

# PYREXIA OF UNKNOWN ORIGIN

AMALDEV  
18

# DEFINITION

- FEVER  $\geq 38.3^{\circ}\text{C}$  ( $\geq 101^{\circ}\text{F}$ ) ON AT LEAST TWO OCCASIONS
- ILLNESS DURATION OF  $\geq 3$  WEEKS
- NO KNOWN IMMUNOCOMPROMISED STATE
- DIAGNOSIS THAT REMAINS UNCERTAIN AFTER
  - THOROUGH HISTORY-TAKING
  - PHYSICAL EXAMINATION
  - OBLIGATORY INVESTIGATIONS

# ETIOLOGY

- **MAJOR CAUSES**

- INFECTION (30%)
- MALIGNANCY (20%)
- MISCELLANEOUS(20%)
- CONNECTIVE TISSUE DISORDERS(15%)
- IDIOPATHIC (15%)

- **MINOR CAUSES**

- PERIODIC FEVER SYNDROME

# INFECTIONS (SPECIFIC ORGANISMS)

- TB (PARTICULARLY EXTRAPULMONARY)
- HIV-1 INFECTION
- OTHER VIRAL INFECTIONS: CYTOMEGALOVIRUS (CMV), EPSTEIN-BARR VIRUS (EBV)
- FUNGAL INFECTIONS (E.G. ASPERGILLUS , CANDIDA . OR DIMORPHIC FUNGI)
- INFECTIONS WITH FASTIDIOUS ORGANISMS (E.G. BARTONELLA , TROPHERYMA )

# MALIGNANCY (~20%)

- HAEMATOLOGICAL MALIGNANCY
- LYMPHOMA, LEUKAEMIA AND MYELOMA
- SOLID TUMOURS
- RENAL, LIVER, COLON, STOMACH, PANCREAS

# MISCELLANEOUS (~20%)

- **CARDIOVASCULAR**
- ATRIAL MYXOMA, AORTITIS, AORTIC DISSECTION
  
- **RESPIRATORY**
- SARCOIDOSIS, PULMONARY EMBOLISM AND OTHER THROMBOEMBOLIC DISEASE, EXTRINSIC ALLERGIC ALVEOLITIS
  
- **GASTROINTESTINAL**
- INFLAMMATORY BOWEL DISEASE, GRANULOMATOUS HEPATITIS, ALCOHOLIC LIVER DISEASE, PANCREATITIS

- **ENDOCRINE/METABOLIC**

- THYROTOXICOSIS, THYROIDITIS, HYPOTHALAMIC LESIONS, PHAEOCHROMOCYTOMA, ADRENAL INSUFFICIENCY, HYPERTRIGLYCERIDAEMIA

- **HAEMATOLOGICAL**

- HAEMOLYTIC ANAEMIA, PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA, THROMBOTIC THROMBOCYTOPENIC PURPURA, MYELOPROLIFERATIVE DISORDERS, CASTLEMAN'S DISEASE, GRAFT-VERSUS-HOST DISEASE (AFTER ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION)

- **INHERITED**
- **FAMILIAL MEDITERRANEAN FEVER AND PERIODIC FEVER SYNDROMES**
- **DRUG REACTIONS**
- **ANTIBIOTIC FEVER, DRUG HYPERSENSITIVITY REACTIONS ETC.**
- **FACTITIOUS FEVER**

# CLINICAL APPROACH

## HISTORY OF PRESENTING ILLNESS

### 1. ONSET

- SUDDEN/ACUTE
- GRADUAL

### 2. DURATION

- HOURS
- DAYS
- WEEKS
- MONTHS

### 3. ASSOCIATED SYMPTOMS

LOW GRADE FEVER & HIGH GRADE FEVER ( CHILLS AND RIGORS)

ABDOMINAL PAIN

NIGHT SWEATS

BONE PAIN

LOSS OF WEIGHT

SORE THROAT

COUGH AND DYSPNEA

DYSURIA AND RECTAL PAIN

HEADACHE

ALTERED BOWEL HABIT

JOINT PAIN

SKIN RASH

PAST HISTORY -

FAMILY HISTORY -

PERSONAL HISTORY —

## GENERAL EXAMINATION

### PALLOR

- ICTERUS
- CYANOSIS
- CLUBBING
- LYMPHADENOPATHY
- EDEMA
- VITALS

# MICROBIOLOGICAL INVESTIGATIONS

## LOCATION-INDEPENDENT INVESTIGATIONS

### MICROSCOPY

- BLOOD FOR ATYPICAL LYMPHOCYTES (, CMV, HIV-1, HEPATITIS VIRUSES OR TOXOPLASMA GONDII)
- RESPIRATORY SAMPLES FOR MYCOBACTERIA AND FUNGI
- STOOL FOR OVA, CYSTS AND PARASITES
- BIOPSY FOR LIGHT MICROSCOPY (BACTERIA, MYCOBACTERIA, FUNGI) AND/OR ELECTRON MICROSCOPY (VIRUSES, PROTOZOA (E.G. MICROSPORIDIA) AND OTHER FASTIDIOUS ORGANISMS (E.G. TROPHERYMA WHIPPLEI))
- URINE FOR WHITE OR RED BLOOD CELLS AND MYCOBACTERIA (EARLY MORNING URINE ×3)

# CULTURE

- ASPIRATES AND BIOPSIES (DEEP ABSCESS, DEBRIDED TISSUES)
- BLOOD, INCLUDING PROLONGED CULTURE AND SPECIAL MEDIA CONDITIONS
- SPUTUM FOR MYCOBACTERIA
- CSF
- GASTRIC ASPIRATE FOR MYCOBACTERIA
- STOOL
- SWABS
- URINE # PROSTATIC MASSAGE IN OLDER MEN

# ANTIGEN DETECTION

- BLOOD, E.G. HIV P24 ANTIGEN (USUALLY COMBINED WITH AN ANTIBODY TEST), CRYPTOCOCCAL ANTIGEN, ASPERGILLUS GALACTOMANNAN ELISA AND (1,3)-B-D-GLUCAN (FOR FUNGI OTHER THAN MUCORACEOUS MOULDS AND CRYPTOCOCCUS)
- CSF FOR CRYPTOCOCCAL ANTIGEN
- BRONCHOALVEOLAR LAVAGE FLUID FOR ASPERGILLUS GALACTOMANNAN
- NASOPHARYNGEAL ASPIRATE/THROAT SWAB FOR RESPIRATORY VIRUSES, E.G. IAV OR RSV
- URINE, E.G. FOR LEGIONELLA ANTIGEN

## NUCLEIC ACID DETECTION

- BLOOD FOR BARTONELLA AND VIRUSES
- CSF FOR VIRUSES AND KEY BACTERIA (MENINGOCOCCUS, PNEUMOCOCCUS, LISTERIA MONOCYTOGENES)
- NASOPHARYNGEAL ASPIRATE/THROAT SWAB FOR RESPIRATORY VIRUSES
- SPUTUM FOR MYCOBACTERIUM TUBERCULOSIS (MTB)
- BRONCHOALVEOLAR LAVAGE FLUID, E.G. FOR RESPIRATORY VIRUSES
- TISSUE SPECIMENS, E.G. FOR T. WHIPPLEI
- URINE, E.G. FOR CHLAMYDIA TRACHOMATIS, NEISSERIA GONORRHOEAE
- STOOL, E.G. FOR NOROVIRUS, ROTAVIRUS

# IMMUNOLOGICAL TESTS

- SEROLOGY (ANTIBODY DETECTION) FOR VIRUSES, INCLUDING HIV-1, AND SOME BACTERIA
- INTERFERON-GAMMA RELEASE ASSAY FOR DIAGNOSIS OF EXPOSURE TO TUBERCULOSIS (BUT NOTE THIS WILL NOT DISTINGUISH LATENT FROM ACTIVE DISEASE)

# GEOGRAPHICALLY RESTRICTED TESTS

## MICROSCOPY

- BLOOD FOR TRYPANOSOMIASIS, MALARIA AND BORRELIA SPP.
- STOOL FOR GEOGRAPHICALLY RESTRICTED OVA, CYSTS AND PARASITES
- BIOPSY FOR LIGHT MICROSCOPY (DIMORPHIC FUNGI, LEISHMANIA SPP. AND OTHER PARASITES)
- URINE FOR RED BLOOD CELLS AND SCHISTOSOME OVA

## ANTIGEN DETECTION

- BLOOD, E.G. DENGUE VIRUS NS1 ANTIGEN, HISTOPLASMA ANTIGEN (RESTRICTED AVAILABILITY) AND MALARIA ANTIGEN (E.G. HRP-2 FOR PLASMODIUM FALCIPARUM OR PARASITE-SPECIFIC LDH FOR P. FALCIPARUM AND P. VIVAX)

## **NUCLEIC ACID DETECTION**

- **BLOOD FOR CAUSES OF VIRAL HAEMORRHAGIC FEVER**
- **CSF FOR GEOGRAPHICALLY RESTRICTED VIRUSES, E.G. JAPANESE ENCEPHALITIS VIRUS**
- **NASOPHARYNGEAL ASPIRATE/THROAT SWAB OR BRONCHOALVEOLAR LAVAGE FLUID FOR GEOGRAPHICALLY RESTRICTED RESPIRATORY VIRUSES, E.G. MERS-CoV**

## **IMMUNOLOGICAL TESTS**

- **SEROLOGY (ANTIBODY DETECTION) FOR VIRUSES, DIMORPHIC FUNGI AND PROTOZOA**

# ADDITIONAL INVESTIGATIONS IN PUO

- **SEROLOGICAL TESTS FOR CONNECTIVE TISSUE DISORDERS:**
  1. **AUTOANTIBODY SCREEN**
  2. **COMPLEMENT LEVELS IMMUNOGLOBULINS**
  3. **CRYOGLOBULINS**
- **FERRITIN**
- **ECHOCARDIOGRAPHY**
- **ULTRASOUND OF ABDOMEN**
- **CT/MRI OF THORAX, ABDOMEN AND/OR BRAIN**
- **IMAGING OF THE SKELETAL SYSTEM:**
  1. **PLAIN X-RAYS**
  2. **CT/MRI SPINE**
  3. **ISOTOPE BONE SCAN**

- LABELLED WHITE CELL SCAN
- FLUORODEOXYGLUCOSE-POSITRON EMISSION TOMOGRAPHY (FDG-PET)/SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)
- BIOPSY:
  1. BRONCHOSCOPY AND LAVAGE + TRANSBRONCHIAL BIOPSY
  2. LYMPH NODE ASPIRATE OR BIOPSY
  3. BIOPSY OF RADIOLOGICAL LESION
  4. BIOPSY OF LIVER
  5. BONE MARROW ASPIRATE AND BIOPSY
  6. LUMBAR PUNCTURE
  7. LAPAROSCOPY AND BIOPSY
  8. TEMPORAL ARTERY BIOPSY

# PROGNOSIS

- 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

## Reference:

- Davidson's principles & practical of medicine
- Archit Bolor Textbook
- Harrison's principles of internal medicine

THANK YOU