community hospital ED 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 |
| 35. 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. | 11 | 617 | 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. | 2 |
| 36. 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. | 10 | 242 | 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 |
| 37. 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. | 10 | 192 | 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. | 2 |
| 38. Bramson RT, Griscom NT, Cleveland RH. Interpretation of chest radiographs in infants with cough and fever. <i>Radiology</i> 2005; 236(1):22-29. | 12 | 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 |
| 39. 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. | 9 | 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. | 2 |
| 40. 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. | 12 | N/A | To review literature on assessment and the preferred treatment strategies for children without a focus of infection. | No results. | 4 |
| 41. 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. | 1 | 37,868 | To determine the efficacy, safety and immunogenicity of the heptavalent CRM197 pneumococcal conjugate vaccine against invasive disease caused by vaccine serotypes and to determine the effectiveness of this vaccine against clinical episodes of otitis media. | The heptavalent pneumococcal conjugate is highly effective in preventing invasive disease in young children and it has a significant impact on otitis media. | 1 |

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| 42. 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. | 15 | 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 | 3 |
| 43. British Thoracic Society Guidelines for the Management of Community Acquired Pneumonia in Childhood. <i>Thorax</i> 2002; 57 Suppl 1:i1-24. | 15 | N/A | Guidelines for the Management of Community Acquired Pneumonia in Childhood. | N/A | 3 |
| 44. 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. | 13 | 20 | 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%). | 3 |
| 45. 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. | 15 (Study on epidemiology compare classical FUO) | 45 (adults) | 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 (SLE) is the main cause within the inflammatory non-infectious 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 | 3 |
| 46. Buonomo C, Treves ST. Gallium scanning in children with fever of unknown origin. <i>Pediatr Radiol</i> 1993; 23(4):307-310. | 10 | 30 | To determine the role of Gallium scanning in children with FUO. | 4 of 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. | 3 |
| 47. 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. | 3a | 41 | Patients with a positive serologic diagnosis in questionable case of cat scratch fever were studied to determine the prevalence of systemic B. henselae infection. Serological diagnosis was done using the indirect fluorescent-antibody (IFA) method. | <ul style="list-style-type: none"> • Fourteen of 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 B. henselae infection is not rare in healthy individuals and that children seem to be more prone to develop a prolonged fever. | 3 |

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| 48. 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. | 13 | 109 | To evaluate patients for prolonged FUO. A two-phase protocol of outpatient followed by inpatient diagnostic studies was performed for most patients. | <ul style="list-style-type: none"> 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 ultrasonography, 43 (8); abdominal computed tomography, 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 computed tomography, 7 (0). | 3 |
| 49. 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. | 9 | 24 | Cost-effectiveness comparing thoracoabdominal CT with abdominal echography (AE) was analyzed to define the role of thoracoabdominal computerized axial tomography in the first diagnostic stage. | CT pointed at diagnosis in 10/24 patients, whereas the AE contributed information in only two patients. The data from CT allowed for a definitive diagnosis in 9 of the 10 patients. Therefore, CT is justified for initial work-up of patients with FUO. | 3 |
| 50. 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. | 10 | 102 | 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. | 3 |
| 51. 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. | 10 | 31 | 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 |

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| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Strength of Evidence |
|---|------------|---------------------|---|---|-------------------------|
| 52. 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. | 9 | 19 | To compare prospectively the diagnostic value of FDG-PET and indium-111 granulocyte scintigraphy in patients with FUO | <ul style="list-style-type: none"> • The sensitivity of granulocyte scintigraphy and FDG-PET were 71% [95% confidence interval (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%). • Positive and negative predictive values for granulocyte scintigraphy were both 85%. Positive and negative predictive values 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 localised infectious/inflammatory or neoplastic cause of FUO. | 2 |
| 53. Sturm E, Rings EH, Scholvinck EH, Gouw AS, Porte RJ, Pruijm 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. | 10 | 11 | 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. | 3 |
| 54. 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. | 9 | 21 | Prospective study to assess the feasibility and the potential role of PET/CT with (18)F-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 |

* See Last Page for Key

Fever without Source—Child
EVIDENCE TABLE

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Strength of Evidence |
|---|------------|----------------------------------|---|---|-------------------------|
| 55. 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. | 10 | 82 patients 88 SPECT/CT | To assess the role of SPECT/CT as an adjunct to 67Ga or 111In-labeled white blood cell 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 GS. It was incorrect in two suggestive sites (1 GS and 1 WBC). The contribution was higher for WBC than for GS ($p<0.05$) in 63% vs 36% of patients, respectively, and in 61% vs 36% of sites, respectively. Because SPECT/CT made an incremental contribution to GS 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. | 2 |
| 56. 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. | 10 | 54 | 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. | 2 |
| 57. 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. | 10 | 83 | 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. | 2 |
| 58. 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 | 10 | 33 | 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 |
| 59. 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. | 10 | 112 | Prospective study to obtain data on the use of high-resolution CT (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 Type Key

Numbers 1-7 are for studies of therapies while numbers 8-15 are used to describe studies of diagnostics.

1. Randomized Controlled Trial — Treatment
2. Controlled Trial
3. Observation Study
 - a. Cohort
 - b. Cross-sectional
 - c. Case-control
4. Clinical Series
5. Case reviews
6. Anecdotes
7. Reviews
8. Randomized Controlled Trial — Diagnostic
9. Comparative Assessment
10. Clinical Assessment
11. Quantitative Review
12. Qualitative Review
13. Descriptive Study
14. Case Report
15. Other (Described in text)

Strength of Evidence Key

- Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.
- Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.
- Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.
- Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.