Modern Approach to Pyrexia of Unknown Origin

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Pyrexia of Unknown Origin (PUO)

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Fever of Unknown Origin (FUO)

(more commonly used in literatures)

Fever of unknown origin (FUO)

- Illness of more than 3 week's duration.
- Fever greater than 38.3° C (101°F) on several occasions.
- Cause uncertain after 1 week of in-hospital investigation.

*Peterdorf and Beeson. Medicine **1961**;40, 1-30.*

FUO redefined

- **CLASSICAL FUO**
  - duration ≥ 3 weeks
  - fever ≥ 38.3° C (101° F)
  - cause uncertain after 3 days despite appropriate in-hospital investigation or 3 out-patient visits
- **NOSOCOMIAL FUO**
- **NEUTROPENIC FUO**
- **HIV-ASSOCIATED FUO**

D.T. Durack & A.C. Street.
*Curr Clin topics Infect Dis **1991**; 11, 35-51.*

- **NOSOCOMIAL FUO**
  - hospitalized patients
  - fever ≥ 38.3°C (101°F) on several occasions
  - infection not present or incubating on admission
  - diagnosis uncertain after 3 days despite appropriate investigations
- **NEUTROPENIC FUO**
  - neutrophil count is $<0.5 \times 10^6$/L or is expected to fall to that level in 1 to 2 days
  - fever ≥ 38.3°C (101°F) on several occasions
  - diagnosis uncertain after 3 days despite appropriate investigations
- **HIV-ASSOCIATED FUO**
  - confirmed HIV infection
  - fever ≥ 38.3°C (101°F) on several occasions
  - duration of > 4 weeks (out-patients), or > 3 days (hospitalized patients)
  - diagnosis uncertain after 3 days despite appropriate investigations

*D.T. Durack & A.C. Street. Curr Clin Topics Infect Dis **1991**, 11, 35-51*

Causes of classical FUO

Infections	22-58%
Neoplasms	up to 30%
Noninfectious inflammatory diseases	up to 25%
Miscellaneous causes	up to 25%
Undiagnosed	up to 30%

Bacterial infections - Abscess (dental; intraabdominal e.g. liver, spleen, psoas; pelvic)
Pyomyositis
Loculated effusion/obstruction not drained
Osteomyelitis, spine infection
Prosthetic infection, catheter related infection
Infective endocarditis, pericarditis
Mycotic aneurysm
Biliary tract infections
Occult urinary tract infection, renal/perinephric abscesses
Extrapulmonary tuberculosis/ miliary tuberculosis/MOTT
Salmonella infections
Clostridium difficile colitis
Cat scratch disease, Tularemia, Yersiniosis
Brucellosis, Melioidosis, Nocardiosis, Rhodococcosis
Q fever, spirochaetal, rickettsial, mycoplasma, chlamydial infections (include psittacosis)

Fungal (e.g. candidiasis, cryptococcosis, aspergillosis, pneumocystis jiroveci, mucormycosis, histoplasmosis, penicilliosis, other endemic fungi)

Viral infection (e.g. acute HIV; HHV8 associated Castleman's Disease; CMV infection, EBV infectious mononucleosis, parvovirus B19 infection)

Parasitic infections (e.g. malaria, Amoebic liver abscess)

Neoplastic diseases

- Tumours may cause fever in their own right
- Solid tumours may cause luminal obstruction & secondary infection e.g. bronchus, bile duct

Hodgkin's lymphoma
Non-Hodgkin's lymphoma
Leukaemias (include aleukemic type)
Myelodysplasia, Multiple myeloma
Renal cell carcinoma
Adenocarcinomas of the breast
HCC/ metastasis to liver
Colonic cancer
Lung cancer
Kaposi sarcoma
Sarcoma
Pancreatic tumor
Atrial myxoma
Disseminated carcinomatosis

Hypersensitivity & autoimmune diseases

1. Systemic lupus erythematosus
2. Rheumatoid arthritis
3. Rheumatic fever
4. Adult Onset Still's disease
5. Macrophage Activation Syndrome/ Hemophagocytosis Syndrome
6. Temporal arteritis (giant cell arteritis)
7. Polymyalgia rheumatica
8. Polyarteritis nodosa
9. Microscopic polyangiitis, Churg-Strauss Syndrome, Wegener's granulomatosis (ANCA sensitive for these)
10. Vasculitis (e.g. Takayasu)
11. Hypersensitivity vasculitis
12. Cryoglobulinemic vasculitis
13. Behcet's disease
14. Relapsing polychondritis
15. Antiphospholipid syndrome
16. Mixed connective tissue disease
17. Hypersensitivity pneumonitis

Miscellaneous causes of Classic FUO

- Kikuchi's Disease
- Sarcoidosis
- Inflammatory bowel disease (ulcerative colitis, Crohn's disease)
- Granulomatous hepatitis
- Alcoholic hepatitis
- Thrombophlebitis
- Deep vein thrombosis
- Recurrent pulmonary emboli
- Thrombotic thrombocytopenic purpura
- Subacute thyroiditis
- Adrenal insufficiency
- Gout, pseudogout
- Hematoma (e.g. retroperitoneal space, aortic dissection/aneurysm, hip, pelvis)
- Heriditary periodic fever syndromes
- Immune reconstitution inflammatory syndrome (IRIS)- especially TB and MAC
- Sweet's Syndrome
- Hyperthermia syndrome
- Drug fever
- Factitious fever

CAUSES OF HYPERTHERMIA SYNDROME

- Heat stroke: Exercise, Anticholinergic
- Drug induced: Cocaine, Amphetamine,MAO inh.
- Neuroleptic malignant syndrome:Phenothiazine
- Malignant hyperthermia: Inhalational anesthetics
- Endocrinopathy: thyrotoxicosis, pheochromocytoma
- Hypothalamic fever– cerebral trauma, haemorrhage, massive stroke or anoxic brain injury

DRUG FEVER

- PATHOGENESIS
  - Contamination of the drug with a pyrogen or microorganism
  - Related to the pharmacologic action of the drug itself (e.g amphotericin B)
  - Allergic (hypersensitivity) reaction to the drug

DRUG FEVER

- Fever out of proportion to clinical picture
- Pattern of fever variable
- Associated findings:
  - Rigor (43%), Myalgia (25%), Rash (18%), Headache (18%),
  - Leukocytosis (22%), Eosinophilia (22%), Serum sickness (fever, swelling, rash, LN enlargement), Proteinuria, Abnormal liver function test

DRUG FEVER

- Onset and duration:
  - Onset: Typically occur 7 to 10 days (can be up to 21 days) after initiation
  - Usually resolves within 48 hrs after discontinuation of the drug (depending on the half-life of the drug)

Most common drugs that cause fever

- Sulfa drugs
- Dapsone
- Pentamidine
- Clindamycin
- Penicillins
- Cephalosporins
- Macrolides
- Aminoglycosides
- Vancomycin
- Nitrofurantoin
- Amphotericin
- Isoniazid
- Rifampicin
- Abacavir
- Nevirapine
- NRTI-lactic acidosis
- Fosamprenavir
- Interferons
- Phenytoin
- Barbiturate
- Carbamazepine
- Hydralazine
- Methyldopa
- Procainamide
- Quinidine
- Haldol
- Amphetamines
- Iodide
- Allopurinol
- Antihistamine
- NSAID

FACTITIOUS FEVER

- Diagnosis should be considered in any FUO, especially in:
  - Young women
  - Persons with medical training
  - If the patients clinically well
  - Disparity between temperature and pulse
  - Absence of the normal diurnal pattern
  - Many have features of Munchausen syndrome

Time for a change in the definition of fever of unknown origin (FUO)

- Neither in the original definition nor in the currently-used definition of FUO, none of the word ‘‘workup’’ or its intensity has been defined clearly. In this way, a patient who is labeled as a case of FUO in one hospital with limited access to new diagnostic tests, might have soon been found to have tuberculosis in another well-equipped hospital.
- Reasonably, only those centers with access to the specified required diagnostic techniques are authorized to label a patient as having FUO.

J Infect. 2008 Aug;57(2):166-7. Epub 2008 Jun 30.

What is fever for adults?

- Fever is present if:
  Temperature in the mouth (oral) is over 37.5 ˚C (99.5 ˚F)

- In UCH, we use the Genius 2 Infrared Tympanic Electronic Thermometer (set at Oral mode).
  Temperature > 37.5 ˚C is regarded as fever.

My proposal for management of patients with fever

- Temperature > 37.5 ˚C by using the Genius 2 Infrared Tympanic Electronic Thermometer (set at Oral mode) is regarded as fever.
- Go through a diagnostic Fever checklist for patients with unexplained fever

Fever Checklist

1. Detailed history
2. Careful (repeated) physical examination
3. Appropriate laboratory tests
4. Appropriate imaging
5. Invasive procedures
    1. Endoscopy
    2. Biopsy

Fever Checklist

Detailed History

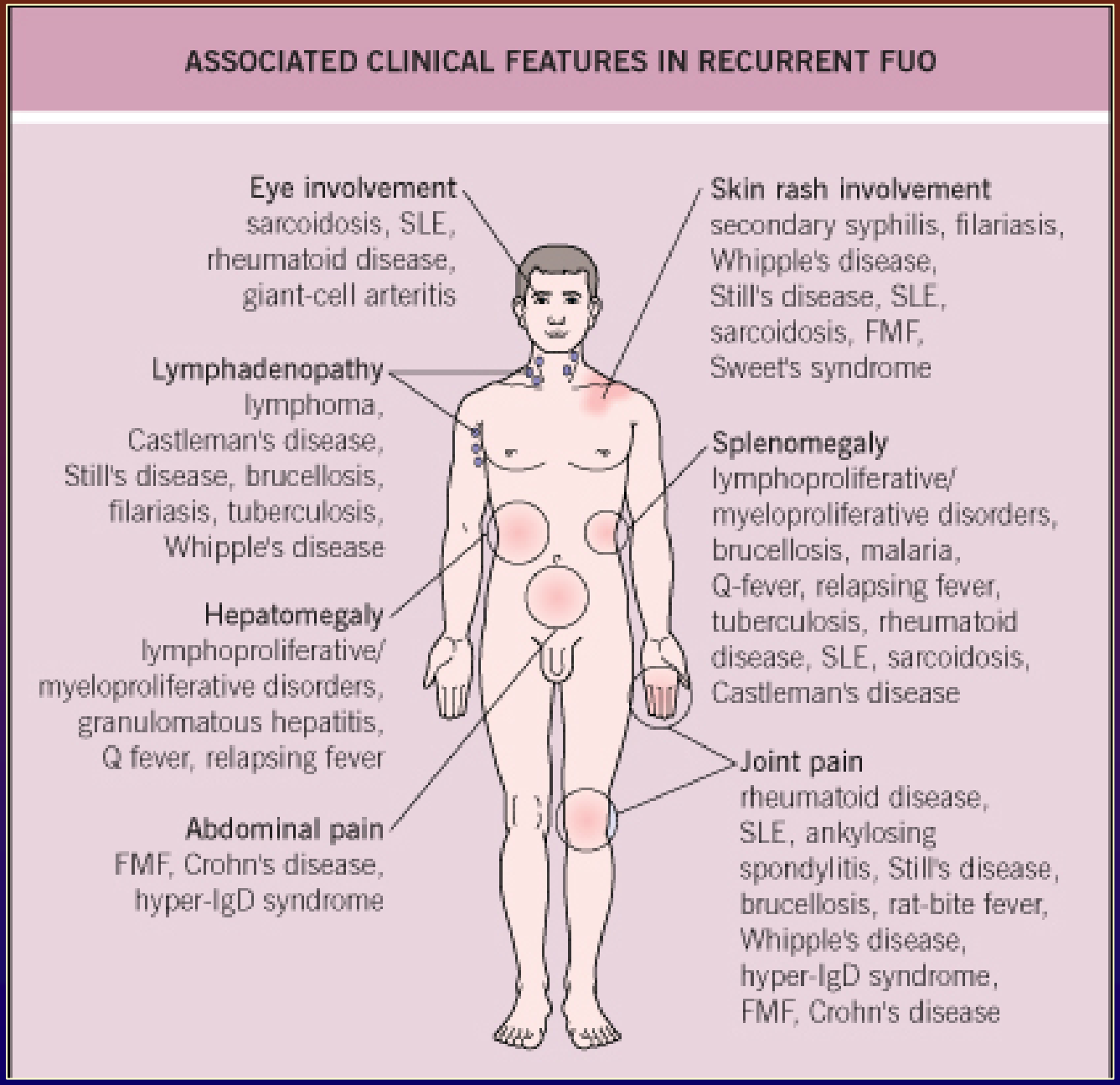
- Diagnostic approach to adults with prolonged unexplained fever
  - Inquire about symptoms from all major organ systems, including a detailed history of general complaints (eg fever, weight loss, night sweats, headaches, rashes).
  - Record all complaints, even if they disappeared before the examination. Previous illnesses are important, including surgeries and psychiatric illnesses.
  - Provide a detailed evaluation including the following:
    - Family history
    - Immunization status
    - Occupational history
    - Travel history
    - Nutrition
    - Drug history (over-the-counter medications, prescription medications, illicit substances)
    - Sexual history
    - Recreational habits
    - Animal contacts (including possible exposure to ticks and other vectors)

Fever Checklist

Careful Physical Examination

- Definitive documentation of fever
- The pattern of fever (continuous, remittent, intermittent) usually is of little help in the evaluation.
  - In general, correlation between fever patterns and specific diseases is weak. Notable exceptions are tertian and quartan malaria.
  - Other diseases (eg, brucellosis, borreliosis, Hodgkin disease) tend to cause recurrent episodes of fever.
- Repeat a regular physical examination daily while the patient is hospitalized. Pay special attention to rash, new or changing cardiac murmurs, signs of arthritis, abdominal tenderness or rigidity, lymph node enlargement, fundoscopic changes, and neurologic deficits.

Fever Checklist



Fever Checklist

Tests & initial imaging based on clinical presentation and system involved:

- CBC (with differential count), ESR, CRP
- LRFT, glucose, PT APTT
- CK, LDH, D-dimer, amylase
- Urine analysis
- NPS/NPA x influenza A/B Ag & PCR, viral culture
- C/ ST (e.g. blood, sputum, urine, wound)
  - Prolong blood C/ST to 14 days for suspected endocarditis/ fungemia (need to specify in request)
- Stool exam (eg viral study, C/ST, ova & cyst, Amoeba, *Clostridium difficile* toxin)
- Sputum/gastric lavage x AFB smear + C/ST x 3
- CXR, X ray of relevant regions
- CT Brain
- Lumbar puncture for CSF examination
- Peripheral blood smear
- Tumor markers (CEA, AFP, PSA)
- TFT
- Serum immunoelectrophoresis, Ig pattern
- ANA, anti ds-DNA, C3, C4, anti ENA, RF, ANCA
- Cryoglobulin
- Ferritin
- MT2 (can be falsely negative for TB)
- Respiratory tract specimen x PCR TB DNA
- EMU x AFB x 3
- Relevant body fluid (e.g. joint, pleural, peritoneal, pericardial) x cell count, protein, glucose. pH, Gram stain & C/ST, AFB smear & C/ST, cytology, fungal culture
- Urine x *Legionella pneumophila* Ag, pneumococcal Ag
- Blood x Malaria screen
- HIV Ab, CD4 count if HIV Ab +ve
- Serology tests:
  - Atypical pneumonia (paired), Mycoplasma pneumoniae IgM, VDRL, Widal test, Weil-felix test (paired), Rickettsial serology (paired), Coxiella burnetii serology (paired), Brucella serology (paired), Monospot test, EBV VCA IgM, EBV EBNA IgG, hepatitis serology, Dengue (IgM/ IgG), Leptospirosis serology (paired), Parvovirus B19 serology (IgM/IgG), Hantavirus serology (paired), CMV IgM, JEV serology
- Sputum x fungal culture/ Nocardia/ Rhodococcus
- Sputum x *Pneumocystis jiroveci* (Cytology Lab)

Fever Checklist

Further microbiological tests for PUO (prior arrangement required)

- Differential time to positivity (blood C/ST from peripheral vein and catheter lumens)- for determination of catheter-related sepsis
- Serology e.g. HTLV1 serology, *Burkholderia pseudomallei* serology, *Bartonella henselae* serology, Aspergillus antibody, *Penicillium marneffei* antibody, *Histoplasma* antibody, *Toxoplasma* IgM/IgG, Amoebic IgG, Cysticercosis serology
- Respiratory tract specimen x PCR *Chlamydia psittaci*
- Blood x cryptococcal Ag
- Blood x AFB culture (Bactec bottle)
- Fresh blood for CMV pp65
- Clotted blood for galactomannan, (1-->3)-beta-D-Glucan

ANCA

antineutrophil cytoplasmic antibodies

Table 4.4 Disease associations of antiproteinase 3 antibodies and antimyeloperoxidase antibodies*

C-ANCA p-ANCA

Disease entity	*Sensitivity*	
	antiproteinase 3 (%)	*antimyeloperoxidase* (%)
Wegener's granulomatosus	85	10
Microscopic polyangiitis	45	45
Idiopathic crescentic glomerulonephritis	25	65
Churg–Strauss syndrome	10	60
Polyarteritis nodosa	5	15

*Data derived from the references cited in the text.

Kallenberg CGM.
The vasculitides: Science and Practice, 1996: 48-64.

Fever Checklist

Other Imaging that may be considered after clinical assessment:

- Ultrasonography
- Echocardiogram
- HRCT thorax (plain)
- CT (contrast) of suspected region(s) (e.g. thorax, abdomen, pelvis)
  - Avoid CT (contrast) if the patient has severe renal failure
  - For mild renal failure, CT (contrast) may still be proceeded.
    - Encourage fluid intake/NS infusion before CT (contrast)
    - Acetylcysteine 600mg bd po x 2 days (the day before CT; the day for CT)
- CT pulmonary angiogram for suspected pulmonary embolism
- Venous Doppler US of leg for suspected deep vein thrombosis
- MRI (contrast) if there is suspected localized pathology (especially for extremity bone/ spine infection)
  - Avoid MRI (contrast) if there the patient has renal failure
- Bone scan
- Gallium SPECT/CT
- PET-CT

PET-CT

- Guide further investigation by detecting site of lesion
- Good at detection of inflammatory lesion (infective/non-infective) and solid tumor
  - high negative predictive value in ruling out these lesions
- Large vessel vasculitis may be detected
- May not detect lesion in bone marrow
- Negative finding can be present in patient with systemic viral infection or drug fever.

- PET-CT (plain) can be performed in patient with renal impairment. Contrast is usually not necessary.
- More sensitive than Gallium SPECT/CT

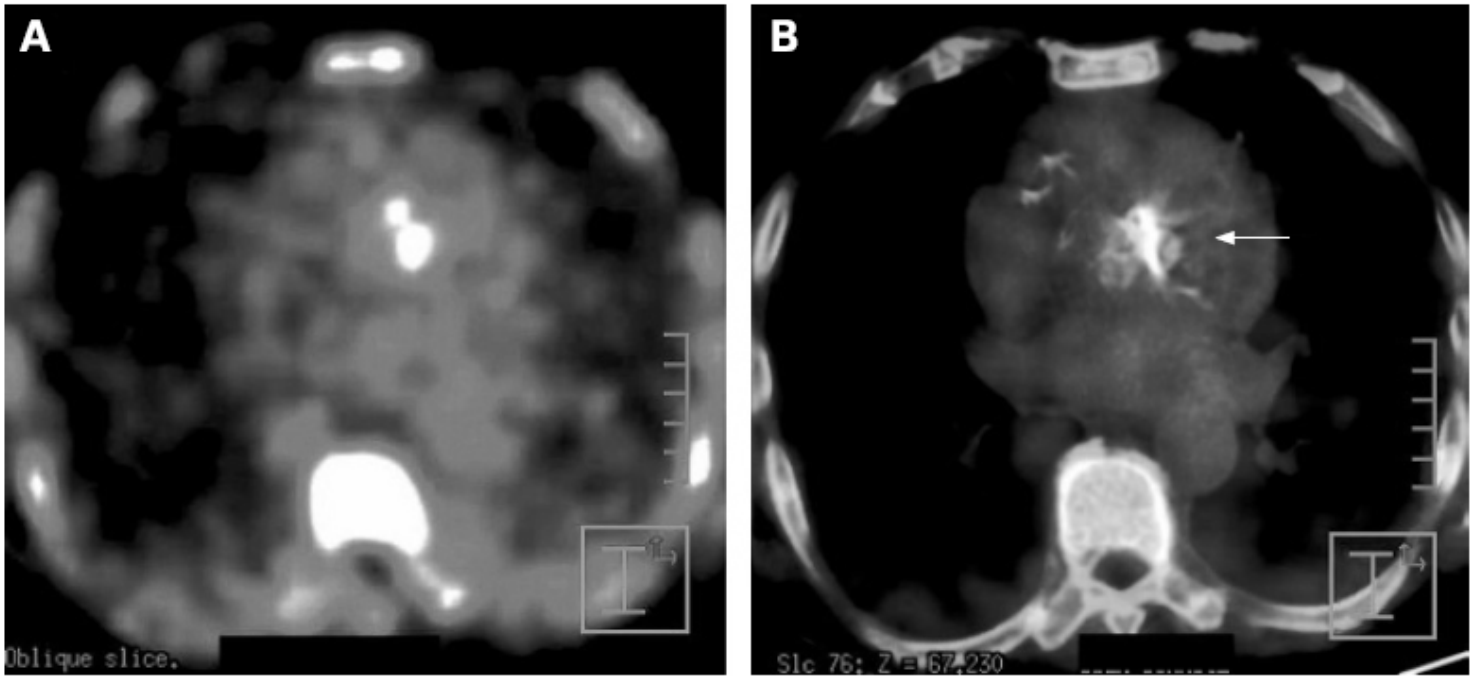


Figure 1 Transverse [^{18}F]FDG-WBC PET and (B) fused transverse [^{18}F]FDG-WBC PET/CT in an 84-year-old man admitted for fever and weight loss with history of biological aortic valve replacement 5 years earlier, followed 2 years later by bacterial endocarditis. [^{18}F]FDG-WBC PET/CT shows intense focal accumulation of leucocytes in the aortic valve. The final diagnosis was bacterial endocarditis caused by *Streptococcus bovis*. [^{18}F]FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; WBC, white blood cells. (Reprinted by permission of the Society of Nuclear Medicine from: Dumarey N, Egrise D, Blocklet D, Stallenberg B, Remmelink M, del Marmol V, Van Simaeys G, Jacobs F, Goldman S. Imaging infection with ^{18}F-FDG-labeled leukocyte PET/CT: initial experience in 21 patients. *J Nucl Med* 2006;**47**:625–32. Figure 3.)

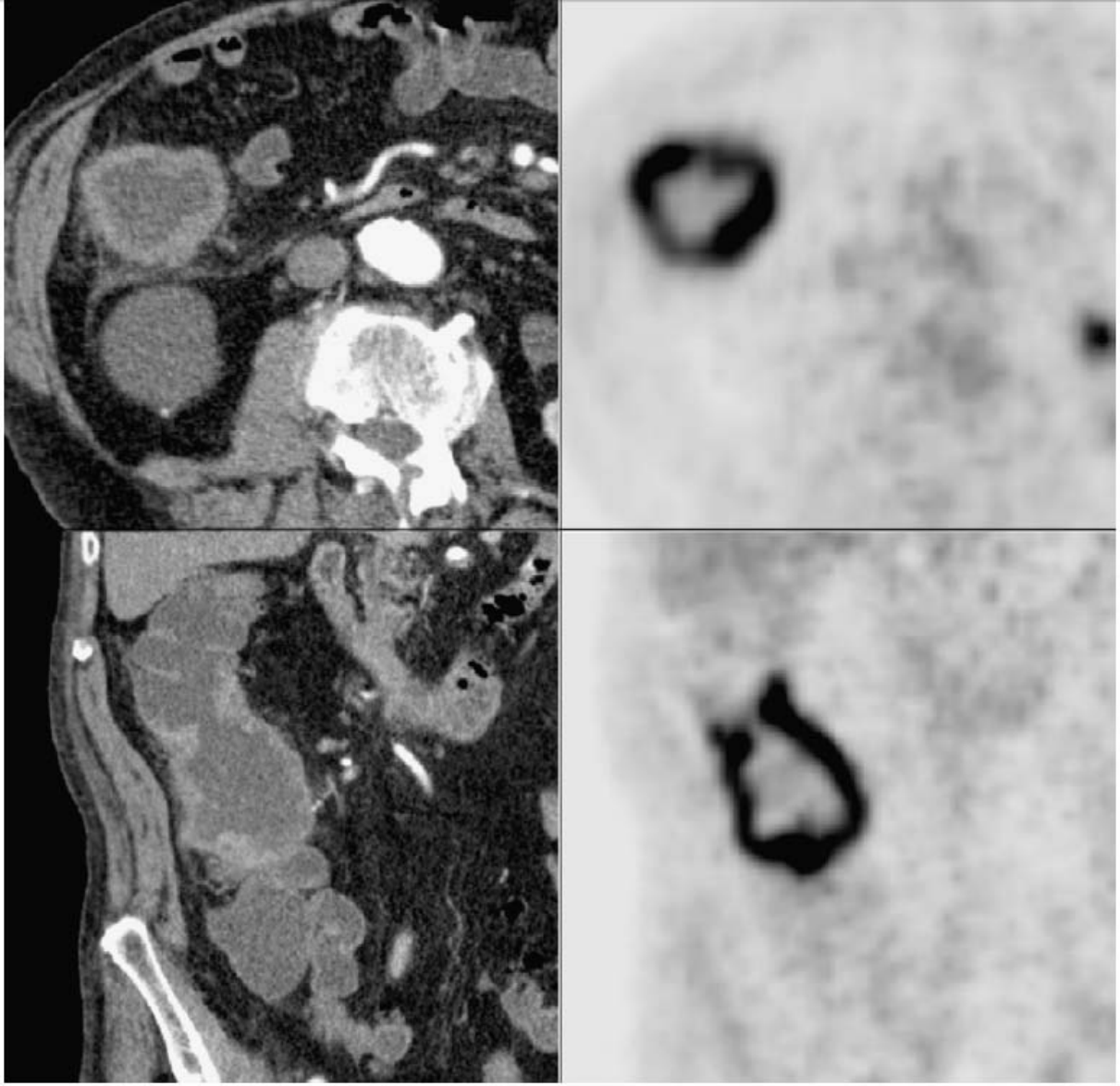


Fig. 6. Solid tumour as a cause of FUO: caecal adenocarcinoma in 89-year-old man. CT images on the left, corresponding PET images on the right.

Fever of unknown origin: A value of ^{18}F-FDG-PET/CT with integrated full diagnostic isotropic CT imaging

Jiří Ferda[a,b,*], Eva Ferdová[a,b], Jan Záhlava[a], Martin Matějovič[c], Boris Kreuzberg[b]

European Journal of Radiology

Fig. 2 [^{18}F]-fluorodeoxyglucose positron emission tomography computed tomography ([^{18}F]-FDG-PET/CT) maximum intensity projection (MIP) of a 31-year-old women referred for fever of unknown origin (FUO). PET showed abnormal uptake at the wall of the great vessels. Fever resolved after medication with glucocorticoids.

Radiol med
DOI 10.1007/s11547-011-0649-x

Fever Checklist

Appropriate Invasive Procedures that may be considered after clinical assessment

- Endoscopy
  - E.g. OGD, colonoscopy, ERCP, bronchoscopy, mediastinoscopy
- Biopsies (for histology, C/ST, AFB C/ST +/- fungal culture)
  - Bone marrow (if abnormal CBP)
  - Pleural
  - Pericardium
  - Skin lesion
  - Lymph node (FNA may be considered before biopsy, but excisional biopsy usually can give a more definitive diagnosis)
  - Liver (if abnormal LFT)
  - Temporal artery
  - Bone

Empirical Treatment

- Empirical broad spectrum antibiotics
  - For unexplained prolonged fever in a stable patient already given empiric antimicrobial agent, empirical trial/switch of broad spectrum big-gun antibiotics without identifying a cause is strongly discouraged
- Empirical anti-TB Trial
  - Once started, there is little potential for obtaining a +ve TB culture afterwards
  - Rifampicin, aminoglycoside or fluoroquinolone can suppress fever in some bacterial infections
- Antipyretic agents
  - May mask temperature
  - Should be indicated only for patient with substantial discomfort due to fever

Fever Checklist

Can be downloaded at

http://uch.home/id&mb/

KEC Online Infectious Diseases & Microbiology Lectures

Keyword Search :

Q&A Forum and Latest News on Infectious Diseases

Photos

UCH Guidelines for Empiric Antimicrobial Therapy of Selected Infections in Adults 2011

Recommended Dosing of Augmentin

Clinical Approach to Adult Patients with Sepsis

Pyrexia of Unknown Origin

Print Fever Checklist

Johns Hopkins ABX Guide

Lectures	Speaker	Date
Malaria	Dr. Rocky Shum	11/7/2011
Serum (1 → 3)-β-D-glucan measurement as an early indicator of Pneumocystis jirovecii pneumonia and evaluation of its prognostic value	Dr. Miranda Tsui & Dr. Eugene Tso	20/6/2011
When would we use Anidulafungin?	Dr. KC Lung	14/4/2011
Mycobacterium chelonae infection	Dr. Kitty Fung	14/2/2011
Management of Patients with Infections Caused by Methicillin-Resistant Staphylococcus Aureus: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA)	Dr. KC Lung	28/1/2011
A man with sorethroat complicated by confusion	Dr. KM Choi & Dr. Eugene Tso	24/1/2011
Important eye infections that should not be missed in clinical practice	Dr. Emily Tang	30/12/2010
A young lady who never gives up intravenous drug abuse	Dr. LL Cheung & Dr. Eugene Tso	5 Nov 2010
An Update on HIV Epidemiology and Antiretroviral Therapy in Hong Kong	Dr. Ada Lin	1 Nov 2010
A man with recurrent sorethroat presented with generalized lymphadenopathy and pyrexia of unknown origin	Dr. KC Lung	28/10/2010
Hepatitis B infection in healthcare workers	Dr. KY Chau	25/10/2010
Consensus Summary of Aerosolized Antimicrobial Agents	Dr. KC Lung	25/10/2010
A 36-year lady developed cardiac arrest in a shopping mall	Dr. Eugene Tso	8/10/2010
A Short Review on Hepatitis C Infection	Dr. KC Lung	22/9/2010
Two patients with fever and deranged liver function tests	Dr. WI Cheung & Dr. Eugene	20/9/2010

Fever Checklist
Department of Medicine & Geriatrics
United Christian Hospital

Fever (pyrexia) is present if oral temperature is over 37.5°C.

Fever Checklist

History

- Inquire about symptoms from all major organ systems, including a detailed history of general complaints (eg. fever, weight loss, night sweats, headaches, rashes).
- Record all complaints, even if they disappeared before the examination. Previous illnesses are important, including surgeries and psychiatric illnesses.
- Provide a detailed evaluation including the following:
  - Family history
  - Immunization status
  - Occupational history
  - Travel history
  - Nutrition
  - Drug history (over-the-counter medications, prescription medications, illicit substances)
  - Sexual history
  - Recreational habits
  - Animal contacts (including possible exposure to ticks and other vectors)

Physical examination

- Complete physical examination
- Repeat a regular physical examination daily while the patient is hospitalized. Pay special attention to rash, new or changing cardiac murmurs, signs of arthritis, abdominal tenderness or rigidity, lymph node enlargement, fundoscopic changes, and neurologic deficits.

Laboratory tests and Initial Imaging that may be considered based on clinical assessment

- CBC (with differential count), ESR, CRP
- LRFT, glucose, PT APTT
- CK, LDH, D-dimer, amylase
- Urine analysis
- NPS/NPA x influenza A/B Ag & PCR, viral culture
- C/ ST (e.g. blood, sputum, urine, wound)
- Prolong blood C/ST to 14 days for suspected endocarditis/fungemia (specify in request)
- Stool exam (eg viral study, C/ST, ova & cyst, Amoeba, *Clostridium difficile* toxin)
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- Urine x *Legionella pneumophila* Ag, pneumococcal Ag
- Blood x Malaria screen
- HIV Ab, CD4 count if HIV Ab +ve

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- Serology tests:
  Atypical pneumonia (paired), Mycoplasma pneumoniae IgM, VDRL, Widal test, Weil-felix test (paired), Rickettsial serology (paired), Coxiella burnetii serology (paired), Brucella serology (paired), Monospot test, EBV VCA IgM, EBV EBNA IgG, hepatitis serology, Dengue (IgM/ IgG), Leptospirosis serology (paired), Parvovirus B19 serology (IgM/IgG), Hantavirus serology (paired), CMV IgM, JEV serology
- Sputum x fungal culture/ Nocardia/ Rhodococcus
- Sputum x *Pneumocystis jiroveci* (Cytology Lab)

Further microbiological tests for unexplained fever (prior arrangement required) that may be considered based on clinical assessment

- Differential time to positivity (blood C/ST from peripheral vein and catheter lumens)- for determination of catheter-related sepsis
- Serology e.g. HTLV1 serology, Burkholderia pseudomallei serology, Bartonella henselae serology, Aspergillus antibody, Penicillium marneffei antibody, Histoplasma antibody, Toxoplasma IgM/IgG, Amoebic IgG, Cysticercosis serology
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- Echocardiogram
- HRCT thorax (plain)
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- MRI (contrast) if there is suspected localized pathology (especially for extremity bone/ spine infection)
  - Avoid MRI (contrast) if there the patient has renal failure
- Bone scan
- Gallium SPECT/CT
- PET-CT

Invasive procedures that may be considered based on clinical assessment

- Endoscopy
- Biopsy (for histology, C/ST, AFB C/ST +/- fungal culture)
  - Bone marrow (if abnormal CBP), pleural, pericardium, skin, lymph node, liver, temporal artery, bone

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Updated on 15 Sept 2011

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Thank you