

Pyrexia of unknown origin (PUO)

Fever

Pathophysiology of fever : Temperature of the body is controlled by core body temperature which is controlled by and in the anterior hypothalamus (thermo-regulator) , so fever is elevation of the temperature of the core body temperature (normally 36.5 – 37.2) . Temperature > 42 or < 35 °C is fatal .

Fever occur when foreign body enter the body like bacteria ,virus ,fungal or malignant cell ,inflammation ...etc (pyrogen)stimulate immune system to stimulate prostaglandin E2 where it affect the hypothalamus to increase body temperature .

Body temperature is examined by thermometer in the mouth which is near the normal core temperature , or rectal exam where it more than mouth temperature by 0.5 degree so we should reduce 0.5 degree from the reading result . or by axillary exam where it less than mouth by 0.5 degree so we should add 0.5 degree to the reading degree .

Types of fever

a) continuous Fever : Temperature remains above normal throughout the day and does not fluctuate more than 1 °C in 24 hours, e.g. lobar pneumonia, typhoid, meningitis, urinary tract infection, brucellosis, or typhus .

b) remittent Fever : Temperature remains above normal throughout the day and fluctuates more than 1 °C in 24 hours, e.g., infective endocarditis.

c) Intermittent fever : The temperature elevation is present only for a certain period, later cycling back to normal, e.g. malaria, kala-azar, pyaemia, or septicemia .

Classification of temperature :

Normal 36.5 -37.2 °C , hypothermia < 35°C , fever > 37.2 °C , low grade fever 37.3 -38°C , hyperpyrexia > 40 °C .

Pyrexia of unknown origin (PUO)

It indicate fever > 38.3 °C without obvious source for 3 weeks and in more than one occasion readings despite 1 week of inpatient investigations or 3 outpatient visits , it is also called fever of unknown origin (FUO) .

Causes

Usually either atypical presentation of common disease or rare disease . Its main causes are infection ,malignancy , autoimmune and connective tissue diseases ,miscellaneous causes and idiopathic . PUO also has subsets classification into nosocomial (hospital acquired) , immunocompromised patient and HIV patient .

1- Infections (~30%) : It is either

A- Specific location : Abscesses ;hepatobiliary , diverticula ,urinary tract including prostate ,pulmonary and CNS .

infection of oral cavity including dental with head and neck including sinuses .Bone and joints infection . infective endocarditis .

B- Specific organisms : tuberculosis especially extrapulmonary . HIV1infection ,other viral infection including Cytomegalovirus CMV and Epstein Barr virus EBV . Fungal infection like aspergillus and candida infection or

dimorphic fungi .Infection with fastidious micro-organisms like Bartonella species .

C- Specific patients group :

Imported infection from outside to inside country like malaria ,dengue ,leishmaniasis ,brucellosis ,enteric fever .

Nosocomial infection occur during surgical procedures or prosthetic materials .

HIV –positive individuals : acute retroviral syndrome or AIDS defining conditions .

- 2- Malignancy (~20%) : Haematological like leukemias ,lymphomas and myeloma or solid malignancy like renal ,hepatic ,colon stomach and pancreas.
- 3- Connective tissue diseases and autoimmune diseases (~15%) : in old age like polyarteritis nodosa and polymyositis rheumatica . in young ages like still 's disease, vasculitis , polymyositis and Behcet's syndrome .
- 4- Miscellaneous (~20%) : like cardiovascular diseases atrial myxoma ,aortitis . respiratory diseases like extrinsic allergic alveolitis , pulmonary embolism and sarcoidosis . Gastrointestinal diseases like inflammatory bowel disease , chronic liver diseases . Endocrine and metabolic diseases like thyrotoxicosis ,thyroiditis Addison disease . haematological diseases like autoimmune haemolytic anemia , graft versus host disease and thrombotic thrombocytopenic purpura . Inherited like familial Mediterranean fever and familial fever syndrome . drug fever due to hypersensitivity reaction or antibiotic fever . Factitious fever .
- 5- Idiopathic (~15%) :fever disappear without reaching the cause .

Clinical assessment : Proper history including travels ,drug use exposure to noxious materials family and inherited diseases ..etc and full examination must be done usually young patients have infectious causes while elderly patients may have infectious and non infectious causes detailed history and examination must be repeated at regular interval to detect any new signs indicate vasculitis or endocarditis in men we should care about hidden area including prostate and breast in female and always we should look for factitious fever in which the patient looks well and his temperature > 41 °C lose of diurnal variation of temperature lose of fever pulse rate relation and no sweating during defervescence , presence of self induce harm normal temperature during observation at hospital .

Investigations : patients should be sent for complete blood count and ESR with C-reactive protein , renal function test RFT , liver function test LFT urinalysis and general stool exam ,blood for culture and sensitivity , radiological study according to need like chest X-ray ,organ suspected affected CT-scan if CNS involvement suspected CSF study cerebrospinal fluid study , infection diagnosis if suspected by nucleic acid amplification serological test ,splenic aspiration for leishmaniasis ,radiolabel led white cell study or positron emission tomography (PET-scan) for detection of hidden infection site . For connective tissue diagnosis by radiological study , antibody studies . more invasive investigation may needed like liver biopsy if

there are elevated liver enzyme or radiological indications , bone marrow aspirate and biopsy used for microscopic study ,histopathological study and culture for microbiological study , blind organ if no abnormal markers indicate for biopsy are unhelpful ,any lymphadenopathy must studied by biopsy ,laparoscopy and organ biopsy may be needed .

Treatment : According to the cause specific antibiotics for infectious causes , steroid for immunological and connective tissue causes and chemotherapy for malignancy .

Prognosis :

Mortality rate 30-40% in malignant conditions in elderly patients . While if long term fever without diagnosis usually the prognosis is good .

PUO in immunocompromised patients

These patients are either congenital causes ,on immunosuppressant drugs ,on corticosteroids medication ,malignant diseases . the patient has neutropenia , lymphopenia , monocytopenia or mixed this lead to ordinary and opportunistic infection in these cases the diagnosis of infection should be rapid because within hours might enter into septicemia and septic shock which carry high mortality rate. The clinical features in these patients are atypical the fever may be absent due to low immunological response, opportunistic infection which not occur in immunocompetant patient must be diagnosed and microbial resistance increase due to previous use of antibiotics . The fever in these patients should be differentiated from primary disease , opportunistic or new infection or drug fever .

PUO in HIV patients

This is due acute seroconversion or AIDS defining condition and it will be studied in the relevant subject .

PUO due to nosocomial infection

This occur in patients after admission to hospital from central venous catheter ,double lumen venous catheter , ventilator ...etc . The bacteria usually meticillin resistant staphylococcus aureus MRSA or coagulase negative staphylococci ,enterococci , gram 's negative bacteria or fungal infection . It proved by blood culture or instrument tip culture . Treated by removing medical instrument and antibiotics against specific bacteria for minimum 2 weeks .