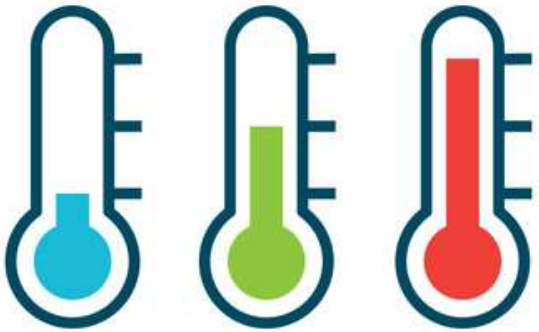


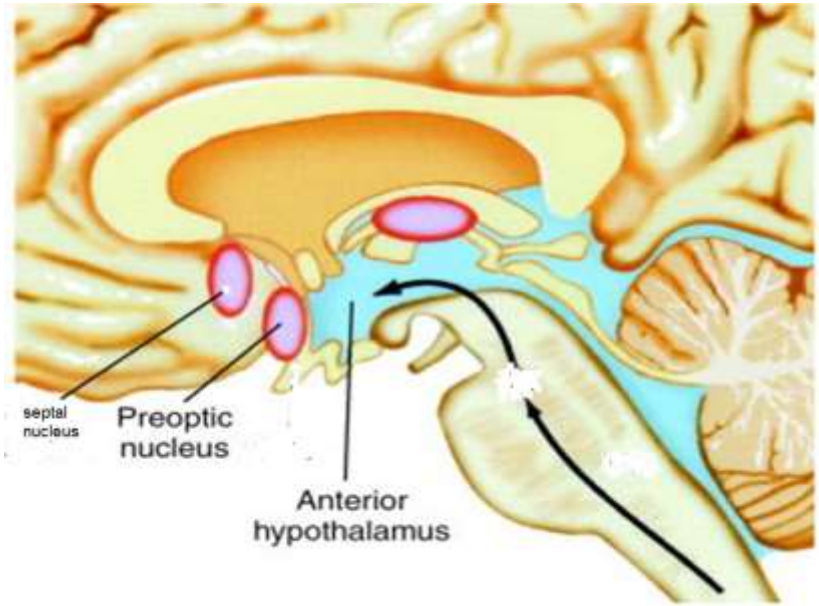
PYREXIA OF UNKNOWN ORIGIN

INTRODUCTION

BODY TEMPERATURE

Body temperature is normally maintained within a range of 37 – 38°c , normal body temperature is generally considered to be 37°c .

PHYSIOLOGY



Normal body temperature is maintained by a complex regulatory system in the anterior hypothalamus, preoptic area, temperature sensitive area, thermal set point.

PATHOGENESIS

PYROGENS

Substances the mediate the elevation of core body temperature

There are two types; **exogenous** and **endogenous** pyrogens.

EXOGENOUS PYROGENS

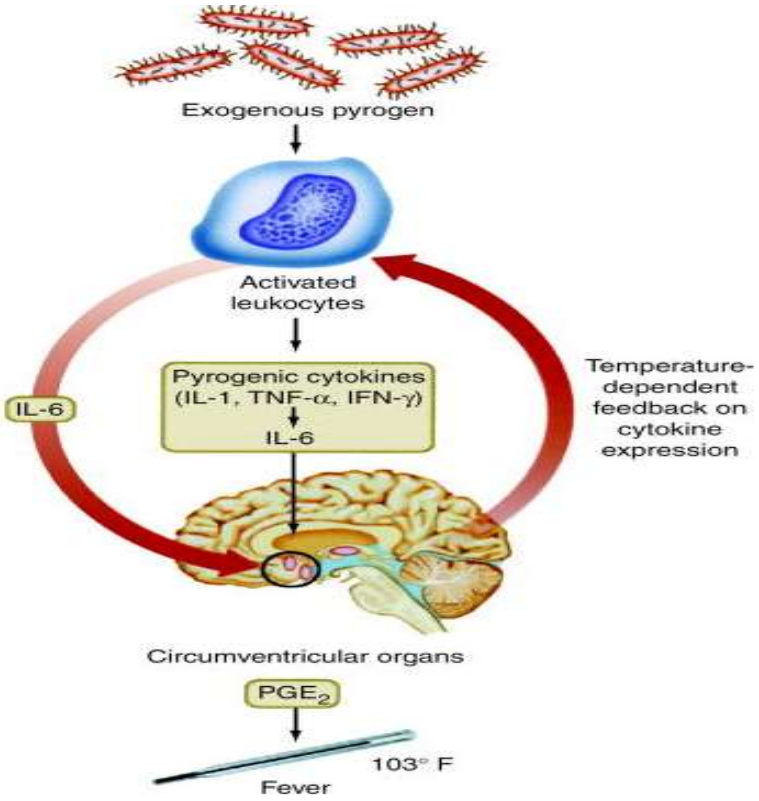
- It is derived from outside of the host, such as **microorganisms, toxins** and **microbial products**
- They are generally large molecules – cannot pass blood brain barrier
- They **induce the release of endogenous pyrogens** from **macrophages**.

PATHOGENESIS

ENDOGENOUS PYROGENS

- Endogenous pyrogens are derived from the **macrophages**.
- They are small molecules – can pass blood brain barrier

- Pyrogen cytokines trigger the hypothalamus to release **PGE2**, resulting in:
  1. Resetting of thermostatic temperature
  2. Activation of vasomotor center
  3. Vasodilatation
  4. Heat production



PYREXIA OF UNKNOWN ORIGIN

ORIGINAL DEFINITION *(Petersdotf anf Beeson, 1961)*

- Temperature ≥ 38.3ºC (101ºF) on several occasions
- Fever **≥ 3 weeks**
- Failure to reach a diagnosis despite **1 week of inpatient investigations** or **3 outpatient visits**

NEW DEFINITION *(Petersdotf anf Beeson, 1961)*

Temperature ≥ 38.3ºC (101ºF) lasting for more than **14 days** without an obvious cause despite a **complete history, physical examination** and **routine screening** with **laboratory evaluation**

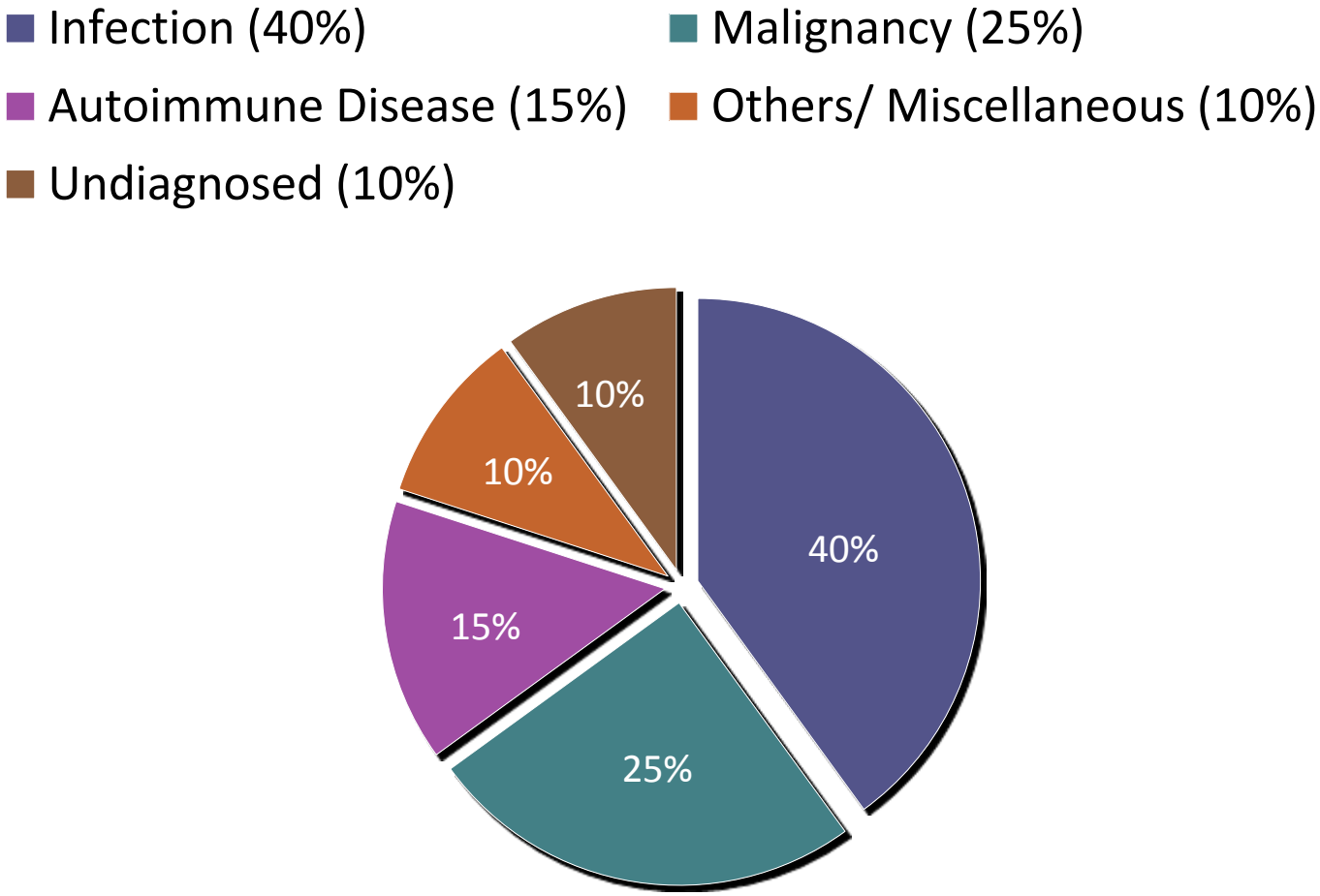
FACTORS

FACTORS THAT MAY HAVE CONTRIBUTED TO THE DIFFICULTY IN FINDING THE CAUSE OF FEVER INCLUDE:

- A common illness that does not have the usual symptoms – may be asymptomatic
- Illness whose symptoms appear later
- Illnesses with possibly **delayed positive test**
- Person is unable to communicate about other symptoms
- Genetic condition that causes periodic fever.

COMMON CAUSES

COMMON CAUSES OF PYREXIA OF UNKNOWN ORIGIN



CLASSIFICATION

DURACK AND STREET'S CLASSIFICATION

1. Classical
2. Nosocomial
3. Neutropenic
4. Pyrexia of unknown origin with HIV infection

CLASSIFICATION

Category	Definition	Aetiologies
Classic	• Temperature >38.3°C (100.9°F) ; • Duration of >3 weeks • Evaluation of at least 3 outpatient visits or 3 days in hospital	• Infection • Malignancy • collagen vascular disease
Nosocomial	• Temperature >38.3°C • Patient hospitalized ≥ 24 hours but no fever or incubating on admission • Evaluation of at least 3 days	• *Clostridium difficile* enterocolitis • drug-induced • pulmonary embolism • septic thrombophlebitis, • sinusitis
Immune deficient (neutropenic)	• Temperature >38.3°C • Neutrophil count ≤ 500 per mm3 • Evaluation of at least 3 days	• Opportunistic bacterial infections, • aspergillosis, • candidiasis, • herpes virus
HIV-associated	• Temperature >38.3°C • Duration of >4 weeks for outpatients, >3 days for inpatients • HIV infection confirmed	• Cytomegalovirus, • *Mycobacterium avium-intracellulare* complex, • *Pneumocystis carinii* pneumonia, • drug-induced, • Kaposi's sarcoma, lymphoma

1. CLASSICAL

CLASSIC PYREXIA OF UNKNOWN ORIGIN

- Temperature >38.3°C (100.9°F)
- Duration of >3 weeks
- Evaluation of at least 3 outpatient visits or 3 days in hospital

AETIOLOGIES

1. Infections
2. Malignancies
3. Collagen vascular disease
4. Others / miscellaneous which includes drug-induced fever

1. CLASSICAL

A. INFECTIONS

- **Bacterial**

  Abscesses, tuberculosis, uncomplicated UTI, endocarditis, osteomyelitis, sinusitis, prostatitis, cholecystitis, empyema, biliary tract infection, brucellosis, typhoid, etc.

- **Viral**

  Cytomegalovirus, infectious mononucleosis, HIV, etc.

- **Parasites**

  Malaria, toxoplasmosis, leishmaniasis, etc.

- **Fungal**

  Histoplasmosis, etc.

As the **duration of fever increases, infectious etiology decreases**. Malignancy and factitious fevers are more common in patients with prolonged pyrexia of unknown origin

1. CLASSICAL

B. MALIGNANCIES

HEMATOLOGICAL	NON-HAEMATOLOGICAL
1. Lymphoma 2. Chronic leukemia	1. Renal cell cancer 2. Pancreatic cancer 3. Colon cancer 4. Hepatoma

1. CLASSICAL

C. COLLAGEN VASCULAR DISEASE / AUTOIMMUNE DISEASE

- Temporal arthritis
- Rheumatoid arthritis
- Rheumatoid fever
- Inflammatory bowel disease
- Reiter’s syndrome
- Systemic lupus erythematosus
- Polyarthritis nodosa
- Giant cell arthritis
- Kawasaki disease

1. CLASSICAL

C. MISCELLANEOUS

- Hyperthyroidism
- Alcoholic hepatitis
- Inflammatory bowel disease
- Deep venous thrombosis

DRUGS

- Allopurinol
- Captopril
- Cimetidine
- Clofibrate
- Erythromycin
- Heparin
- Hydralazine
- Hydrochlorothiazide
- Isoniazid
- Meperidine
- Methydopa
- Nifedipine
- Nitrofurantoin
- Penicillin
- Phenytoin
- Procainamide
- Quinidine

1. CLASSICAL

C. MISCELLANEOUS

FACTITIOUS FEVER

Munchausen syndrome

Munchausen by proxy

THERMOREGULATORY DISORDER

Central

1. Brain tumor
2. Hypothalamic dysfunction

Peripheral

1. Hyperthyroidism
2. Pheochromocytoma

FEVER PATTERN

- **Intermittent Fever**
  - Any fever characterized by intervals of normal temperature
  - Malaria, pyaemia, septicemia

- **Continuous Fever**
  - Temperature **remains above normal throughout the day** and does not fluctuate more than 1C in 24 hours
  - Lobar pneumonia, Typhoid, Meningitis, UTI, Brucellosis

- **Remittent Fever**
  - A fever pattern in **which temperature varies during each 24 hour** period but **never reaches normal**.
  - Enteric Fever, Bacterial Endocarditis, Viral Pneumonia

FEVER PATTERN

- **Relapsing Fever**
  An **acute infection with recurrent episodes** of fever caused by spirochetes of the genus Borrelia which are borne by ticks or lice.

- **Undulant Fever**
  An infectious disease due to the bacteria Brucella.
  It is called undulant because the fever is typically undulant, **rising and falling like a wave.**
  It is also called brucellosis after its bacterial cause

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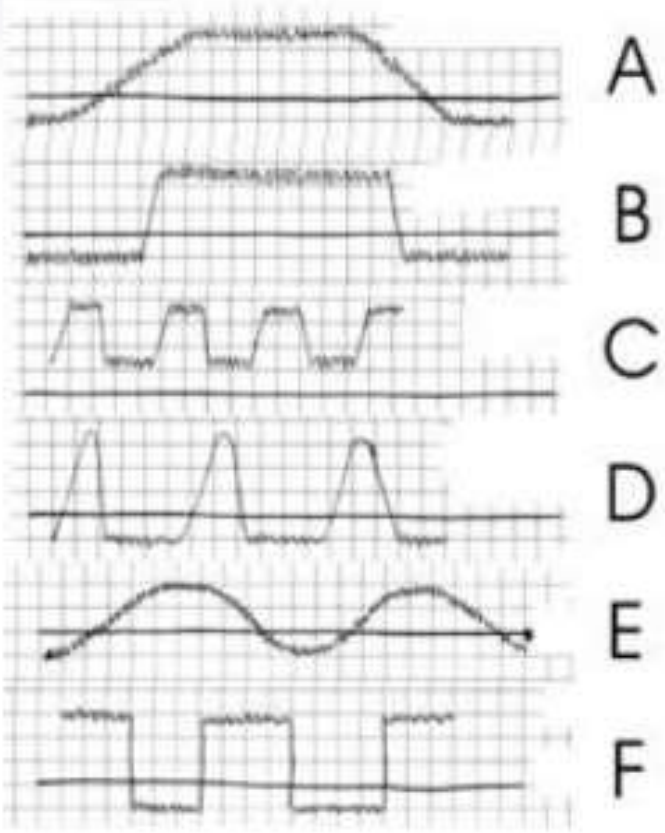
FEVER PATTERN



- A&B-Continuous fever
- C-Remittent
- D-Intermittent
- E-Relapsing fever
- F-Undulant fever

2. NOSOCOMIAL

NOSOCOMIAL PYREXIA OF UNKNOWN ORIGIN

- Temperature > 38.3°C
- Patient hospitalized ≥ 24 hours but no fever or incubating on admission
- Evaluation of at least 3 days

- More than 50% of patients with nosocomial PUO are due to **infection**
- Focus on sites where occult infections may be sequested, such as:
  - Sinusitis of patients with NG or Oro-tracheal tubes
  - Prostatic abscess in a man with urinary catheter

- 25% of **non-infectious cause** includes:
  - Acalculous colecystitis
  - Deep vein thrombophlebitis
  - Pulmonary embolism

3. NEUTROPENIC

IMMUNE DEFICIENT / NEUTROPENIC PUO

- Temperature >38.3°C
- Neutrophil count ≤ 500 per mm^3
- Evaluation of at least 3 days

- Patients on **chemotherapy** or **immune deficiencies** are susceptible to:
  - Opportunistic bacterial infection
  - Fungal infections such as candidiasis
  - Infections involving catheters
  - Perianal infections

- Examples of **etiological agent**:
  - Aspergillus
  - Candida
  - CMV
  - Herpes simplex

4. HIV-ASSOCIATED

IMMUNE DEFICIENT / NEUTROPENIC PUO

- Temperature > 38.3°C
- Duration of > 4 weeks for outpatients, > 3 days for inpatients
- HIV infection confirmed

- **HIV infection** alone may be a cause of fever

- Common **secondary causes** include:
  - Tuberculosis
  - CMV infection
  - Non-hodgkin lymphoma
  - Drug-induced fever

CLINICAL APPROACH

PYREXIA OF UNKNOWN ORIGIN : A CLINICAL APPROACH

HISTORY OF PRESENTING ILLNESS

1. **Onset**
   a. Acute
   b. Gradual

2. **Character**

2. **Antecedents**
   a. Dental extraction
   b. Urinary catheterization

CLINICAL APPROACH

PYREXIA OF UNKNOWN ORIGIN : A CLINICAL APPROACH

4. Associated symptoms

- Chills and rigors
- Night sweats
- Loss of weight
- Cough and dyspnea
- Headache
- Joint pain
- Abdominal pain
- Bone pain
- Sore throat
- Dysuria and rectal pain
- Altered bowel habit
- Skin rash

CLINICAL APPROACH

PYREXIA OF UNKNOWN ORIGIN : A CLINICAL APPROACH

PAST MEDICAL HISTORY

PAST SURGICAL HISTORY

DRUG HISTORY

FAMILY HISTORY

CLINICAL APPROACH

PYREXIA OF UNKNOWN ORIGIN : A CLINICAL APPROACH

- Travel
- Residential area
- Occupation
- Contact with domestic / wild animals / birds
- Diet history
- Sexual orientation
- Close contact with TB patients

PHYSICAL EXAMINATION

GENERAL

- Pattern of fever – continuous, intermittent, relapsing
- Ill or not ill
- Weight loss – chronic illness
- Skin rash

HANDS

- Stigmata of infective endocarditis
- Vasculitis changes
- Clubbing
- Presence of arthropathy
- Raynaud's phenomenon

PHYSICAL EXAMINATION

ARMS

- Drug injection sites (IV drug usage)
- Epithrochlear and axillary nodes (lymphoma, sarcoidosis, focal infection)
- Skin

HEAD AND NECK

- Feel temporal arteries (tender and thicken)
- **Eyes** – iritis / conjunctivitis
- Jaundice (ascending cholangitis)
- **Fundus** – choroidal tubercle (miliary TB), Roth's spot (infective endocarditis) and retinal hemorrhage (leukemia)
- Lymphadenopathy

PHYSICAL EXAMINATION

FACE AND MOUTH

- Butterfly rash
- Mucous membranes
- Seborrhoic dermatitis (HIV)
- Mouth ulcers (SLE)
- Buccal candidiasis
- Teeth and tonsil infections (abscess)
- Parotid enlargement
- **Ears** – otitis media

CHEST

- Bony tenderness
- **Cardiovascular** – murmurs
- **Respiratory** – signs of pneumonia, tuberculosis, empyema and lung cancer

PHYSICAL EXAMINATION

ABDOMEN

- Rose colored spot – typhoid fever
- Hepatomegaly
- Splenomegaly – haemopoietic malignancy, IE, malaria
- Renal enlargement – renal cell carcinoma
- Testicular enlargement – seminoma
- Penis & scrotum – discharge/rash
- Inguinal ligament

Per-rectal exam

Mass / tenderness in rectum/pelvis (abscess, carcinoma, prostatitis)

Vaginal examination

Collection of pelvic pus/ pelvic inflammatory disease

PHYSICAL EXAMINATION

CENTRAL NERVOUS SYSTEM

- Signs of meningism (chronic TB meningitis)
- Focal neurological signs (brain abscess, mononeuritis multiplex in plyarthritis nodosa)

INVESTIGATION

STAGE 1 – SCREENING TESTS

a. Full blood count
b. ESR and CRP
c. BUSE
d. LFTs
e. Blood culture
f. Serum virology
g. Urinalysis and culture
h. Sputum culture and sensitivity
i. Stool FEME and occult blood
j. Chest x-ray
k. Mantoux test

INVESTIGATION

STAGE 2

a. Repeat history and examination
b. Protein electrophoresis
c. CT (chest, abdomen, pelvis)
d. Autoantibody screen
e. Electrocardiogram (ECG)
f. Bone marrow examination
g. Lumbar puncture
h. Temporal artery biopsy
i. HIV test counselling
j. Ultrasonography

INVESTIGATION

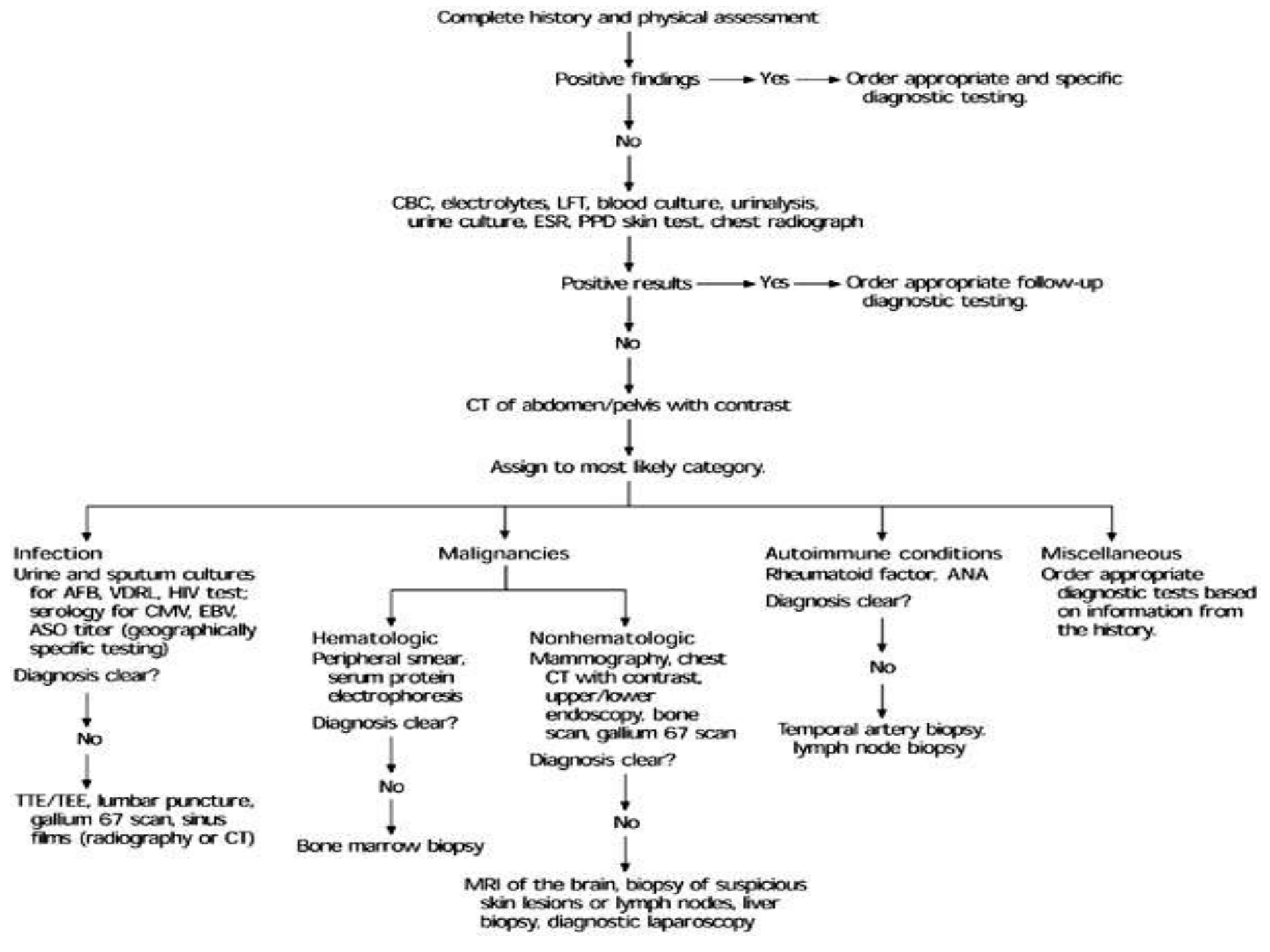
STAGE 3

Chest radiograph	• Tuberculosis, malignancy, *Pneumocystis carinii* pneumonia
CT of abdomen or pelvis with contrast agent	• Abscess, malignancy
Gallium 67 scan	• Infection, malignancy
Indium-labeled leukocytes	• Occult septicemia
Technetium Tc 99m	• Acute infection and inflammation of bones and soft tissue
MRI of brain	• Malignancy, autoimmune conditions
	• Malignancy, inflammation
Transthoracic or transesophageal echocardiography	• Bacterial endocarditis
Venous Doppler study	• Venous thrombosis

INVESTIGATION

STAGE 4

a. Treat TB
b. Endocarditis
c. Vasculitis
d. Trial of aspirin / steroids


Complete history and physical assessment
Positive findings
Yes
Order appropriate and specific diagnostic testing.
No
CBC, electrolytes, LFT, blood culture, urinalysis, urine culture, ESR, PPD skin test, chest radiograph
Positive results
Yes
Order appropriate follow-up diagnostic testing.
No
CT of abdomen/pelvis with contrast
Assign to most likely category.
Infection
Urine and sputum cultures for AFB, VDRL, HIV test; serology for CMV, EBV, ASO titer (geographically specific testing)
Diagnosis clear?
No
TTE/TEE, lumbar puncture, gallium 67 scan, sinus films (radiography or CT)
Malignancies
Hematologic
Peripheral smear, serum protein electrophoresis
Diagnosis clear?
No
Bone marrow biopsy
Nonhematologic
Mammography, chest CT with contrast, upper/lower endoscopy, bone scan, gallium 67 scan
Diagnosis clear?
No
MRI of the brain, biopsy of suspicious skin lesions or lymph nodes, liver biopsy, diagnostic laparoscopy
Autoimmune conditions
Rheumatoid factor, ANA
Diagnosis clear?
No
Temporal artery biopsy, lymph node biopsy
Miscellaneous
Order appropriate diagnostic tests based on information from the history.

DIAGNOSIS

- More invasive testing, such as LP or biopsy of bone marrow, liver, or lymph nodes, should be performed only when clinical suspicion shows that these tests are indicated or when the source of the fever remains unidentified after extensive evaluation.

- When the definitive diagnosis remains elusive and the complexity of the case increases, an infectious disease, rheumatology, or oncology consultation may be helpful.

THERAPEUTIC TRIALS

WHAT IS THE BEST THERAPEUTIC TRERAPY FOR PUO PATIENTS?

Therapeutic trials consist of combination of **broad spectrum antibiotics** and are given in :-

1. Patient who is very sick to wait.
2. All tests have failed to uncover the etiology.

PROGNOSIS

WHAT IS THE BEST THERAPEUTIC TRERAPY FOR PUO PATIENTS?

- Prognosis is determined primarily by the underlying disease.
- Outcome is worst for neoplasms.
- PUO patients who remain undiagnosed after extensive evaluation generally have a favorable outcome and the fever usually resolves after 4 - 5 weeks

SUMMARY

WHAT IS THE BEST THERAPEUTIC TRERAPY FOR PUO PATIENTS?

- PUO is often a diagnostic dilemma, quandary.
- Infections comprise ~30% of cases
- Bone marrow biopsies are of low diagnostic yield
- Diagnostic approach should occur in a step-wise fashion based on the H&P
- Patient's that remain undiagnosed generally have a good prognosis

REFERENCES

WHAT IS THE BEST THERAPEUTIC TRERAPY FOR PUO PATIENTS?

1. Nelson Essenssials Of Pediatrics 6th Edition
2. Harrison's Principles Of Internal Medicine 18th Edition.
3. Mandell, Bennet & Dolin's, Principle Of Infectious Disease 6th Edition.

THANK YOU