Pyrexia of Unknown Origin (PUO)

Definition

- A temperature greater than 38.3°C on several occasions by more than three weeks of illness (OR)
- Failure to reach a diagnosis after one week of inpatient investigations
    - 30 to 50% of cases are due to infections
    - 10-20% autoimmune disorders
    - 5-10% cancer
    - 10-15%of patients remain undiagnosed despite extensive investigations and in 75% of these,the fever resolves spontaneously.

Diagnosis

- Thorough history including:
    - Family contact
    - Immunization status
    - Travel history
    - Nutrition (including consumption of dairy products)
    - Drug history (over-the-counter medications, prescription medications, illicit substances)
    - Animal contacts (including possible exposure to ticks and other vectors)
    - Chemical contacts
    - Previous history of surgery
    - Psychiatric problems.
- Symptoms from all major systems: general complaint, weight loss, nightsweats, headache and rashes, etc.
- Examination of the patient
    - Documentation of fever and exclusion of factitious fever (may be up to10% of cases)
    - Look for signs usually accompanying fever (e.g. Tachycardia and chills)

- Physical examination should be repeated daily while the patient is in hospital.
- Particularly watch for:
  - Rash
  - Lymph node enlargement
  - Signs of arthritis
  - New /changing cardiac murmurs
  - Abdominal tenderness or rigidity
  - Fundoscopic changes and neurological deficits

Investigations

Table 9.26 Stages of assessment

Stage 1	**Stage 2**	**Stage 3**
• Thorough history and examination • Preliminary investigations – ○ FBC and differential count ○ ESR and CRP ○ Malaria blood films (if travel history) ○ Widal test ○ Urinalysis and culture ○ Blood culture ○ Chest X-ray ○ Mantoux test ○ USG (Abdomen)	• Review history and repeat examination • Specific investigations – ○ ASO titre ○ Hepatitis serology ○ HIV, ○ VDRL/TPHA ○ Viral screen – CMV, EBV ○ LDH ○ ANA ○ RA factor ○ CPK	• Review the patient's history and examination again before invasive investigatons – • invasive investigations ○ CT/ MRl (Chest & abdomen) ○ ECHO ○ Bone marrow aspirate ○ Tissue/liver/lymph node biopsy ○ Lumbar puncture ○ Nuclear medicine – bone scan

Management

- Specific management depends on specific diagnosis.
- Empirical treatment has never been advocated in case of ***PUO except three following*** important conditions:
    - Cases that meet criteria for culture-negative endocarditis
    - Cases suggestive of cryptic disseminated tuberculosis (or other granulomatous infections)
    - Cases in which temporal arteritis (with vision loss) is suspected

Management in Immunocompromised or Neutropenic Patients

- Gram-negative organisms were mainly responsible in the past, but now Gram-positive ones can be isolated, especially coagulase-negative *Staphylococci*.
- Treatment according to febrile neutropenic regime
- Take cultures and institute immediate antibiotic therapy before waiting for results
- Commonly used regimens include:
    - Anti-pseudomonal penicillin plus aminoglycoside e.g. Piperacillin/Gentamicin;
    - Third generation cephalosporin e.g. Ceftazidime or Meropenem
- These are very effective against common Gram-negative organisms, but lessso against Gram-positive ones which are now a more common problem.
- Reliably effective antibiotic against these are glycopeptides e.g. Vancomycin.
- Vancomycin & 4^{th} -generation Cephalosporin e.g. Cefepime should be used when blood culture results are known or if no response after 48 hour of empirical antibiotic therapy
- In high swinging fever without any obvious focus or positive cultures, deep fungal infection is likely and if fever persisting for >72 hours in cancer patients with neutropenia, add Amphotericin B.