FEVER UNKNOWN ORIGIN (FUO)

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DEFINITION

Temperatures of $>38.3^\circ\text{C}$ on several occasions

Duration of fever of $>3$ weeks

Uncertain diagnosis after one week in hospital
CLASSIFICATION

classic  nosocomial  Neutropenic
neutrophil count is <500/ L  associated with HIV infection
ETIOLOGY

- Unidentified cause
- Infections
- Noninfectious inflammatory diseases
- Miscellaneous
- Neoplasms
# Symptoms Associated with Fever

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency (n=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>69 (47.9%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>63 (43.7%)</td>
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<tr>
<td>Decreased activity</td>
<td>54 (37.5%)</td>
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<tr>
<td>General body ache/pain</td>
<td>52 (36.1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>48 (33.3%)</td>
</tr>
<tr>
<td>Excessive cry</td>
<td>45 (31.2%)</td>
</tr>
<tr>
<td>Passage of loose stools</td>
<td>45 (31.2%)</td>
</tr>
<tr>
<td>Cough</td>
<td>45 (31.2%)</td>
</tr>
<tr>
<td>Runny nose</td>
<td>39 (27.1%)</td>
</tr>
<tr>
<td>Shivering</td>
<td>39 (27.1%)</td>
</tr>
<tr>
<td>Passage of yellow coloured urine</td>
<td>30 (20.8%)</td>
</tr>
<tr>
<td>Excessive sweating</td>
<td>30 (20.8%)</td>
</tr>
<tr>
<td>Yellowness of the eye</td>
<td>27 (18.7%)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>27 (18.7%)</td>
</tr>
<tr>
<td>Fretfulness</td>
<td>27 (18.7%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24 (16.7%)</td>
</tr>
<tr>
<td>Flushing of the face</td>
<td>21 (14.6%)</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>15 (10.4%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (10.4%)</td>
</tr>
<tr>
<td>Shortage of blood</td>
<td>3 (2.1%)</td>
</tr>
</tbody>
</table>

* Frequency indicates multiple responses
Timing is essential.
<table>
<thead>
<tr>
<th>Cause</th>
<th>Cases %</th>
</tr>
</thead>
<tbody>
<tr>
<td>None identified</td>
<td>19</td>
</tr>
<tr>
<td>Miscellaneous causes</td>
<td>13</td>
</tr>
<tr>
<td>Factitious causes</td>
<td>9</td>
</tr>
<tr>
<td>Granulomatous hepatitis</td>
<td>8</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>7</td>
</tr>
<tr>
<td>Still's disease</td>
<td>6</td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>4</td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>3</td>
</tr>
</tbody>
</table>
CAUSES OF FUO IN ADULTS

Infections ≈ 36%

Localized pyogenic infections
Appendicitis
Cat-scratch disease
Cholangitis
Cholecystitis
Dental abscess
Diverticulitis/abscess
Lesser sac abscess
Liver abscess
Mesenteric lymphadenitis
Osteomyelitis

Pancreatic abscess
Pelvic inflammatory disease
Perinephric/intrarenal abscess
Prostatic abscess
Renal malacoplakia
Sinusitis
Subphrenic abscess
Suppurative thrombophlebitis
Tuboovarian abscess
CAUSES OF FUO IN ADULTS

Infections 36%

Intravascular infections
- Legionnaires' disease
- Leptospirosis
- Listeriosis
- Lyme disease
- Melioidosis
- Meningococcemia
- Rat-bite fever
- Relapsing fever
- Salmonellosis
- Syphilis
- Tularemia
- Typhoid fever
- Vibriosis
- Yersinia infection

Systemic bacterial infections
- Bartonellosis
- Brucellosis
- Campylobacter infection
- Cat-scratch disease/bacillary angiomatosis (B. henselae)
- Gonococcemia
CAUSES OF FUO IN ADULTS

Infections

Mycobacterial infections
M. avium/M. intracellulare infections
Other atypical mycobacterial infections
Tuberculosis

Rickettsial infections
Anaplasmosis
Ehrlichioses
Murine typhus
Q fever
Rickettsialpox
Rocky Mountain spotted fever
Scrub typhus

Other bacterial infections
Actinomycosis
Bacillary angiomatosis
Nocardiosis
Whipple's disease
CAUSES OF FUO IN ADULTS

Infections

Mycoplasmal infections
Chlamydial infections
Lymphogranuloma venereum
Psittacosis
TWAR (C. pneumoniae) infection

Viral infections
Chikungunya fever
Colorado tick fever

Coxsackievirus group B infection
Cytomegalovirus infection
Dengue
Epstein-Barr virus infection
Hepatitis A, B, C, D, and E HIV infection
Human herpesvirus 6 infection
Lymphocytic choriomeningitis
Parvovirus B19 infection
Picornavirus infection
CAUSES OF FUO IN ADULTS

Infections

Fungal infections
Aspergillosis
Blastomycosis
Candidiasis
Coccidioidomycosis
Cryptococcosis
Histoplasmosis
Mucormycosis
Paracoccidioidomycosis
Pneumocystis infection
Sporotrichosis

Parasitic infections
Amebiasis
Babesiosis
Chagas' disease
Leishmaniasis
Malaria
Strongyloidiasis
Toxocariasis
Toxoplasmosis
Trichinellosis

Presumed infections, agent undetermined
Kawasaki's disease (mucocutaneous lymph node syndrome)
Kikuchi's necrotizing lymphadenitis
CAUSES OF FUO IN ADULTS

Neoplasms ≈ 15 %*

Malignant
Colon cancer
Gall bladder carcinoma
Hepatoma
Hodgkin's lymphoma
Immunoblastic T-cell lymphoma
Leukemia
Lymphomatoid granulomatosis
Malignant histiocytosis
Non-Hodgkin's lymphoma
Pancreatic cancer

Renal cell carcinoma
Sarcoma

Benign
Atrial myxoma
Castleman's disease
Renal angiomyolipoma

*Chinese Anti-Cancer Association and Springer-Verlag Berlin Heidelberg 2012
CAUSES OF FUO IN ADULTS

Habitual Hyperthermia
(Exaggerated circadian rhythm)

Collagen
Vascular/Hypersensitivity Diseases ≈19%

Adult Still's disease
Behçet's disease
Erythema multiforme
Erythema nodosum
Giant-cell arteritis/polymyalgia rheumatica
Hypersensitivity pneumonitis

Hypersensitivity vasculitis
Mixed connective-tissue disease
Polyarteritis nodosa
Relapsing polychondritis
Rheumatic fever
Rheumatoid arthritis
Schnitzler's syndrome
Systemic lupus erythematosus
Takayasu's aortitis
Weber-Christian disease
Granulomatosis with polyangiitis
(Wegener's)
CAUSES OF FUO IN ADULTS

Granulomatous Diseases
- Crohn's disease
- Granulomatous hepatitis
- Midline granuloma
- Sarcoidosis

Miscellaneous Conditions
- Gout
- Hematomas
- Hemoglobinopathies
- Laennec's cirrhosis
- PFPA syndrome: periodic fever, adenitis, pharyngitis, aphthae
- Postmyocardial infarction syndrome
- Recurrent pulmonary emboli
- Subacute thyroiditis (de Quervain's)
- Tissue infarction/necrosis
CAUSES OF FUO IN ADULTS

Inherited and Metabolic Diseases
- Adrenal insufficiency
- Cyclic neutropenia
- Deafness, urticaria, and amyloidosis
- Fabry disease
- Familial cold urticaria
- Familial Mediterranean fever
- Hyperimmunoglobulinemia D and periodic fever
- Muckle-Wells syndrome
- Tumor necrosis factor receptor–associated periodic syndrome (familial Hibernian fever)

Thermoregulatory Disorders
- Central
- Brain tumor
- Cerebrovascular accident
- Encephalitis
- Hypothalamic dysfunction
- Peripheral
- Hyperthyroidism
- Pheochromocytoma

Factitious Fevers
- "Afebrile" FUO [<38.3°C (100.94°F)]

Type V hypertriglyceridemia
FEVER OF UNKNOWN ORIGIN OR FEVER OF TOO MANY ORIGINS?
Other Useful Procedures

Fundoscopy

- Infections
  - Choroidal lesions
- Malignancies
  - Choroidal metastases
- Vasculitis
  - Cotton-wood exsudates
- Sarcoidosis
  - Perivascular sheathing
TREATMENT

Continued observation and examination

Antibiotic therapy

Vital-sign instability or neutropenia
OUTCOME, CONCLUSIONS

Many FUO end up with no definitive diagnosis

About 50% of people without diagnosis improve within hospitalization or soon thereafter

15% have persistent fever that lasts at least 1 year

Rarely does death develop from fuo-five-year mortality of 3.2%.
NEW STUDIES

H. Balink et al. – A Rationale for the Use of F18-FDG PET/CT in Fever and Inflammation of Unknown Origin, International Journal of Molecular Imaging, 2012

Sherman JM et al. – Current challenges in the diagnosis and management of fever, Pediatr., 2012

Crouzet J 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

Manohar K et al. – F-18 FDG-PET/CT in evaluation of patients with fever of unknown origin, Jpn J Radiol, 2013

Nazar et al. – Spectrum of 18F-FDG PET/CT findings in patients presenting with fever of unknown origin, AJR, 2012
2001-2007
- F 18-FDG PET
- 39% standalone
- 67% final diagnosis

2008-2012
- F 18-FDG PET/CT hybrid
- 57% standalone
- 73% final diagnosis
THE FUTURE
Thank you for your attention!

Happy Women's Day!