Fever without Source or Unknown Origin-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. *Compr Ther.* 1995;21(3):109-114.	Review/Other-Dx	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. *Pediatr Ann.* 2008;37(10):673-679.	Review/Other-Dx	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. Ishimine P. The evolving approach to the young child who has fever and no obvious source. *Emerg Med Clin North Am.* 2007;25(4):1087-1115, vii.	Review/Other-Dx	N/A	To review newer strategies in the evaluation and management of the young child with fever, incorporating changes based on the shifting epidemiology of bacterial infection.	A systematic plan for the evaluation and treatment of the febrile child may help reduce unnecessary testing and morbidity associated with serious infection; however, no single strategy can capture the nuances of all febrile young patients.	4
4. Arnow PM, Flaherty JP. Fever of unknown origin. *Lancet.* 1997;350(9077):575-580.	Review/Other-Dx	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
5. Baraff LJ. Management of fever without source in infants and children. *Ann Emerg Med.* 2000;36(6):602-614.	Review/Other-Dx	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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
6. Ishimine P. Fever without source in children 0 to 36 months of age. *Pediatr Clin North Am.* 2006;53(2):167-194.	Review/Other-Dx	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
7. 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. *Clin Pediatr (Phila).* 2004;43(1):11-16.	Review/Other-Dx	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
8. Massin MM, Montesanti J, Lepage P. Management of fever without source in young children presenting to an emergency room. *Acta Paediatr.* 2006;95(11):1446-1450.	Review/Other-Dx	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. Tolan RW, Jr. Fever of unknown origin: a diagnostic approach to this vexing problem. *Clin Pediatr (Phila).* 2010;49(3):207-213.	Review/Other-Dx	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
10. Gabriel ME, Aiuto L, Kohn N, Barone SR. Management of febrile children in the conjugate pneumococcal vaccine era. *Clin Pediatr (Phila).* 2004;43(1):75-82.	Review/Other-Dx	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
11. Lohr JA, Hendley JO. Prolonged fever of unknown origin: a record of experiences with 54 childhood patients. *Clin Pediatr (Phila).* 1977;16(9):768-773.	Review/Other-Dx	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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
12. McClung HJ. Prolonged fever of unknown origin in children. *Am J Dis Child.* 1972;124(4):544-550.	Review/Other-Dx	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
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. *Eur J Emerg Med.* 2009;16(4):199-205.	Observational-Dx	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%). 1,040/1,586 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 2 doses of PCV-7, 1 (0.23%) had a pneumococcal OB (vs 9/1090 (0.82%) with no dose or 1 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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. Rutman MS, Bachur R, Harper MB. Radiographic pneumonia in young, highly febrile children with leukocytosis before and after universal conjugate pneumococcal vaccination. *Pediatr Emerg Care.* 2009;25(1):1-7.	Observational-Dx	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 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
15. Gartner JC, Jr. Fever of unknown origin. *Adv Pediatr Infect Dis.* 1992;7:1-24.	Review/Other-Dx	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
16. Brook I. Unexplained fever in young children: how to manage severe bacterial infection. *Bmj.* 2003;327(7423):1094-1097.	Review/Other-Dx	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
17. Aronson PL. Evaluation of the febrile young infant: an update. *Pediatr Emerg Med Pract.* 2013;10(2):1-17.	Review/Other-Dx	N/A	A review on the evaluation of the febrile young infant.	Performance of a full sepsis workup is recommended to rule out bacteremia, urinary tract infection, and bacterial meningitis in addition to other invasive bacterial diseases including pneumonia, bacterial enteritis, cellulitis, and osteomyelitis. Parents and emergency clinicians often question the necessity of this approach in the well-appearing febrile young infant, and it is important to understand and communicate the evidence that guides the approach to these patients.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
18. Lacour AG, Zamora SA, Gervaix A. A score identifying serious bacterial infections in children with fever without source. *Pediatr Infect Dis J.* 2008;27(7):654-656.	Observational-Dx	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
19. Semeraro M, Thomee C, Rolland E, et al. A predictor of unfavourable outcome in neutropenic paediatric patients presenting with fever of unknown origin. *Pediatr Blood Cancer.* 2010;54(2):284-290.	Observational-Dx	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
20. Cogulu O, Koturoglu G, Kurugol Z, Ozkinay F, Vardar F, Ozkinay C. Evaluation of 80 children with prolonged fever. *Pediatr Int.* 2003;45(5):564-569.	Observational-Dx	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
21. Arora R, Mahajan P. Evaluation of child with fever without source: review of literature and update. Pediatr Clin North Am. 2013;60(5):1049-1062.	Review/Other-Dx	N/A	To review the literature on the evaluation and management of the febrile child, and comment on recent advances that may have potential to change the paradigm for detection of pathogens. The authors discuss evaluation of the febrile child in 2 age groups, febrile infants 3 months or younger and those between 3 and 36 months of age.	No results stated in abstract.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
22. Goldman RD, Scolnik D, Chauvin-Kimoff L, et al. Practice variations in the treatment of febrile infants among pediatric emergency physicians. *Pediatrics*. 2009;124(2):439-445.	Observational-Dx	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
23. Machado BM, Cardoso DM, de Paulis M, Escobar AM, Gilio AE. Fever without source: evaluation of a guideline. *J Pediatr (Rio J)*. 2009;85(5):426-432.	Review/Other-Dx	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 1 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
24. Pasic S, Minic A, Djuric P, et al. Fever of unknown origin in 185 paediatric patients: a single-centre experience. *Acta Paediatr*. 2006;95(4):463-466.	Review/Other-Dx	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

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25. McCarthy P. Fever without apparent source on clinical examination. *Curr Opin Pediatr.* 2005;17(1):93-110.	Review/Other-Dx	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 S. pneumoniae 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
26. Hofer M, Mahlaoui N, Prieur AM. A child with a systemic febrile illness - differential diagnosis and management. *Best Pract Res Clin Rheumatol.* 2006;20(4):627-640.	Review/Other-Dx	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. Palazzi DL. Fever of unknown origin in children: Evaluation. 2014; Available at: http://www.uptodate.com/contents/fever-of-unknown-origin-in-children-evaluation. Accessed September 30, 2015.	Review/Other-Dx	N/A	To evaluate FUO in children.	No results stated.	4
28. Moher D, Hui C, Neto G, et al. Diagnosis and Management of Febrile Infants (0–3 Months). Evidence Report/Technology Assessment No. 205. 2012; 1-18. Available at: http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1015. Accessed September 30, 2015.	Review/Other-Dx	84 studies	To review the literature to answer Key Questions about the management of the febrile infant and to identify needs for future research.	Overall, the focus of the literature has been on ruling out SBI. Harms associated with testing or management strategies have been poorly reported. Attempts to identify high-risk groups, as described in the minority of reports, were not accurate. The Boston, Philadelphia, Rochester, and Milwaukee were fairly accurate in identifying a low-risk group for SBI in infants younger than 3 months of age.	4

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29. Albaum MN, Hill LC, Murphy M, et al. Interobserver reliability of the chest radiograph in community-acquired pneumonia. PORT Investigators. *Chest.* 1996;110(2):343-350.	Observational-Dx	282 patients	To evaluate the interobserver reliability of pulmonary radiographic findings in patients with community-acquired pneumonia.	Among the 282 patients whose initial pulmonary radiographs were evaluated, there was agreement between the 2 staff radiologists on the presence of infiltrate in 79.4% and on the absence of an infiltrate in 6.0% (kappa = 0.37; 95% CI = 0.22 to 0.52). For the 224 patients with an infiltrate identified by both radiologists, there was further agreement that the infiltrate was unilobar in 41.5% and multilobar in 33.9% (kappa = 0.51; 95% CI = 0.28 to 0.62), pleural effusion was present in 10.7% and absent in 73.2% (kappa = 0.46; 95% CI = 0.33 to 0.50), and the infiltrate was alveolar in 96.3% of patients and interstitial in no patients (kappa = -0.01; 95% CI = -0.03 to 0.00). Among the 210 patients with an alveolar infiltrate, both radiologists classified the infiltrate as lobar in 74.6% and bronchopneumonia in 2.4% (kappa = 0.09; 95% CI = -0.04 to 0.22), and agreed on the presence of air bronchograms in 7.6% and their absence in 52.9% (kappa = 0.01; 95% CI = -0.13 to 0.15).	3
30. Bettenay FA, de Campo JF, McCrossin DB. Differentiating bacterial from viral pneumonias in children. *Pediatr Radiol.* 1988;18(6):453-454.	Observational-Dx	58 patients	To assess the accuracy of Swischuk's clinical and radiological criteria in differentiating proven bacterial and viral pneumonias.	When clinical features suggested a bacterial infection the chance of isolating a bacteria as opposed to a virus was 18%. When radiological features suggested a bacterial infection the chance of isolating a bacteria as opposed to a virus was 30%.	3
31. Johnson J, Kline JA. Intraobserver and interobserver agreement of the interpretation of pediatric chest radiographs. *Emerg Radiol.* 2010;17(4):285-290.	Experimental-Dx	24 radiographs	To quantify the magnitude of intraobserver and interobserver agreement among physicians for the interpretation of pneumonia on pediatric chest radiographs.	Intraobserver agreement was good for pediatric radiologists (kappa = 0.87; 95% CI, 0.60–0.99) for both but was lower for senior emergency physicians (mean kappa = 0.68; 95% CI, 0.40–0.95) and junior pediatric emergency physicians (mean kappa = 0.62; 95% CI, 0.35–0.98). Interobserver agreement was fair to moderate overall; between pediatric radiologists, kappa = 0.51 (0.39–0.64); between senior emergency physicians, kappa = 0.55 (0.41–69), and between junior pediatric emergency medicine physicians, kappa = 0.37 (0.25–0.51).	2

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32. Korppi M, Don M, Valent F, Canciani M. The value of clinical features in differentiating between viral, pneumococcal and atypical bacterial pneumonia in children. *Acta Paediatr.* 2008;97(7):943-947.	Review/Other-Dx	101 children	To evaluate the value of clinical features in differentiating between viral, pneumococcal and atypical bacterial pneumonia in children.	Among symptoms, cough was present in 89% and fever (>37.5 degrees C) in 88% of the cases. Among physical signs, crackles were present in 49% and decreased breath sounds in 58%. No significant associations were found between any of the clinical signs or symptoms and the etiology of pneumonia. In multivariate analyses, age >5 years and serum procalcitonin over 1.0 ng/mL were the only independent predictors of bacterial etiology, but no finding was able to screen between pneumococcal and atypical bacterial etiology of infection.	4
33. Spottswood SE, Liaw K, Hernanz-Schulman M, et al. The clinical impact of the radiology report in wheezing and nonwheezing febrile children: a survey of clinicians. *Pediatr Radiol.* 2009;39(4):348-353.	Review/Other-Dx	112 respondents	To determine how clinicians interpret specific terms commonly used in a chest radiograph report, and to assess how these terms impact the management of children with respiratory symptoms.	There were 112 respondents. Most practitioners defined the term "PAD" as viral pneumonia (61.5%) or asthma (56.9%), “consolidation” as atelectasis (83%) followed by pneumonia (69.6%), and “infiltrate” as pneumonia (100%), followed by atelectasis (22.3%). Practitioners were more likely to treat a nonwheezing child with antibiotics if the report stated “focal airspace consolidation” (80%) or “focal infiltrate” (100%; *P*=0.001).	4
34. Williams GJ, Macaskill P, Kerr M, et al. Variability and accuracy in interpretation of consolidation on chest radiography for diagnosing pneumonia in children under 5 years of age. *Pediatr Pulmonol.* 2013;48(12):1195-1200.	Observational-Dx	3,033 chest radiographs in children	To determine the agreement between 3 reviewers for identification of consolidation in children under 5 years old presenting to an emergency department with a febrile illness and suspected pneumonia.	Using the majority rule, 456 (15%) chest radiographs were positive for consolidation while the latent class estimate was 17%. The radiologist was most likely (21.3%) and respiratory physician least likely (13.7%) to diagnose consolidation. Overall percentage agreement for pairs of readers was 85%–90%. However, chance corrected agreement between the readers was moderate, with kappa scores 0.4–0.6 and did not vary with patient characteristics (age, gender, and presence of chronic illness). Estimated sensitivity ranged from 0.71 to 0.81 across readers, and specificity 0.91 to 0.98.	2

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35. Agrawal AK, Saini N, Gildengorin G, Feusner JH. Is routine computed tomographic scanning justified in the first week of persistent febrile neutropenia in children with malignancies? *Pediatr Blood Cancer.* 2011;57(4):620-624.	Review/Other-Dx	52 patients	To evaluate the diagnostic utility of CT obtained during prolonged fever and neutropenia in pediatric oncology patients. A secondary aim was to see if underlying diagnosis, symptomatology at time of CT, or length of febrile neutropenia prior to imaging predicted positive CT findings.	52 patients had 68 unique episodes of prolonged febrile neutropenia that resulted in CT imaging. Positive findings occurred in 18%, 12%, and 25% of initial chest, abdomen, and sinus CTs, respectively. There were no positive findings on initial pelvic CT. Only 2 of the initial positive CT scans led to a change in management (6.5% of positive scans, 0.8% of all initial scans). These were both scans of the chest. All patients with concern for occult fungal infection had findings on chest CT. Patients with clinically important infections had no statistical difference in days of fever or neutropenia or type of underlying malignancy compared with those without infection. Clinical symptomatology was most helpful for typhlitis.	4
36. Archibald S, Park J, Geyer JR, Hawkins DS. Computed tomography in the evaluation of febrile neutropenic pediatric oncology patients. *Pediatr Infect Dis J.* 2001;20(1):5-10.	Review/Other-Dx	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
37. del Rosal T, Goycochea WA, Mendez-Echevarria A, et al. (1)(8)F-FDG PET/CT in the diagnosis of occult bacterial infections in children. *Eur J Pediatr.* 2013;172(8):1111-1115.	Review/Other-Dx	3 pediatric patients	The authors communicate their experience regarding the role of FDG-PET/CT in the diagnosis and management of occult bacterial infections in children.	1 patient had streptococcal endocarditis and prolonged fever. FDG-PET/CT identified pneumonia and osteomyelitis, and was also used to monitor therapeutic response. Other patient had a cerebrospinal shunt fluid infection. FDG-PET/CT was used to determine the exact localization of infection and establish the best surgical approach. The last patient had FUO. FDG-PET/CT identified splenic abscesses, which were surgically treated.	4

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38. 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. *Eur J Nucl Med Mol Imaging.* 2010;37(1):136-145.	Review/Other-Dx	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
39. Blokhuis GJ, Bleeker-Rovers CP, Diender MG, Oyen WJ, Draaisma JM, de Geus-Oei LF. Diagnostic value of FDG-PET/(CT) in children with fever of unknown origin and unexplained fever during immune suppression. *Eur J Nucl Med Mol Imaging.* 2014;41(10):1916-1923.	Observational-Dx	31 children	To investigate the diagnostic value of FDG-PET and FDG-PET/CT in children with FUO and in children with unexplained fever during immune suppression.	FDG-PET/CT scans were performed in 31 children with FUO. A final diagnosis was established in 16 cases (52%). Of the total number of scans, 32% were clinically helpful. The sensitivity and specificity of FDG-PET/CT in these patients was 80% and 78%, respectively. FDG-PET/CT scans were performed in 12 children with unexplained fever during immune suppression. A final diagnosis was established in 9 patients (75%). Of the total number of these scans, 58% were clinically helpful. The sensitivity and specificity of FDG-PET/CT in children with unexplained fever during immune suppression was 78% and 67%, respectively.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Pantell RH, Newman TB, Bernzweig J, et al. Management and outcomes of care of fever in early infancy. *JAMA.* 2004;291(10):1203-1212.	Observational-Dx	3,066 infants	To characterize the management and clinical outcomes of fever in infants, develop a clinical prediction model for the identification of bacteremia/bacterial meningitis, and compare the accuracy of various strategies.	The PROS clinicians hospitalized 36% of the infants, performed laboratory testing in 75%, and initially treated 57% with antibiotics. The majority (64%) were treated exclusively outside of the hospital. Bacteremia was detected in 1.8% of infants (2.4% of those tested) and bacterial meningitis in 0.5%. Well-appearing infants aged 25 days or older with fever of <38.6 degrees C had a rate of 0.4% for bacteremia/bacterial meningitis. Frequency of other illnesses included urinary tract infection, 5.4%; otitis media, 12.2%; upper respiratory tract infection, 25.6%; bronchiolitis, 7.8%; and gastroenteritis, 7.2%. Practitioners followed current guidelines in 42% of episodes. However, in the initial visit, they treated 61/63 cases of bacteremia/bacterial meningitis with antibiotics. Neither current guidelines nor the model developed in this study performed with greater accuracy than observed practitioner management.	3
41. Patterson RJ, Bisset GS, 3rd, Kirks DR, Vanness A. Chest radiographs in the evaluation of the febrile infant. *AJR Am J Roentgenol.* 1990;155(4):833-835.	Observational-Dx	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.	4
42. Heulitt MJ, Ablow RC, Santos CC, O'Shea TM, Hilfer CL. Febrile infants less than 3 months old: value of chest radiography. *Radiology.* 1988;167(1):135-137.	Observational-Dx	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.	3
43. Bramson RT, Meyer TL, Silbiger ML, Blickman JG, Halpern E. The futility of the chest radiograph in the febrile infant without respiratory symptoms. *Pediatrics.* 1993;92(4):524-526.	Review/Other-Dx	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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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. *Ann Emerg Med.* 1993;22(7):1198-1210.	Review/Other-Tx	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 as 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
45. McCarthy PL. The pediatric clinical evaluation and pneumonia. *Curr Opin Pediatr.* 1996;8(5):427-429.	Review/Other-Dx	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. Antonyrajah B, Mukundan D. Fever without apparent source on clinical examination. *Curr Opin Pediatr.* 2008;20(1):96-102.	Review/Other-Dx	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
47. 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? *Pediatrics.* 1991;88(4):821-824.	Observational-Dx	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.	Of the 242 cases, 228 had chest radiographs available for interpretation. Of these, 27 chest radiographs (12%) were identified as abnormal, including 6 where there was initial disagreement as to the presence of an abnormality. Twenty-five (31%) of 80 infants with any respiratory signs had an abnormal chest radiograph, whereas only 2 (1%) of 148 asymptomatic infants did. The sensitivity of respiratory signs was 93% (confidence interval = 76% to 99%). These findings suggest that in the absence of respiratory signs, febrile infants are unlikely to have an abnormal chest radiograph.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Bramson RT, Griscom NT, Cleveland RH. Interpretation of chest radiographs in infants with cough and fever. *Radiology.* 2005;236(1):22-29.	Review/Other-Dx	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
49. Murphy CG, van de Pol AC, Harper MB, Bachur RG. Clinical predictors of occult pneumonia in the febrile child. *Acad Emerg Med.* 2007;14(3):243-249.	Review/Other-Dx	2,128 patients	To identify predictors of OP in pediatric patients in the postconjugate pneumococcal vaccination era.	2,128 patients were studied. Among patients categorized as having no signs of pneumonia (n = 1,084), 5.3% (95% CI = 4.0% to 6.8%) had OP. Presence of cough and longer duration of cough (>10 days) had positive likelihood ratios of 1.24 (95% CI = 1.15 to 1.33) and 2.25 (95% CI = 1.21 to 4.20), respectively. Absence of cough had a negative likelihood ratio of 0.19 (95% CI = 0.05 to 0.75). The likelihood of OP increased with increasing duration of fever (positive likelihood ratios for more than 3 days and more than 5 days of fever, respectively: 1.62; 95% CI = 1.13 to 2.31 and 2.24; 95% CI = 1.35 to 3.71). When obtained (56% of patients), WBC was a predictor of OP, with a positive likelihood ratios of 1.76 (95% CI = 1.40 to 2.22) and 2.17 (95% CI = 1.58 to 2.96) for WBC of >15,000/mm3 and >20,000/mm3, respectively.	4
50. Leventhal JM. Clinical predictors of pneumonia as a guide to ordering chest roentgenograms. *Clin Pediatr (Phila).* 1982;21(12):730-734.	Review/Other-Dx	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
51. 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. *Acta Paediatr.* 2007;96(1):100-104.	Observational-Dx	381 patients	Patients ages1-36 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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
52. Mahabee-Gittens EM, Grupp-Phelan J, Brody AS, et al. Identifying children with pneumonia in the emergency department. *Clin Pediatr (Phila).* 2005;44(5):427-435.	Observational-Dx	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
53. Lynch T, Platt R, Gouin S, Larson C, Patenaude Y. Can we predict which children with clinically suspected pneumonia will have the presence of focal infiltrates on chest radiographs? *Pediatrics.* 2004;113(3 Pt 1):e186-189.	Observational-Dx	570 patients	To determine predictive factors for the presence of focal infiltrates in children with clinically suspected pneumonia in a pediatric emergency department.	Risk factors (OR; 95% CI) for the presence of focal infiltrates included history of fever (3.1; 1.7–5.3), decreased breath sounds (1.4; 1.0–2.0), crackles (2.0; 1.4–2.9), retractions (2.8; 1.0-7.6), grunting (7.3; 1.1–48.1), fever (1.5; 1.2–1.9), tachypnea (1.8; 1.3–2.5), and tachycardia (1.3; 1.0–1.6).The authors used logistic regression to develop a candidate prediction rule for the variables of fever, decreased breath sounds, crackles, and tachypnea, which had an area under the ROC of 0.668. This rule had excellent sensitivity (93.1%–98%) yet poor specificity (5.7%–19.4%).	3
54. Losek JD, Kishaba RG, Berens RJ, Bonadio WA, Wells RG. Indications for chest roentgenogram in the febrile young infant. *Pediatr Emerg Care.* 1989;5(3):149-152.	Review/Other-Dx	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/mm3.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
55. Zukin DD, Hoffman JR, Cleveland RH, Kushner DC, Herman TE. Correlation of pulmonary signs and symptoms with chest radiographs in the pediatric age group. *Ann Emerg Med.* 1986;15(7):792-796.	Observational-Dx	125 patients	Prospective study to determine whether findings on clinical examination are predictive of abnormalities seen on chest radiograph.	The best screen for pneumonia was presence of fever (temperature greater than two standard deviations above age-related norms), with a sensitivity of 94% and a negative predictive value of 97%. The sign with highest positive and negative predictive value for the presence of any radiographic abnormalities was tachypnea. A subgroup with either normal breath sounds, or findings limited to wheezing, prolonged expiration, cough and/or rhonchi on chest examination proved to be at low risk for any major chest radiographic abnormality. Patients with other chest examination findings comprised a high-risk group with a 34% risk of a major radiographic abnormality, as compared to a 7% incidence in the low-risk group.	2
56. Bachur R, Perry H, Harper MB. Occult pneumonias: empiric chest radiographs in febrile children with leukocytosis. *Ann Emerg Med.* 1999;33(2):166-173.	Observational-Dx	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
57. 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. *Pediatr Infect Dis J.* 2000;19(3):187-195.	Experimental-Tx	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.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
58. Clinical policy for children younger than three years presenting to the emergency department with fever. *Ann Emerg Med.* 2003;42(4):530-545.	Review/Other-Dx	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
59. British Thoracic Society Guidelines for the Management of Community Acquired Pneumonia in Childhood. *Thorax.* 2002;57 Suppl 1:i1-24.	Review/Other-Dx	N/A	Guidelines for the Management of Community Acquired Pneumonia in Childhood.	N/A	4
60. Paulus S, Dobson S. Febrile neutropenia in children with cancer. *Adv Exp Med Biol.* 2009;634:185-204.	Review/Other-Dx	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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
61. Korones DN, Hussong MR, Gullace MA. Routine chest radiography of children with cancer hospitalized for fever and neutropenia: is it really necessary? *Cancer.* 1997;80(6):1160-1164.	Review/Other-Dx	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.	Pneumonia was documented by chest radiograph in 4 of the 108 episodes (3.7%) of fever and neutropenia. In 10 of the 108 episodes, the children had abnormal respiratory findings; this group included the 4 children with pneumonia documented by chest X-ray examination. None of the children with normal respiratory findings hospitalized for the remaining 98 episodes had pneumonia. Chest radiographs were not obtained for 40 of the 108 episodes of fever and neutropenia. None of the children with these 40 episodes had respiratory abnormalities and all recovered without a problem. Chest radiographs were obtained for the remaining 68 episodes of fever and neutropenia. Of the four children in this group with pneumonia documented by chest X-ray, two were diagnosed on admission, and another two whose initial radiographs were normal developed pneumonia later in their hospital course. There were no differences in age, absolute neutrophil count, temperature at presentation, or type of malignancy between the children who had chest radiographs and the children who did not.	4
62. Phillips B, Wade R, Westwood M, Riley R, Sutton AJ. Systematic review and meta-analysis of the value of clinical features to exclude radiographic pneumonia in febrile neutropenic episodes in children and young people. *J Paediatr Child Health.* 2012;48(8):641-648.	Meta-analysis	4 studies	To determine the value of the absence of clinical features of lower respiratory tract infection in excluding radiographic pneumonia at presentation of FNP using Centre for Reviews and Dissemination methods.	Synthesis of the 3 higher-quality studies gave imprecise estimates of the average sensitivity (75%; 95% CI, 52% to 89%) and average specificity (69%; 95% CI, 57% to 78%) for clinical examination in the detection of radiographic pneumonia. If the prevalence of pneumonia is 5%, these estimates produce a NPV of 98% (95% CI, 96% to 99%). Alternatively, there remains a 1.9% probability of pneumonia (95% CI, 0.7% to 4.2%).	M
63. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis.* 2002;34(6):730-751.	Review/Other-Dx	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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
64. Cox JA, DeMasi J, McCollom S, Jackson G, Scothorn D, Aquino VM. The diagnostic utility of routine chest radiography in the evaluation of the initial fever in patients undergoing hematopoietic stem cell. *Pediatr Blood Cancer.* 2011;57(4):666-668.	Review/Other-Dx	81 patients	Retrospective review of pediatric stem cell transplant recipients to determine if chest radiographs are useful in the evaluation of initial fever.	76 (94%) of the chest radiographs performed had no evidence of pulmonary infiltrate. Of the 5 children with positive radiographs, 3 had symptomatic respiratory infection and 2 (40%) were asymptomatic. 1 asymptomatic patient had a history of pulmonary infection with persistent stable infiltrates prior to transplantation. This patient did not have any evidence of pneumonia during the transplant. The second asymptomatic patient had subsequent resolution of the infiltrate with antibiotic administration. None of the patients had a change made in the empiric antibiotic regimen based upon the results of the chest film.	4
65. Gasparetto TD, Escuissato DL, Marchiori E. Pulmonary infections following bone marrow transplantation: high-resolution CT findings in 35 paediatric patients. *Eur J Radiol.* 2008;66(1):117-121.	Review/Other-Dx	35 patients	To assess the HRCT findings of pediatric patients who had pulmonary infections following bone marrow transplantation and to evaluate the differential diagnosis through HRCT of the various pathogens responsible for pulmonary infections after bone marrow transplantation.	4 patients with confirmed pneumonia had normal HRCT scans. Regarding the viral infections, the most frequent features were areas of ground-glass attenuation (43.7%) and small centrilobular nodules (31.2%). Airspace consolidation (88.9%), small centrilobular nodules (22.2%) and ground-glass attenuation (22.2%) were the most frequent findings in patients with bacterial pneumonia following bone marrow transplantation. Large nodules were seen in 66.7% of the patients with fungal pneumonia, and in only 1 case of virus infection. The "halo sign" (n=5) was seen only in patients with fungal pneumonia.	4
66. Abdulsalam AM, Al-Jahdali HH, Memish ZA, Ahmad AH. Fever of unknown origin. Experience of a large tertiary care hospital in Saudi Arabia. *Saudi Med J.* 2005;26(2):352-354.	Review/Other-Dx	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
67. Arce-Salinas CA, Morales-Velazquez JL, Villasenor-Ovies P, Muro-Cruz D. Classical fever of unknown origin (FUO): current causes in Mexico. *Rev Invest Clin.* 2005;57(6):762-769.	Review/Other-Dx	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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
68. Ciftci E, Ince E, Dogru U. Pyrexia of unknown origin in children: a review of 102 patients from Turkey. *Ann Trop Paediatr.* 2003;23(4):259-263.	Review/Other-Dx	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
69. Tsukahara M, Tsuneoka H, Iino H, Murano I, Takahashi H, Uchida M. Bartonella henselae infection as a cause of fever of unknown origin. *J Clin Microbiol.* 2000;38(5):1990-1991.	Review/Other-Dx	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
70. Steele RW, Jones SM, Lowe BA, Glasier CM. Usefulness of scanning procedures for diagnosis of fever of unknown origin in children. *J Pediatr.* 1991;119(4):526-530.	Review/Other-Dx	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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
71. 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. *Eur J Intern Med.* 2011;22(1):112-116.	Observational-Dx	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
72. 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. *Intensive Care Med.* 2010;36(3):504-511.	Observational-Dx	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. 3 FDG-PET/CT scans were considered false positive, in 1 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.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
73. 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. *Eur J Radiol.* 2011;80(3):834-844.	Meta-analysis	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.	M
74. Hao R, Yuan L, Kan Y, Li C, Yang J. Diagnostic performance of 18F-FDG PET/CT in patients with fever of unknown origin: a meta-analysis. *Nucl Med Commun.* 2013;34(7):682-688.	Meta-analysis	15 studies	To systematically review and perform a meta-analysis of published data on the diagnostic value of FDG-PET/CT in the diagnosis of patients with FUO.	15 studies comprising 595 patients with FUO were included in this meta-analysis. The pooled sensitivity of FDG-PET/CT in detecting the cause of FUO was 85% (95% CI, 81%–88%) on a per-patient-based analysis. The area under the ROC curve was 0.88.	M
75. Crouzet J, Boudousq V, Lechiche C, et al. Place of (18)F-FDG-PET with computed tomography in the diagnostic algorithm of patients with fever of unknown origin. *Eur J Clin Microbiol Infect Dis.* 2012;31(8):1727-1733.	Observational-Dx	79 patients	To evaluate the clinical value of FDG-PET/CT in patients with FUO and identify patients who need early FDG-PET/CT rather than a last-resort procedure.	A total of 79 patients (36 men, 43 women, mean age 54.0 +/- 16.2 years) with FUO underwent FDG-PET/CT. A final diagnosis was established in 61 (77.2 %) cases. Etiologies of FUO were determined using FDG-PET/CT findings in 45 (73.8 % of patients with diagnosis) cases. The sensibility and specificity value were 98% and 87%, respectively. The presence of adenopathy, low hemoglobin and increased C-reactive protein were predictors of high-yield FDG-PET/CT. FDG-PET/CT may help to detect most causes of FUO. The predictors of high-yield FDG-PET/CT found in this study can help identify patients likely to benefit from specific and early imaging techniques.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
76. Darge K, Jaramillo D, Siegel MJ. Whole-body MRI in children: current status and future applications. *Eur J Radiol.* 2008;68(2):289-298.	Review/Other-Dx	N/A	To review the current status and future of WB-MRI in children.	WB-MRI is a sensitive method for imaging the entire body in a short time. It is a reliable alternative to conventional imaging for detecting metastatic disease, especially skeletal metastases. An important advantage of this technique is the absence of ionizing radiation. For young patients in particular, undergoing serial longitudinal follow-up examinations, WB-MRI offers a radiation free alternative to scintigraphy and CT for diagnosis, staging and monitoring.	4
77. Korchi AM, Hanquinet S, Anooshiravani M, Merlini L. Whole-body magnetic resonance imaging: an essential tool for diagnosis and work up of non-oncological systemic diseases in children. *Minerva Pediatr.* 2014;66(3):169-176.	Review/Other-Dx	42 children	To determine the real impact of WB-MRI on diagnosis and management of non-oncological pediatric diseases remains unclear. The authors present their experience of pediatric WB-MRI in various pathologies.	21 children underwent general anesthesia. WB-MRI was a useful tool to provide correct diagnosis in chronic recurrent multifocal osteomyelitis, and to identify the origin of fever or arthralgia of unknown etiology. WB-MRI allowed to determine the extent of disease in juvenile idiopathic arthritis, chronic granulomatous disorder, enchondromatosis, Langerhans cell histiocytosis, and in the assessment of tumor burden in neurofibromatosis type I. For the battered child syndrome, the influence on management was rather minimal. For each of these pathologies we performed a review of recent literature.	4
78. Ley S, Ley-Zaporozhan J, Schenk JP. Whole-body MRI in the pediatric patient. *Eur J Radiol.* 2009;70(3):442-451.	Review/Other-Dx	N/A	To review WB-MRI in pediatric patients.	WB-MRI is a fast and accurate modality for detection and monitoring of disease throughout the entire body. For pediatric use the technique is of special interest twofold: first it is a radiological method without radiation exposure and second it allows for whole-body staging as well as for detailed local evaluation for surgical treatment thus reducing the number of examinations to be performed in sedation. In the pediatric population the technique is used for oncological, non-oncological (ie, FUO, osteonecrosis) staging and for disease severity assessment of syndromes affecting the whole body.	4

Fever without Source or Unknown Origin-Child
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
79. Purz S, Sabri O, Viehweger A, et al. Potential Pediatric Applications of PET/MR. *J Nucl Med.* 2014;55(Supplement 2):32S-39S.	Review/Other-Dx	N/A	To review possible pediatric applications of PET/MR hybrid imaging, particularly pediatric oncology and neurology but also the diagnosis of infectious or inflammatory diseases.	For noninvasive pediatric diagnostics, molecular imaging and WB-MRI have become important, especially in pediatric oncology. Because it has a lower radiation exposure than PET/CT, combined PET/MR is expected to be of special use in pediatric diagnostics.	4

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.
- M = Meta-analysis

Dx = Diagnostic

Tx = Treatment

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

SBI = Serious bacterial infection

US = Ultrasound

WBC = White blood cell

WB-MRI = Whole-body magnetic resonance imaging