Fever of Unknown Origin

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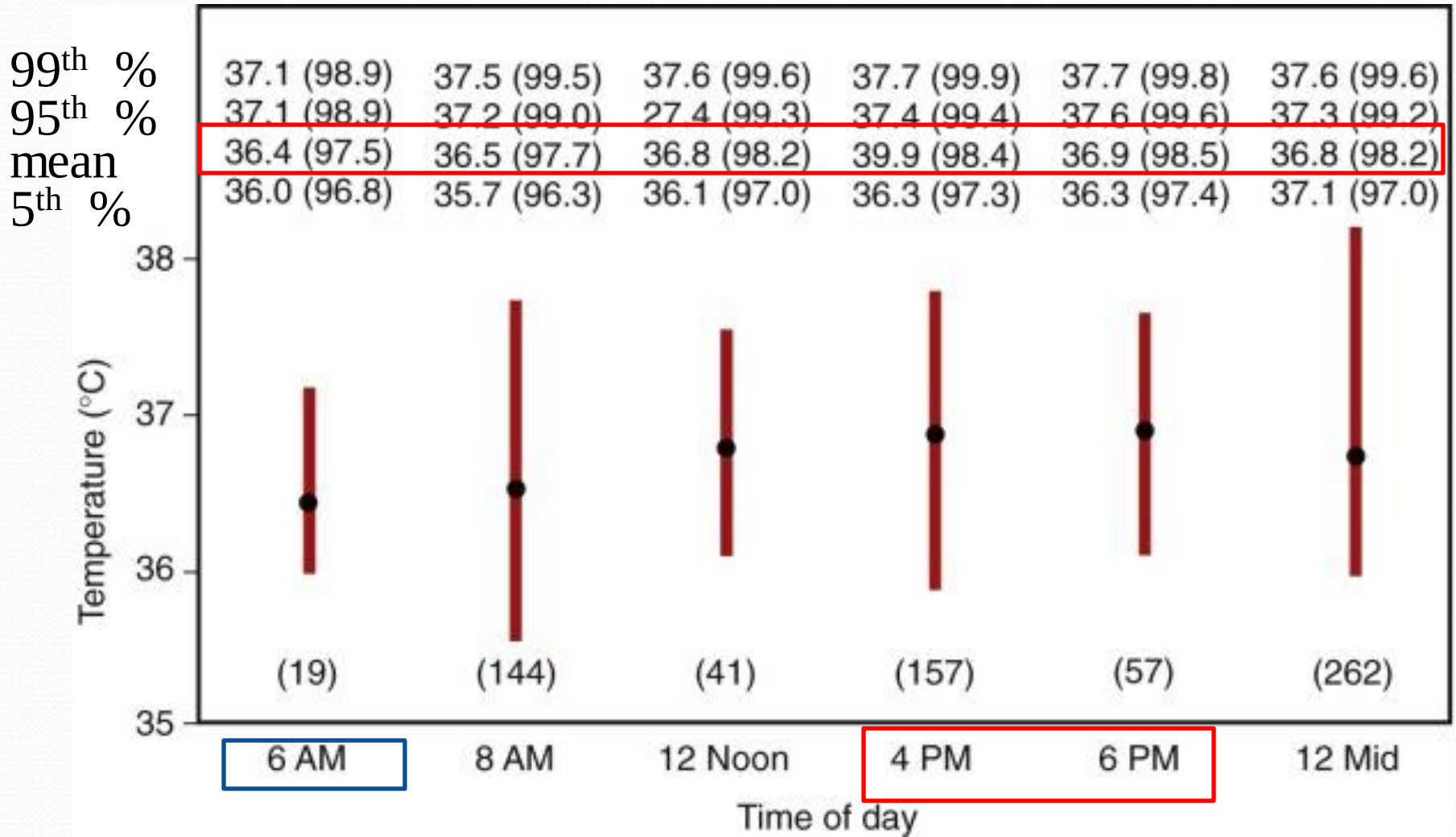
Fever / Hyperthermia

- Normal : BT = 36.8° ± 0.4°C (98.2° ± 0.7°F)
- Hypothalamus : controller of BT
- Daily variation : 0.5°C (0.9°F)
- Fever : BT ≥ 38.3°C (101°F).

Diurnal temperature oscillations



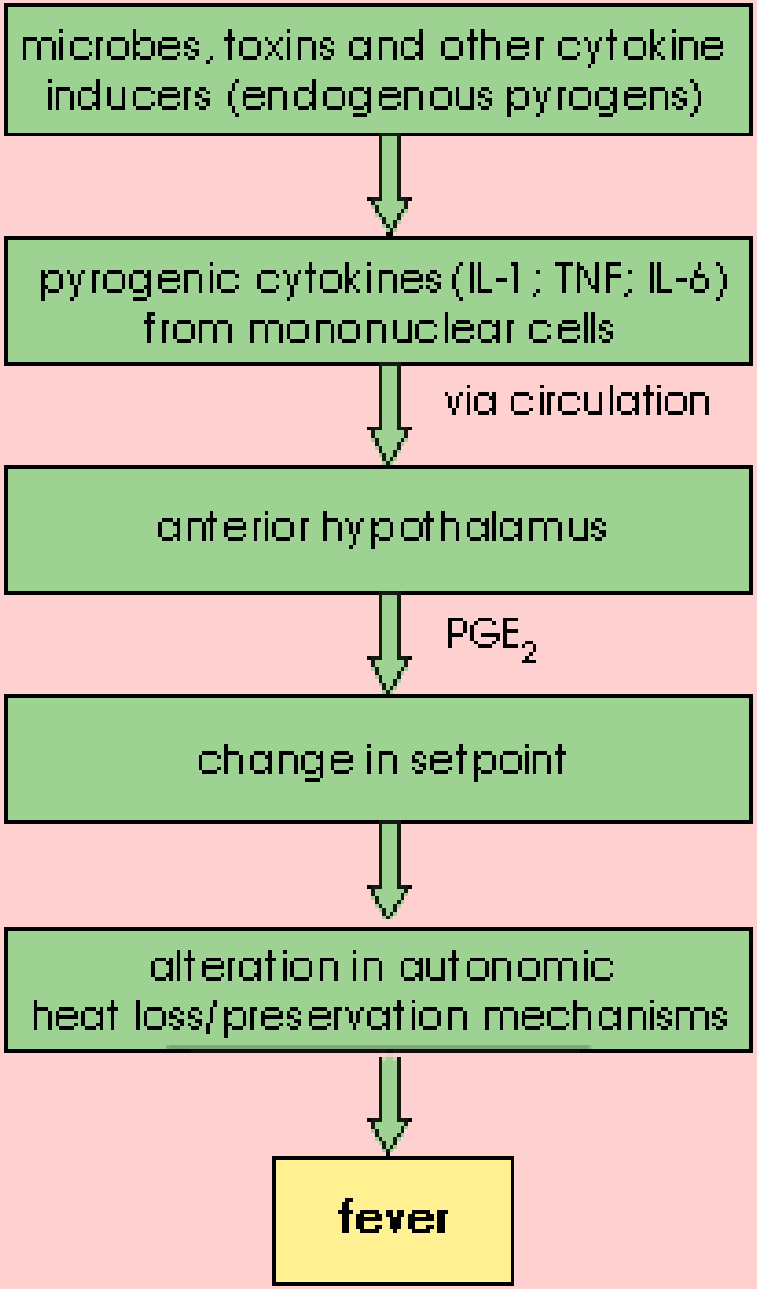
Definition of fever

- Sustained elevations in body temperature

- Oral temperature above 37.2°C (98.9°F) in the early morning and 37.7°C (99.9°F) in the late afternoon or evening considered fever for healthy adults 40 years of age or younger.

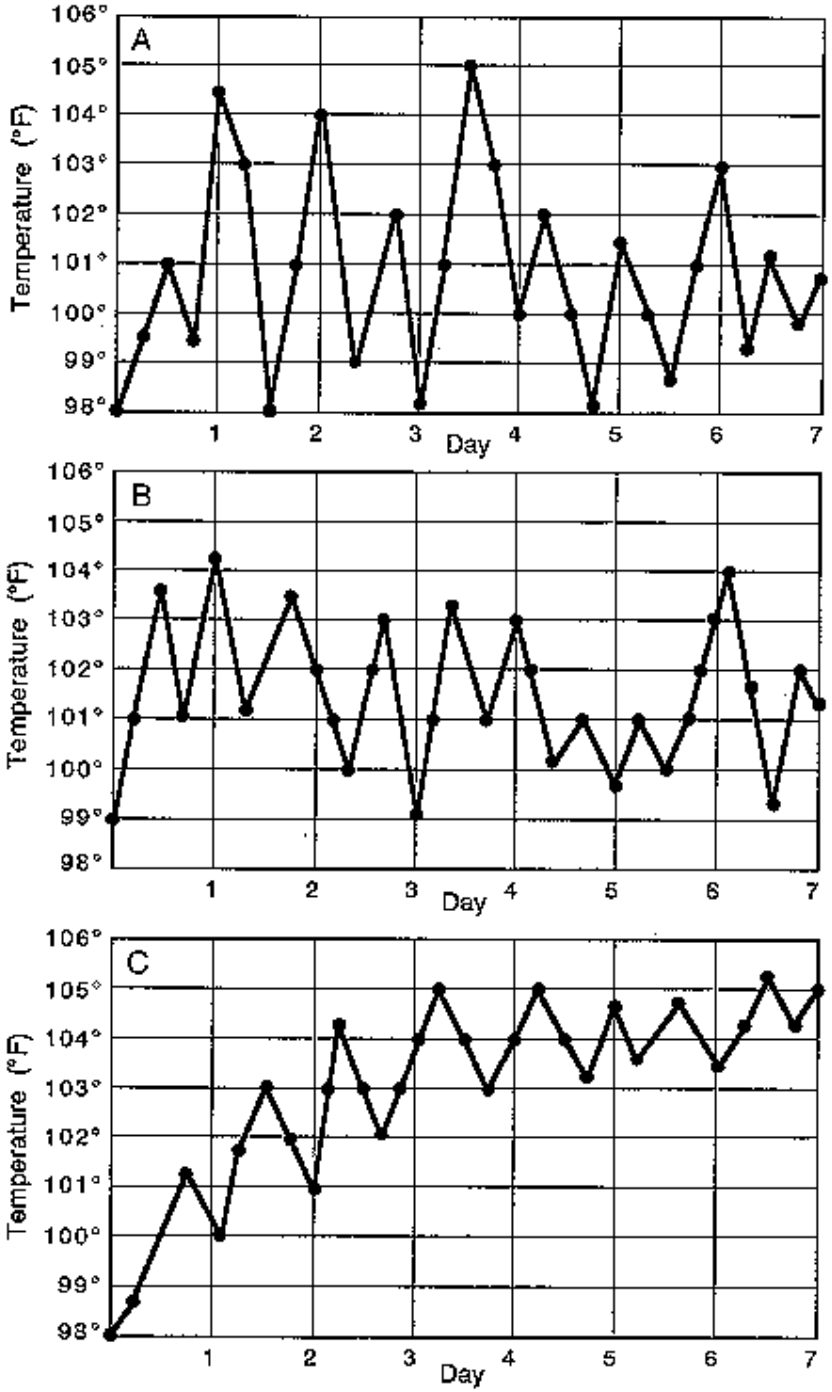
- 38°C肛溫(Rectal)/耳溫(Typamic)=
- 37°C口溫(Tympanic)=36°C腋溫(Axillary)

Mechanisms of Fever



Fever Patterns

- Intermittent fevers
  - Pyogenic abscesses and irregular use of antipyretics
- Remittent fever
- Hectic ("septic") fever:
  - a difference of 1.4^{o}C (peak & trough)
- Sustained (continuous) fever
  - G(–) bacterial pneumonia, brucellosis, typhoid fever, tularemia, psittacosis, pneumococcal pneumonia, rickettsial infections, central fever
- Relapsing (recurrent) fever
  - Lymphomas, rat-bite fever, borreliosis (Lyme disease), and dengue



***A*, Intermittent (hectic/septic) fevers**

***B*, remittent fever**

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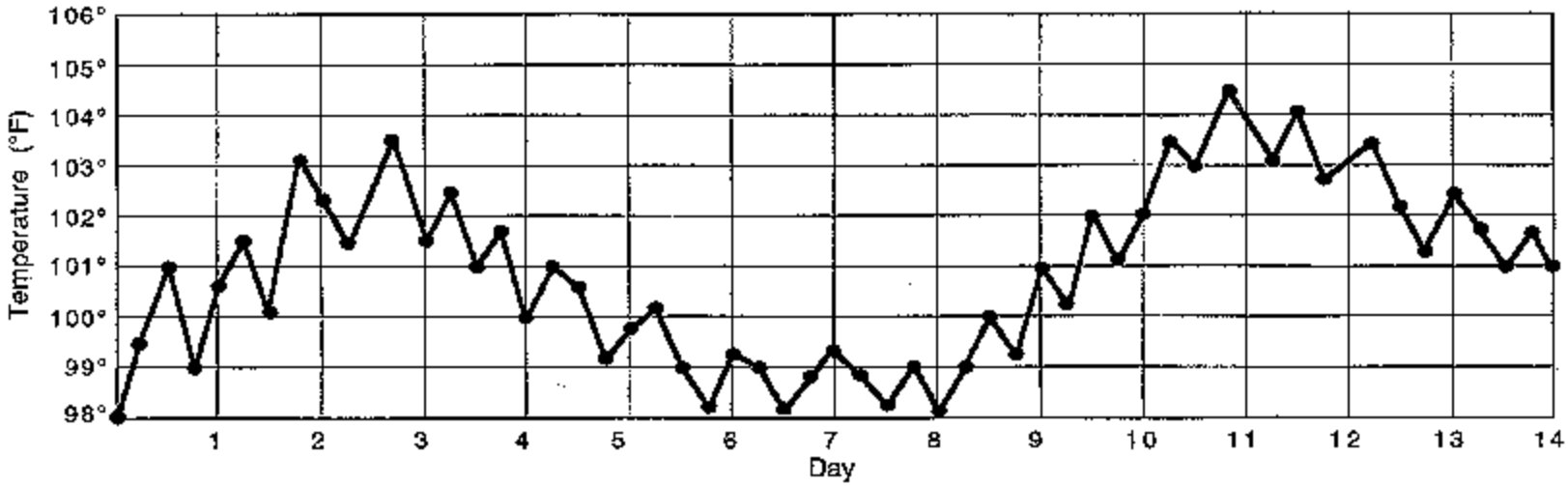
***C*, sustained/continuous fever.**

Relapsing (camelback/dromedary) fever.



Metabolic Changes of Fever 重要

- Metabolic rate increases of about 10% to 12% with each 1°C elevation in body temperature.
- Increased insensible water loss; generally there will be an increased loss of 300 to 500 $mL/m^2/^oC/day$
- Heart rate increases of up to 15 beats/min per °C increase in temperature.
- Electrolyte depletion

Lethal Temperature Ranges

- The lower lethal temperature is about 26°C (78.8°F).
- The average upper lethal limit is about 43°C (109.4°F).

Traditional FUO

- Fever 38.3°C (101°F) or higher on several occasions
- Fever of more than 3 weeks' duration
- Failure to reach a diagnosis despite 1 week of inpatient investigation

Defined by Petersdorf and Beeson in 1961

New Categories for Fevers of FUO

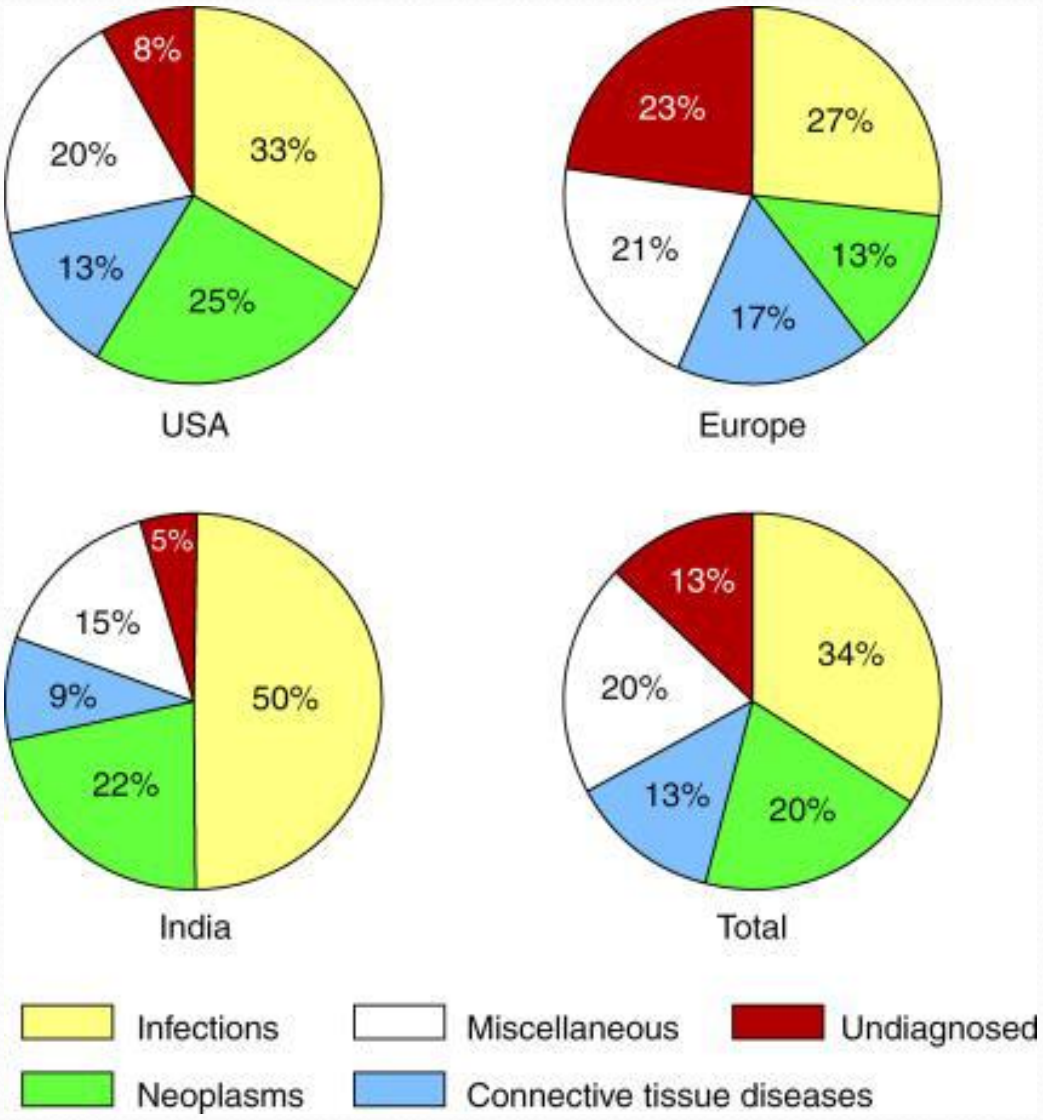
- **Classical FUO**
- **Nosocomial FUO**
- **Neutropenic FUO**
- **HIV-associated FUO**

Modified from DT Durack, AC Street, in JS Remington, MN Swartz (eds): *Current Clinical Topics in Infectious Diseases*. Cambridge, MA,Blackwell, 1991

Classical FUO

- Fever 38.3^{o}C (101^{o}F) or higher on several occasions
- Fever of more than 3 weeks' duration
- Diagnosis uncertain despite appropriate investigation after at least three outpatient visits or at least 3 days in hospital

Classical FUO 重要



Infections (30–40%)
Tuberculosis
Endocarditis
Localized abscesses (particularly int

Neoplasia (20–30%)
Lymphoma
Renal carcinoma
Gastrointestinal carcinoma
Ovarian carcinoma

Collagen-vascular diseases (15%)
SLE
Rheumatoid arthritis
Vasculitis

Others (15–20%)
Drugs
Pulmonary emboli
Inflammatory bowel disease
Factitious fever
Sarcoidosis

Infections for FUO

- Infections, especially extrapulmonary tuberculosis, remain the leading diagnosable cause of FUO.
- Prolonged mononucleosis syndromes caused by EBV, CMV, or HIV are conditions whose consideration as a cause of FUO is sometimes confounded by delayed antibody responses.

Infections for FUO

- Intraabdominal abscesses (sometimes poorly localized) renal, retroperitoneal, and paraspinal abscesses continue to be difficult to diagnose.
- Osteomyelitis, especially where prosthetic devices have been implanted

Infections for FUO

- Infective endocarditis must be considered. Although true culture-negative infective endocarditis is rare, one may be misled by slow-growing organisms of the HACEK group, *Bartonella* spp. (previously *Rochalimaea*), *Legionella* spp., *Coxiella burnetii*, *Chlamydia psittaci*, and fungi.
- Prostatitis, dental abscesses, sinusitis, and cholangitis continue to be sources of occult fever.

Malignancies That Commonly Cause FUO

- Hodgkin's disease
- Non-Hodgkin's lymphoma
- Leukemia
- Renal cell carcinoma
- Hepatoma
- Colon carcinoma

Collagen vascular/hypersensitivity diseases for FUO

- Adult Still's disease
- Behcet's disease
- Erythema multiforme
- Erythema nodosum
- Giant-cell arteritis/polymyalgia rheumatica
- Hypersensitivity pneumonitis (e.g., "metal fume fever," "farmer's lung," "air-conditioner lung")
- 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
- Wegener's granulomatosis

Granulomatous Diseases for FUO

- Crohn's disease
- Idiopathic granulomatous hepatitis
- Midline granuloma
- Sarcoidosis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Nosocomial FUO

- Fever 38.3°C (100.4°F) or higher on several occasions in a hospitalized patient receiving acute care
- Infection not present or incubating on admission
- Diagnosis uncertain after 3 days despite appropriate investigation, including at least 2 days' incubation of microbiologic cultures

Causes of Nosocomial FUO

- More than 50% of patients with nosocomial FUO are infected, and intravascular lines, septic phlebitis, and prostheses are all suspect.
- The sinuses of intubated patients or a prostatic abscess in a man with a urinary catheter.
- In approximately 25% of patients with nosocomial FUO, the fever has a noninfectious cause.

Causes of Nosocomial FUO

- Among these causes are acalculous cholecystitis, deep vein thrombophlebitis, and pulmonary embolism.
- Drug fever, transfusion reactions, alcohol/drug withdrawal, adrenal insufficiency, thyroiditis, pancreatitis, gout, and pseudogout are among the many possible causes to consider.
- 20% of cases of nosocomial FUO may go undiagnosed.

Neutropenic FUO

- Fever 38.3°C (100.4°F) or higher on several occasions
- Patient has fewer than 500 neutrophils per cubic millimeter in peripheral blood or expected to fall below 500/mm^3 within 1 or 2 days
- Diagnosis uncertain after 3 days despite appropriate investigation, including at least 2 days' incubation of microbiologic cultures

Causes of Neutropenic FUO

- Neutropenic patients are susceptible to focal bacterial and fungal infections, to bacteremic infections, to infections involving catheters (including septic thrombophlebitis), and to perianal infections.
- *Candida* and *Aspergillus* infections are common.

Causes of Neutropenic FUO

- Infections due to herpes simplex virus or CMV are sometimes causes of FUO in this group.
- While the duration of illness may be short in these patients, the consequences of untreated infection may be catastrophic,
- With 50 to 60% infected, and 20% are bacteremic.

HIV-Associated FUO

- Fever 38.3°C (100.4°F) or higher on several occasions
- Confirmed positive serology for HIV infection
- Fever of more than **4 weeks**' duration for outpatients or more than 3 days' duration in hospital
- Diagnosis uncertain after 3 days despite appropriate investigation, including at least 2 days' incubation of microbiologic cultures

Causes of HIV-Associated FUO

- HIV infection alone may be a cause of fever.
- Infection due to *Mycobacterium avium* or *Mycobacterium intracellulare*, tuberculosis, toxoplasmosis, CMV infection, *P. carinii* infection, salmonellosis, cryptococcosis, histoplasmosis,
- Mycobacterial infection can be diagnosed by blood cultures and by liver, bone marrow, and lymph node biopsies.
- Chest CT should be performed to identify enlarged mediastinal nodes. Serologic studies may reveal cryptococcal antigen, and ^{67}Ga scan may help identify *P. carinii* pulmonary infection.
- More than 80% of HIV patients with FUO are infected, but drug fever and lymphoma remain important considerations.

Miscellaneous conditions for FUO

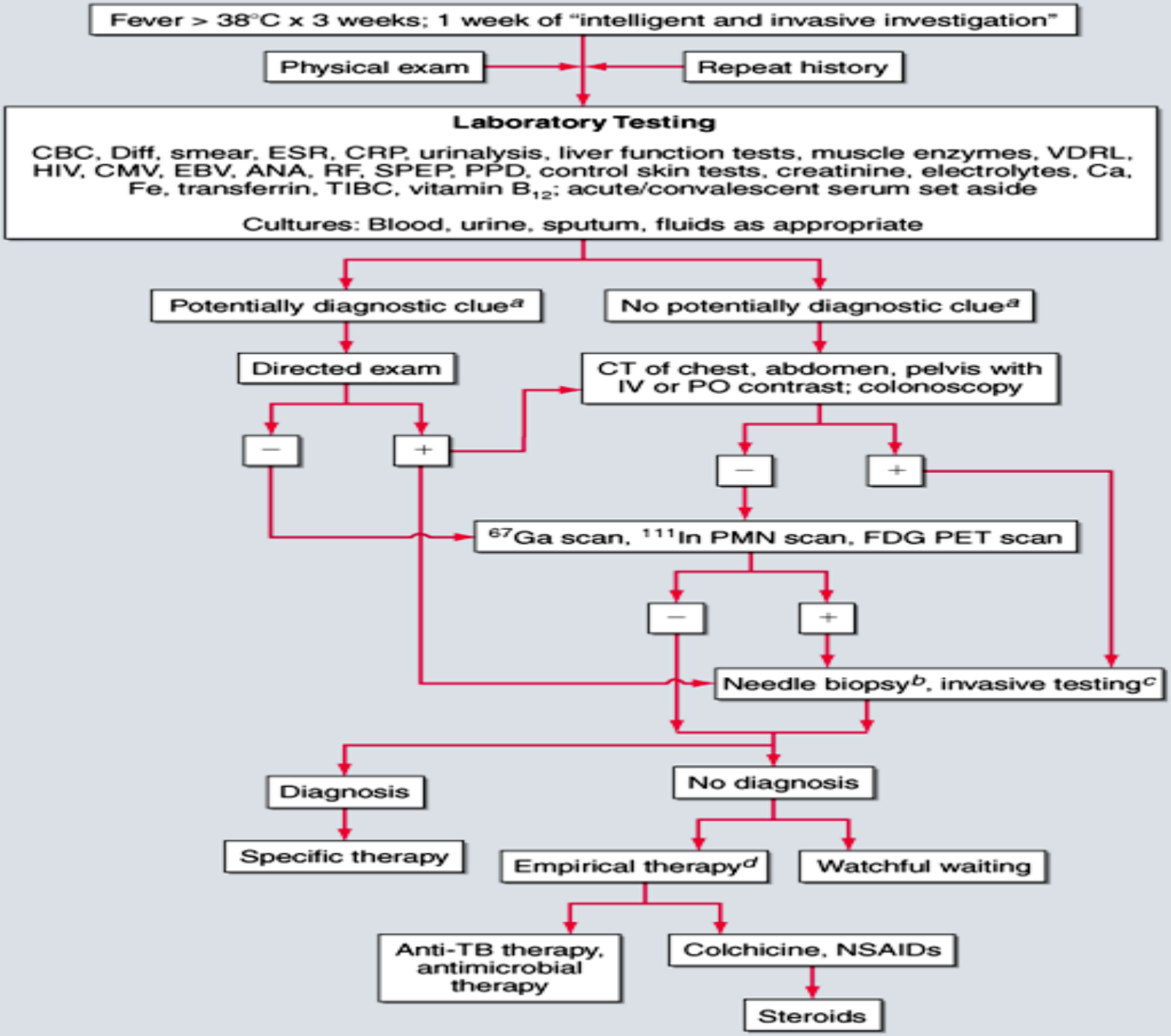
- Aortic dissection
- **Drug fever**
- Factitious fever
- Gout
- Hematomas
- Hemolytic diseases/hemoglobinopathies
- Laennec's cirrhosis
- PFPA syndrome: periodic fever, adenitis, pharyngitis, aphthae
- Postmyocardial infarction syndrome
- Recurrent pulmonary emboli
- Subacute thyroiditis (de Quervain's)
- Tissue infarction/necrosis
- Habitual hyperthermia (exaggerated circadian rhythm)

Central Nervous System Causes of FUO

- Primary CNS tumor
- Metastatic tumor
- Hemorrhage
- Infections
- Vascular abnormalities
- Metabolic disorders
- Degenerative diseases

Approach to FUO 重要

- Diligence and clinical acumen of clinicians
- **Repeatedly interview** and **examine** the patient
- Review laboratory test results & imaging studies
- Discontinue as many medicines as possible
- Avoid procrastination when faced with the need to obtain tissue for diagnosis


Fever > 38°C x 3 weeks; 1 week of "intelligent and invasive investigation"
Physical exam
Repeat history
Laboratory Testing
CBC, Diff, smear, ESR, CRP, urinalysis, liver function tests, muscle enzymes, VDRL, HIV, CMV, EBV, ANA, RF, SPEP, PPD, control skin tests, creatinine, electrolytes, Ca, Fe, transferrin, TIBC, vitamin B_{12}; acute/convalescent serum set aside
Cultures: Blood, urine, sputum, fluids as appropriate
Potentially diagnostic clue[a]
No potentially diagnostic clue[a]
Directed exam
CT of chest, abdomen, pelvis with IV or PO contrast; colonoscopy
−
+
−
+
^{67}Ga scan, ^{111}In PMN scan, FDG PET scan
−
+
Needle biopsy[b], invasive testing[c]
Diagnosis
No diagnosis
Specific therapy
Empirical therapy[d]
Watchful waiting
Anti-TB therapy, antimicrobial therapy
Colchicine, NSAIDs
Steroids

Initial Studies for FUO

- CBC-H, U/A, ESR, CRP
- Blood and tissue fluid examination, such as smears, stains, cultures
- Serologic studies (ANA, RF, VDRL, Widal test, serum protein electrophoresis, ferritin, LDH...)
- PCR (EBV,CMV,HSV)
- PPD skin test

Noninvasive Diagnostic Procedures for FUO

- Sonograrphy of abdomen and pelvis
- Echocardiography
- CT scan of chest and abdomen
- MRI
- Radionuclide scanning procedures, such as technetium (Tc) 99m sulfur colloid, gallium (Ga) 67 citrate, or indium (In) 111-labeled leukocytes or immunoglobulin

Invasive Diagnostic procedures for FUO

- Biopsy of liver and bone marrow
- Biopsy of temporal arteries in selected cases
- Biopsy of lymph nodes
- Bronchoscopy and laparoscopy
- Exploratroy laparotomy

Diagnostic strategy

When no clues are found or when a clue does not point to the cause of the FUO, the subsequent approach may be:

(1) a wait and see strategy

(2) a 'whole body' inflammation tracer scintigraphy

(3) a staged approach

(4) therapeutic trials.

Reasons to Treat Fever

- To avoid potentially harmful secondary effects
  - Tachycardia
  - Febrile convulsions
  - Encephalopathy
- Patient's comfort

Methods of Lowering Temperature

- Antipyretics 選擇題選項 *
  - NSAIDs: act by inhibiting COX, esp. COX-2
  - Alternatives to NSAIDs:acetaminophen, steroids
- Sponging the body
- Turkish massage of Weinstein
  - Rubbing skin with a Turkish towel and tepid water
- Cooling blankets
- Combined evaporation and convection
  - Sprays of water at an ambient temperature of **$20^{o}C$**
- Ice water immersion

Outcome of FUO

- "…90% of patients with FUO should have a diagnosable conditions, the remaining patients willl recover. Patients should rarely die with a diagnosis of FUO"

  Petersdorf 1992

Conclusions

- FUO will remain a challenging problem because the differential diagnosis is probably the longest of any condition in medicine.
- Despite the enormous evolution of our diagnostic capabilities it remains a complex issue about which there are differing opinions but few data about the diagnostic strategy.
- The best approach is probably a general internistic approach.

THANK YOU

要記住老師的名字喔！