Nosocomial Fever of Unknown Origin

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Case

A 28-year-old woman was admitted to the intensive care unit with severe respiratory distress secondary to uncontrolled asthma. In spite of standard acute asthma therapy, the patient's mental status deteriorated, and she developed severe hypoxia requiring intubation. On day two of admission, the patient developed a fever of 38.7°C that persisted for four days without any known etiology after extensive laboratory work-up, chest x-rays, and an abdominal ultrasound. She is diagnosed with nosocomial fever of unknown origin. What is the appropriate work-up and management for patients with nosocomial fever of unknown origin, and what additional tests might help evaluate patients who are intubated?

Discussion

Fever is often a self-limiting occurrence in which an etiology can be promptly determined. However, in some circumstances fever can persist for an extended period of time without an identifiable cause in spite of an extensive work-up. This clinical scenario is called fever of unknown origin (FUO).[1,2] Four categories of FUO are defined in Table 1. All categories share a temperature threshold of >38.3°C with varying duration, patient location, and confounding diagnoses.

In pediatric hematology/oncology patients, bacteremia and fever of unknown origin were identified as the most common nosocomial infections.[4] In a study of adult hematology/oncology patients, 33 FUOs were documented in 116 patients hospitalized for a total of 4,002 days, with 66.7% of the FUOs occurring when the patients were neutropenic.[5]

Table 1: Durack and Street classification of fever of unknown origin[3]

Category	Distinguishing Factors
Classic	>3 weeks Evaluation of ≥3 visits or 3 days in the hospital
Nosocomial	Patient hospitalized ≥24 hours without fever being present or incubating on admission Evaluation of at least 3 days
Neutropenic	Evaluation of at least 3 days with absolute neutrophil count ≤500 per mm^3
HIV associated	>4 weeks for outpatient and >3 days for inpatients with confirmed HIV infection

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DOI: 10.12746/swrccc2015.0311.139

FUOs have multiple causes, and the list of diagnoses has changed over time secondary to widespread use of antibiotics, increased knowledge of disease pathology, and advances in diagnostic testing. For example, early imaging utilization has decreased the proportion of FUO caused by intra-abdominal abscesses and tumors. Infection continues to be the predominant cause of FUO followed by neoplasms and noninfectious inflammatory diseases. FUO is often caused by atypical presentations of common diseases, with endocarditis, diverticulitis, vertebral osteomyelitis, and extrapulmonary tuberculosis being the most frequent. The prevalence of infection as a leading cause is even more significant in non-Western nations, where tuberculosis accounts for up to 50% of cases in some countries.[2] In some cases nosocomial fever occurs in postoperative patients after the release of cytokines and interleukins from tissue injury and not infection.[6] In a prospective cross sectional study conducted in pediatric and adult ICUs (n=63), 82% of patients with nosocomial FUO were found to have acute bacterial nosocomial sinusitis diagnosed by microbiological analysis of sinus fluid aspirates.[7] Other common causes of nosocomial FUO include drug fever, health care associated infections, thrombosis, pulmonary embolism, and neoplasm.[2]

Evaluation of FUO

FUO is a diagnosis made after thorough history taking, physical examination, and obligatory investigations as listed in Table 2. No symptom should be regarded as irrelevant due to the likelihood of atypical manifestations of common diseases with FUO. Repeating the history taking by different members of the team and gathering information from family and friends of the patient can also be valuable.[1,2]

In addition to imaging by chest x-ray and abdominal ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) are often used. Since localizing signs or symptoms are often absent, clinicians have started to use positron emission tomography/computed tomography (PET/CT) to detect focal sites of inflammation.[8] Sinusitis develops frequently in patients with orotracheal or nasotracheal intubation, limited mobilization, facial trauma, or prior sinus disease, and can be detected with sinus x-rays, ultrasound, or CT scans as part of the work-up for FUO.[9]

Case conclusion

Our 28-year-old patient has nosocomial fever of unknown origin and is currently intubated. She underwent the obligatory laboratory and imaging studies done for an FUO work-up, and later had sinus x-rays due to her intubation status. Other considerations included drug fever and venous thromboembolic disease. Additionally, reevaluating the patient's history and physical examination and speaking with family and friends of the patient brought attention to a previous history of sinus disease. With the additional studies our patient was found to have acute bacterial nosocomial rhinosinusitis and was started on the appropriate antibiotic treatment. Patients with FUO usually have good outcomes even without a diagnosis, and if there is no indication for a particular etiology, subsequent approaches include a "wait and see" strategy, whole body inflammation tracer scintigraphy, a staged approach, or therapeutic trials.[10]

Key points

1. There are four classifications of FUO, all requiring a fever >38.3°C and an extensive work-up (Table 1).
2. A thorough history and physical are crucial in determining the etiology of FUO, as atypical manifestations of common diseases often occur.
3. In patients who have been intubated, diagnostic imaging for sinusitis can be a valuable addition to the FUO work-up.

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Received: 04/25/2015
Accepted: 05/10/2015
Reviewers: Richard Winn MD
Published electronically: 7/15/2015
Conflict of Interest Disclosures: None

Table 2: Initial evaluation for FUO		
Specific factors to address in history for suspected FUO[1]		
Sick contacts	Prosthetic devices	Living & working conditions
Tuberculosis exposure	Psychiatric illness	Recreational activities
Previous chronic infections	Prescribed medications	Dietary habits
History of transfusions	Over the counter medications	Recreational drugs
Diagnosis of malignancies	Herbal remedies	Sexual activity
Immunosuppressive therapy	Country of origin	Animal exposure
Indwelling foreign materials	Vaccination status	Travel history
Specific factors to address in physical examination for suspected FUO[1]		
Fundi	Thyroid gland	Genital area
Conjunctivae	Lymphatic system	Pulses
Oropharynx	Heart murmurs	Skin
Temporal artery	Abdomen	Joints
Obligatory laboratory and imaging investigations[2]		
Erythrocyte sedimentation rate	Total protein	Rheumatoid factor
C-reactive protein	Alkaline phosphatase	Protein electrophoresis
Platelet count	Alanine aminotransferase	Urinalysis
Leukocyte count	Aspartate aminotransferase	Blood cultures (n=3)
Leukocyte differential	Lactate dehydrogenase	Urine culture
Electrolytes	Creatine kinase	Tuberculin skin test
Creatinine	Ferritin	Chest x-ray
Hemoglobin	Antinuclear antibodies	Abdominal ultrasonography

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