

Pyrexia of Unknown Origin

Terminology

■ Old Definition:

1. Fever higher than 38.3°C on several occasions.
2. Duration of fever – 3 weeks
3. Uncertain diagnosis after one week of study in hospital

■ New Definition:

- Eliminated the in-hospital evaluation requirements → 2 outpatient visits, or 3 days in hospital. ... Ambulatory as well as in hospital



Definition Expansion

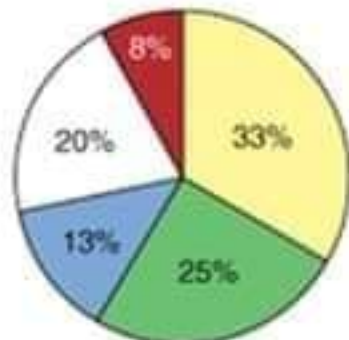
1. Classical PUO
2. Nosocomial PUO
3. Neutropenic PUO
4. HIV-Associated
5. Transplant

Epidemiology and Etiology

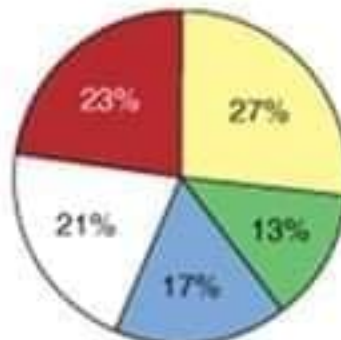
Categories of Illness Causing PUO

Infections	30 - 40 %
Malignancies	20 – 25 %
Collagen Vascular Disease	10 – 20 %
Miscellaneous	15 – 20 %
Undiagnosed	10 – 15 %

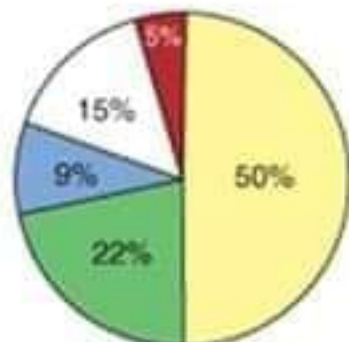
Categories of Illness Causing PUO



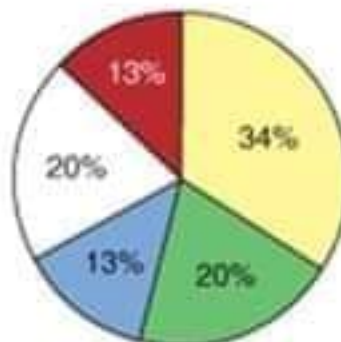
USA



Europe



India



Total



Epidemiology and Etiology

A. 1970 → up to date:

Infection is the most frequent.

- 1930 → 70% undiagnosed PUO
- 2000 → 5-10% undiagnosed PUO

B. Diagnostic Advances:

Modify the spectrum of PUO causing diseases:

1. Serology: HIV / Brucella / SLE
2. Imaging Tech: Abscesses/Solid Tumor

Epidemiology and Etiology

c. Fever lasting > 1 yr:

- | | |
|---------------|--------------|
| 1. Infection | } Decline in |
| 2. Malignancy | } frequency |

Pyrexia of Unknown Origin

The majority of disease remaining after an initial **NEGATIVE** work-up are:

1. **Neoplasm**
2. **Seronegative Collagen Vascular Disease**
3. **Increasing Tuberculosis**
4. **Increasing Drug Addition**
5. **Elderly with Endocarditis**
6. **HIV with or without infection or malignancy**
7. **Implanted prosthetic devices**
8. **Travel ... New Exposure**

The Age

- Children → infection is the most frequent.
 - EBV, CMV... others
- Elderly → Neoplasm & CT-Disorders
 - Giant cell arteritis } > 50 yr (30%)
 - Polymyalgia Rheumatica }

Geography

Malaria	Saudi (malaria area)/Africa/India
Brucella	Saudi/Gulf Area
Kala-Azar	Yemen/Jazan/Sudan/India
Leprosy	Yemen/Najran...
Typhoid	India/Pakistan/Egypt/Indonesia
Histoplasmosis	USA ... (West Coast)
N.B.: Ease of Travel → Infection → All parts of the world.	
Tuberculosis	All over the world.
Liver Abscess	
AIDS	

Neutropenia

- Fever without source → Bacteremia.
- Fever lasts > 7 days → Fungal Infection.
- Fever is usually co-founding:
 1. Underlying disease
 2. Drugs
 3. Blood Products
 4. Allograft rejection

Neutropenia

- Fever if unexplained → abates with return of neutrophil.
- Fever if persists → Systemic fungal infection.

Etiologies of PUO

- Infection: Three major causes
- Abscess .. especially occult ..
- Intracellular organisms. (salmonella mycobacterium, brucella)
- Intravascular ... SBE

Etiologies of PUO

■ Infection

□ Tuberculosis: .. Disseminated

- The single most common infection in most PUO series except in children and elderly.
- Usually extrapulmonary or military, or
- Occurs in the lungs and significant pre-existing lung disease.
- Pulmonary TB in AIDS is often subtle (normal chest x-rays → 15 – 30%).
- PPD is (+ve) < 50% of TB with PUO.
- Diagnosis often requires Bx of LN/Liver/Bone marrow.
- Sputum smear (+) only 25%

Etiologies of PUO

□ Abscess:

- Usually located in abdomen or pelvis.
- Secondary to appendicitis or diverticulitis.
- Pyogenic liver abscess usually follow biliary tract dis./abd. Suppuration.
- Amoebic liver abscess is similar to pyogenic → amoebic serology is positive > 95% of cases.
- Splenic abscess is usually secondary to hematogenous seeding.
- Perinephric or renal abscess is usually secondary to UTI.

Etiologies of PUO

□ Bacterial Endocarditis

- Culture remains negative in 5% of patient.
- Culture negative is likely with the following organisms:
 - *Coxiella burnetii* → no growth.
 - HACEK group → incubate blood 7 – 21 days
 - *Brucella* } Special media/
 - *Legionelle* } long time
 - *Mycoplasma/Chlamydia* }
 - Fungal → usually sterile
- Peripheral signs may not be detected.
- Right-side Endocarditis → Lack murmurs → self antibiotics → growth (-ve).

Etiologies of PUO

□ Occult Source of Infections:

■ Odontogenic infection

- ... ask about symptomatology

■ Sinusitis

- ... ask about headache and nasal congestion with or without purulent discharge

■ Prosthetic Devices

- ... Always consider it the source if there is none!

■ Prolonged mononucleosis syndrome. EBV, CMV, HIV

■ Prostatitis ... bacterial.

Etiologies of PUO

■ Malignancy

- Lymphoma ... Fever is a presenting feature
- Leukemia ... M. Myeloma (fever means infection)
- Renal cell carcinoma ... only rarely fever in there
- HCC or secondary metastasis to the liver

Etiologies of PUO

■ Lymphoma:

- Fever is a well-recognized manifestation.
- A Pel-Ebstein phenomenon is rare.
- Source of fever → production of cytokines.
- Fever is a negative prognostic factor ...

■ Renal Cell Carcinoma (Adult)

- 20% → Fever
- Microscopic hematuria/Erythromytosis

Etiologies of PUO

■ Wilms Tumor (Children)

- Peak incidence 2-3 years.
- Abdominal mass but FEVER can be a presentation.

■ Solid Tumor

- Fever is rare except:
 - Secondary metastasis to the liver
 - Ductal obstruction or perforation ... like cholangioacarcinoma or ampulla ca.
 - Lung carcinoma with obstruction and pneumonia.

Etiologies of PUO

■ Collagen-Vascular-Disease

No diagnostic serology...

You need to recognize the syndrome
otherwise no diagnosis

- ☐ Still's disease (young or adult)
- ☐ Giant cell arteritis } → 15% of PUO
- ☐ Polymyalgia Rheumatica }
- ☐ Behcet's Disease
- ☐ Relapsing polychondritis

Etiologies of PUO

■ Still's Disease Adult Onset

- Age 16 – 33 % with (-ve) RF & ANA
- Fever is Chx high and spiking with Temp. up to 41.6°C ... hectic
- Fever is either intermittent or remittent ... peaks typically at night
- Most patient seek medical attention within 2 weeks.
- A distinctive evanescent macular or M. popular rash is typically present during the course of the illness.

Etiologies of PUO

- Dx is strictly a clinical one ... RF is almost uniformly negative.
- Other features → myalgias, arthritis may appear after weeks or months & leukocytosis (neutrophils), hepatosplenomegaly & lymphadenopathy.
- Very high serum ferritin ... more than 2000

Etiologies of PUO

■ Temporal Arteritis:

Very serious condition if not diagnosed early

... Very difficult to establish the etiology of fever if you do not have the index of suspicion

Typically Caucasian but it occurs in others

- ☐ Fever and malaise may be the only manifestation. Headache is the most common.

Etiologies of PUO

- Careful Questioning → jaw claudication or visual loss.
- If there is unexplained fever, anaemia and high ESR in an elderly without an obvious cause ...
- Unilateral vs. bilateral bx ... short vs long segment ..
- Treat for 2 years ..

Etiologies of PUO

■ Polymyalgia Rheumatica:

- Can cause fever, arthralgia, myalgia & \uparrow ESR > 50 .
- Chx. Muscle complaints \rightarrow symmetrical pain and stiffness that are typically worse at AM and affects lumbar spine and large proximal m.

■ Other vasculitides that cause PUO:

- Polyarteritis nodosa \rightarrow Mononeuritis multiplex (60%)
- Wegener's Granulomatosis
- Mixed Cryoglobulinemia

Etiologies of PUO

■ Miscellaneous Causes: (Non-Infectious)

□ Vascular Causes:

■ Pulmonary Emboli

- 50% are febrile
- Fever is chx. $< 39^{\circ}\text{C}$
- Patient typically has predisposing factors → cancer or recent immobility.

■ Hematoma in closed space

- When it cause PUO → usually arise from hemorrhage in the retroperitoneal space or within the wall of an aneurysm or dissection of the thoracic or abdominal aorta.

Etiologies of PUO

□ Hyperthyroidism

- Occasionally cause PUO → most frequently diagnosed clinically.
- Often accompanied by weight loss.
- No local neck pain and typically enlarged non-tender thyroid.

Etiologies of PUO

■ Adrenal Insufficiency

- Rare, potentially fatal, but eminently treatable cause of PUO.
- Consider Dx if there is: Nausea, vomiting, weight loss, ↓ BP, ↓ Na & ↑ K.

Etiologies of PUO

■ Familial Mediterranean Fever

Ask the patient about the disease in Arabic

- Recurrent fever
- Arthritis pain out of proportional to signs
- Polyserositis (peritonitis ... may be pleuritis)
- Leukocytosis
- Affect mainly Arabs
- Not always hereditary

Etiologies of PUO

■ Alcoholic Hepatitis

- Often unsuspected → pt. deny
- Fever is usually low grade $< 38.5^{\circ}\text{C}$
- May have jaundice and hepatomegaly.
- AST $\uparrow >$ ALT 2:1 AST < 500
- Leukocytosis is often there.
- If you do not think about it in the right time and with the right patient ... then you will be troubled and will work a lot in order to get the atiology.

Etiologies of PUO

■ Factitious Fever

Febrile PUO

In one study ... 9% of cases of PUO

□ False fever: thermometer manipulation using external heat or substitute thermometer. Men use this way ... physician are rare for this disorder. Increasing somewhat in elderly ... 115 ... 116 ...

□ Genuine fever (self induced)

Administration of pyrogenic substances (bacterial suspensions)

Generally young women with connection to health care ... often NURSES.



Drug Fever

- Almost any drug can cause fever



PART 2

DIAGNOSIS AND TREATMENT



Diagnostic Approach

- Careful History
- Physical Examination (repeated)
- Diagnostic Testing

History

- Verify the presence of fever:

- ☐ Series of 347 patients → for prolonged fever
→ 35% were ultimately: a. No fever
b. Factitious Fever

- Duration of Fever:

- ☐ The longer the duration → the less likely to have infection and malignancy.

History

■ Travel:

□ Travel to an area known to be endemic for certain disease:

- Name of the area, duration of stay
- Onset of illness ... (incubation period)

1 – 10 Days	10 – 21 Days	Weeks - Months
Malaria	Malaria	Kala Azar
Plague	Typhoid	Amoebiasis
Dengue	Brucella	HIV
Salmonella	Hepatitis A	Hepatitis

History

■ Drug and Toxin History:

- ☐ Drug-induced fever ... almost all drug can cause drug fever ... Antihistamine/beta lactam/hepatrin/coumarin/anti-TB ... Salicylates and other NSAID ...
- ☐ Alcohol Intake (regular use)

History

■ Localizing Symptoms:

□ May Indicate the source of fever:

Back Pain	TB Spondylitis
	Bone Metastasis
Headache	Chronic Meningitis/GCA
RUQ Pain	Liver Abscess
LUQ Pain	Splenic Abscess
Oral & Genital Ulcer	Behcet's Disease
Jaw Claudication	Temporal Arteritis
Subtle changes in behavior	Granulomatous Meningitis

History

■ Family History:

- Scrutinized for possible infectious or hereditary disorders
 - Tuberculosis
 - FMF

■ Past Medical Condition:

Lymphoma	→	may recur
Rheumatic Fever	→	may recur
Still's Disease	→	may recur
Behcet's Disease	→	may recur

- Exposure to sexual partner ... Acute HIV
- Illicit drug abuse (IV) ... infective endocarditis, Hepatitis ... HIV

Physical Examination

..... Looking for the KEY physical sign Diagnostic yield 60% in children (50%repeated)

- Document the Fever:

- ☐ Significant and persistent for more than ONE occasion.

- Analyzing the Pattern:

- ☐ Neither specific Nor sensitive enough to be considered diagnostic ... EXCEPT

Tertian & Quarter Pattern →

Malaria

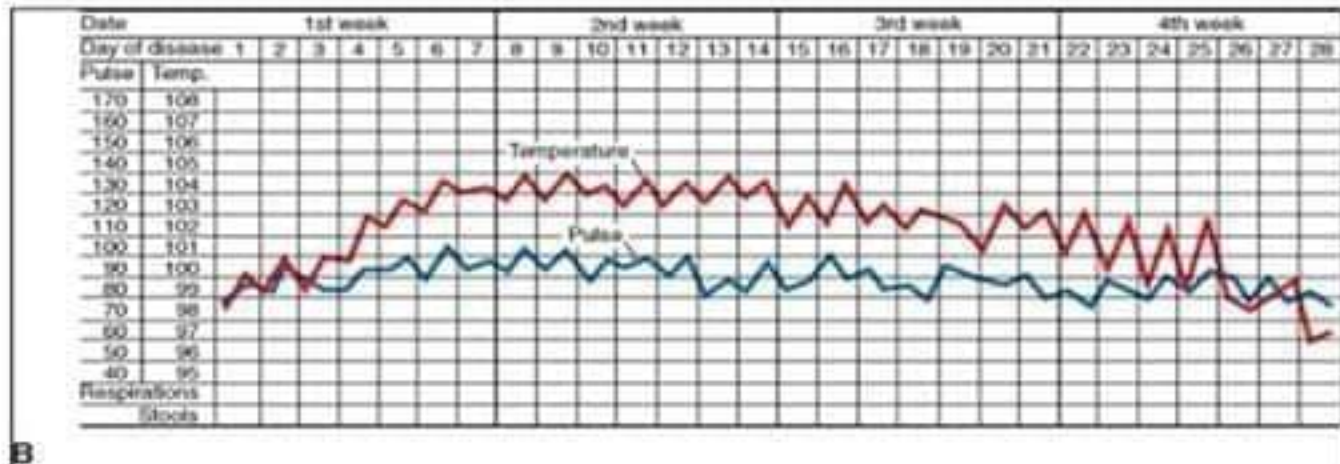
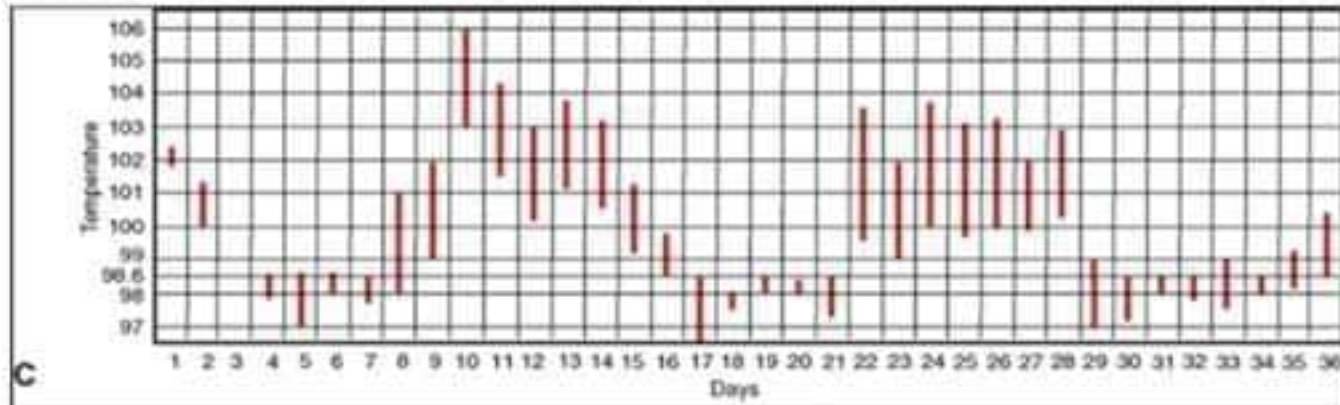
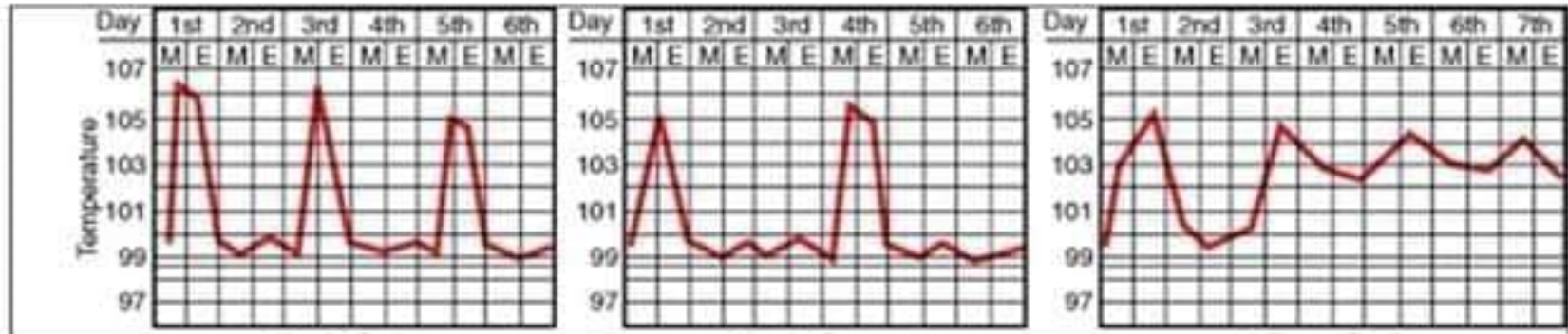
Pel-Ebstein Pattern →

Lymphoma/
Tuberculosis

Pulse-Temp Dissociation →

Typhoid/
Brucellosis

Pattern of Fever



Physical Examination

■ Examine for Lymphadenopathy

Site



☐ Cervical Area
(Localized)

1. Lymphoma
2. Tuberculosis
3. Infectious Mononucleosis
4. *****
5. Lymphadenitis (bacterial)

■ Supraclavicular lymphadenopathy:

Highest risk of malignancy: Patient > 40 yr → 90%
Patient < 40 yr → 25%

Case ...

- 32 year old woman with one month history of right post neck mass with fever and malaise ... received 10 days antibiotic but no response ...
- EXAM ...: T = 38.4 ... several lymph node in the neck ... non-tender and rubbery ...
- LAB ...: WBC = 2000 ... ESR = 42 ... CT scan ... paratracheal LN ... all other lab result and tuberculin test -ve
- What is next...?

Histopathology of the LN

- Intact Capsule
 - Discrete Area of Necrosis
 - Many Histocytes are Present
 - No Plasma or Neutrophil Cells
 - No Follicular Hyperplasia
 - No Granuloma
-
- What is the diagnosis?

Kikuchi's Disease

- * Histocytic Necrotizing Lymphadenitis *
- Benign, rare and self limiting
- Young asian female
- Cervical lymph node with fever
- Leukopenia ... 50%
- Leukocytosis 5%
- Diagnosis is by typical histopathology ...:
 - Expert and familiar one with the disease
 - Histocytes and necrosis with NO plasma or neutrophil cells

Physical Examination

■ Examine for Lymphadenopathy

- Paraumbilical hernia → abdomen or pelvis neoplasm.
- Generalized → look for hepatomegaly & splenomegaly
→ indicate significant systemic disease
 1. Lymphoma
 2. Lymphocytic – Leukemia
 3. Infectious mononucleosis
- Painful gland
 - Inflammatory process or suppuration +++
 - Hemorrhage into the necrotic center of a malignant node.

Physical Examination

☐ Consistency

- Stony hard node → cancer & usually metastasis
- Firm & rubbery → Lymphoma
- Soft & fluctuant → infection & Tuberculosis
- Matting
 - ☐ Benign: Tuberculosis/Sarcoid
 - ☐ Malignant: Metastatic Carcinoma/Lymphoma

- Examine the thyroid and look for peripheral signs of thyrotoxicosis

Physical Examination

■ Examine the Skin:

□ Rash:

- SLE All types of rashes is described
- Still's Disease Evanescent erythematous rash over the trunk
- Infectious Mononucleosis ... macular rash
- Infective Endocarditis (Janeway's lesion)
- Typhoid Fever ... rose spots over abdomen

□ Osler's Nodes: Painful nodule on the pads of toes & fingers → Infective Endocarditis



Embolic Skin Lesions ...

Janeway Lesion



**Conjunctival petechiae in a patient with
bacterial endocarditis**

Physical Examination

■ Examine for Oral Ulcer

- SLE
- Behcet's Syndrome

■ Examine for Arthritis

■ Examine the Fundus

- Roth's spots (white-centered haemorrhage)
→ Infective Endocarditis
- Yellowish-white choroidal lesion →
Tuberculosis
- Chorioretinitis → Active Toxo or CMV in
HIV patient.

Physical Examination

- New or Changing Murmur
- Temporal Artery ... nodular, weakly pulsatile
- Sinus Tenderness
- Tender Tooth
- Thyroid Enlargement or Tenderness
- Calf Tenderness
- Nails: splinter haemorrhage, clubbing

Diagnostic Testing

Blind application leads to excessive noof tests ...

■ Complete Blood Count

- ☐ Anemia if present → suggest a serious underlying disease
- ☐ Leukocytosis with bands → occult bacterial infection
- ☐ Lymphocytosis & atypical Lymphocyte → Infectious mononucleosis
- ☐ Leucopenia and Lymphopenia → advanced HIV
- ☐ Leukoerythroblastic Anemia → Disseminated TB
- ☐ Thrombocytopenia → Malaria/Leukemia
- ☐ Peripheral Blood → Malaria

Diagnostic Testing

- Urinalysis, Urine Culture, U/E, LFT

- ESR

- ☐ If elevated → significant inflammatory process

- ☐ Greatest use in establishing a serious underlying disease, esp. if v. high → ESR > 100 mm/h ...

- Tuberculosis ... m myeloma ... temporal arteritis

Diagnostic Testing

- CRP-closely associated with inflammatory process

- ☐ Not invariable components of the febrile response.
- ☐ Usually does not go up with viral infection.

* ESR & CRP is elevated in:

1. Bacterial Infection
2. Neoplasm
3. Immunological-mediated inflammatory states
4. Tissue infarction

Diagnostic Testing

■ Acute Phase Proteins

Proteins Increased	Proteins Decreased
Fibronogen	Albumin
Ferritin	Transferrin
Plasminogen	Alpha-
Fetoprotein	
Protein S	
Ceruloplasmin	

New England J Med. 1999, 340.448-454

Diagnostic Testing

■ Blood Testing

- ☐ Anti-nuclear Antibodies
- ☐ Rheumatoid Factor
- ☐ CMV Antibody ... IgM
- ☐ Heterophile Antibody Test in children and young adult
- ☐ Tuberculin Skin Test ... 5 unit ID
- ☐ Thyroid Function Test
- ☐ HIV Screening

Diagnostic Testing

■ Cultures

☐ Blood

- Obtain more than 3 blood cultures from separate venipunctures over 24 hr period if you are suspecting inf. Endocarditis prior antimicrobial use.
- Incubate the blood for 4 weeks, to detect the presence of SBE & Brucellosis

☐ Sputum: For Tuberculosis

☐ Any normal sterile:

- CSF/urine/pleural or peritoneal fluid
- Bone marrow aspirate → Tuberculosis/Brucellosis
- Lymph node Bx → TB

- Imaging Studies: ... to localize abnormalities for definite tests or treatment
 - Chest x-ray:
 - Military shadows → disseminated tuberculosis
 - Atelectasis }
 - ↑ Hemi diaphragm } Abscess 1. Liver
 - Pleural Effusion }
 - 2. Spleen
 - 3. Pancreatic
 - 4. Subphrenic
 - Mediastinal mass → Lymphoma/Tuberculosis/Sarcoid
 - If CXR is (N) → Repeat on weekly basis

Diagnostic Testing

- CT-Scan → CT scan chest
 - Mediastinal mass → Tuberculosis/Lymphoma/Sarcoidosis
 - Dorsal Spine → Spondylitis and disc space disease
 - CT-Scan Abdomen → very effective to visualize
 - All types of abscesses
 - Retroperitoneal tumor, lymph node or haematoma
- MRI: spleen, lymph node and the brain

Diagnostic Testing

■ Serology Test

- ☐ Brucella Titer
- ☐ CMV & EBV antibody test
- ☐ HIV testing (Elisa screening)
- ☐ ANF

■ Radionuclear Scanning

- ☐ Bone TC-scan → osteomyelitis (skeletal)
- ☐ Gallium scan → occult inflammation
- ☐ Indium labeled WBC-scan → occult abscesses

Diagnostic Testing

■ Radionuclear Scanning

□ Overall Assessment:

- Non-specific tests to localize a site for more specific evaluation (such as CT-scan)
- Impressive no. of false (+) and false (-) results
- True positive scan only indicates an area of increased uptake → no anatomic detail

Gallium Scan

- Will be hot if there is:
 - Increased blood flow
 - Uptake by bacteria (lactoferrin)
 - Uptake by WBC
- Sensitive but not specific
- Not good for abdomen or pelvis .. False +ve
- Effective in:
 - Chronic Infection
 - Lymphoma

Indium-Labelled Leukocyte

- Uptake by WBC
- Only for acute problem .. less than 4 weeks
- Study at UK has found the sensitivity for infective PUO: 25% and specificity was 100%
- Not sensitive enough
- Recommended for strongly suspected infective PUO if done within the 1st 2-4 weeks
- False positive ... post op wound ... mastitis

The British Journal of Radiology, 70 (1997), 918-922.

Therapeutic Trials

- Limitation and risk of empirical therapeutic trials:
 - Rarely specific
 - Underlying disease may remit spontaneously false impression of success.
 - Disease may respond partially and this may lead to delay in specific diagnosis.
 - Side effect of the drugs can be misleading.

Diagnostic Testing

- Hepatomegaly or Abnormal LFT
 - Hepatic Granuloma
 - Non-caseating: Tuberculosis/Sarcoidosis & Brucellosis
 - Caseating: Tuberculosis
- Bone Marrow
 - Granuloma ± Tubercle Bacilli → Tuberculosis
 - Aplastic Cells → Leukemia
 - Leishmania Bodies → Kala-Azar
 - Atypical Cells → Lymphoma
 - Atypical Plasma Cells → M. myeloma
- Temporal Artery → Giant Cell Arteritis
- Pleural or Pericardial → Extrapulmonary Tuberculosis

Therapeutic Trials

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 - Rarely specific
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Therapeutic Trials

- What is the best therapy for PUO patient?
 - To hold therapeutic trials in the early stage... except in:
 - Patient who is very sick to wait.
 - All tests have failed to uncover the etiology.

Therapeutic Trials

■ Antimicrobial Trials:

- Expected to suppress, but not cure, an infectious process such as abscess → may have false feeling of response.
- Failure to have quick response → does not mean wrong diagnosis:
 - Endocarditis
 - Pelvic inflam. Disease
 - Typhoid Fever

Therapeutic Trials

■ Empiric Drug:

- ☐ Tuberculosis
- ☐ Culture-negative Endocarditis
- ☐ Vasculitis ... Temporal Arteritis
- ☐ Pulmonary Emboli

Therapeutic Trials

- Empiric drug trial for suspected T.B.:
 - Presence of granuloma on Bx before culture result.
 - Elderly or immunocompromised patient with (+ve) TB skin test and deteriorating clinical condition.
 - No drug for stable patient without any suggestive features laboratory result.

Therapeutic Trials

- Empiric drug trial for suspected culture (-ve) Endocarditis:
 - Patient with new or changing murmur or peripheral signs of endocarditis.
 - Vancomycin or ampicillin + Gentamycin, may be used.

Therapeutic Trials

- Empiric drug trials for suspected Vasculitis:
 - Elderly with weight loss and any symptoms suggestive (headache, visual disturbance, jaw claudication) and \uparrow ESR > 50 mm/hr \rightarrow Prednisolone 60 PO
 - Patient above 50 yrs who is c/o muscle pain and stiffness around hip and shoulder with \uparrow ESR \rightarrow Prednisolone 20 mg PO OD

Dramatic response is enough to establish the DX.

Prognosis

- It depends on:
 - Cause of fever
 - Nature of the underlying disease(s) BUT .. Generally poor in:
 - Elderly
 - Neoplasm
- Diagnostic delay has adverse effect in:
 - Intra Abdominal Infection
 - Miliary Tuberculosis
 - Recurrent Pulmonary Emboli
 - Disseminated Fungal Infection
 - Temporal Arteritis

Outcome

- If the cause of fever remains elusive → repeat history and examination.
- 5 – 15% of cases → The diagnosis remain obscure. However, most of these patients defervesce without treatment → no disease later.

Prognosis

- Undiagnosed PUO patient generally have favorable outcome.
- Recovery in 4 weeks time ... 80%
- Recovery in 2 years time ... 90%
- Require NSAIDS or steroid ... 10%
- Mortality rate 5 years after discharge 3%