Infectious Diseases

Lesson 1

THE FEBRILE PATIENT

Bernardino Roca Villanueva
Servicio de Medicina Interna, Hospital General de Castellón
Departamento de Medicina, Universidad Jaume I
broca@uji.es
Objectives and learning goal
Objectives

• To study the clinical significance of increased body temperature
• To know the concept of fever of undetermined origin
Learning goal

To achieve enough theoretical information for an initial clinical assessment of a patient who presents with fever
Contents

• Normal temperature and fever
• New onset fever in the hospitalized patient
• Fever of undetermined origin (FUO)
• Diagnostic workup of FUO
• Key messages
• Further reading
Normal temperature and fever
Anatomy of body temperature regulation

- Anterior hypothalamus, region close to the optic chiasm
- Other neural structures, including
  - Brain stem
  - Spinal cord
  - Sympathetic ganglia
Mechanisms of temperature regulation

- A distinct temperature set point is established
- When the body’s core temperature drops below that set point, the nervous system →
  - increases body metabolism
  - stimulates shivering and chills
- When core temperature exceeds that set point, the nervous system →
  - increases peripheral blood flow
  - sweating occurs
Normal body temperature

- 37 °C ( = 98.6 °F)
- Varies from individual to individual, i.e., the set point may be lower or higher than 37 °C
- Each individual’s core temperature varies during the day, being lower in the morning and increasing in the evening
- Before concluding that a patient has a fever, the two previous circumstances must be taken into account
Mechanisms of the febrile response

Infection
Other stimuli

Monocytes
Macrophages
Other

Interleukin 1
Tumor necrosis factor α
Interleukin 6
Interferon γ

Circumventricular organs
near the optic chiasm

Phospholipase A₂
Cyclooxygenase pathway
Prostaglandin E₂

Anterior hypothalamus
Brain stem

↑ Core temperature set point

Blood–brain barrier
Benefits of fever

- **Warning** sign for the onset of infection or other disease
- Growth of some viruses, bacteria, fungi, and parasites are **inhibited** by a rise in temperature above 37 °C
- **Enhances** the ability of macrophages and neutrophils to kill foreign pathogens
- Improves cell-mediated **immune** function
Harmful effects of fever

- Patients with heart disease may suffer cardiac ischemia because of increase in heart rate and oxygen demands
- Patients with severe pulmonary disease may similarly be unable to cope with the increased oxygen demands
- Elderly patients with limited mental capacity may develop confusion and lethargy
- Children may suffer febrile seizures
Treatment of fever - I

- Controversial
- Clearly indicated only in patients who may suffer harmful effects
- The most important is treating the underlying cause
- Acetaminophen, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs, (all ↓ prostaglandin E2 and ↓ temperature set point), on a regular schedule
Treatment of fever - II

- **Direct cooling** of the body (ice, cold water, etc.):
  - Secondary role
  - Only with drugs that reset the thermal set point, otherwise CNS → chills and shivering → discomfort

- Acetaminophen, high dose, to be avoided in patients with serious underlying liver disease

- Acetylsalicylic acid generally to be avoided in:
  - Children, risk of **Reye’s syndrome** (fatal hepatic and renal failure)
  - Patients with coronary heart disease, risk of coronary artery vasoconstriction
Common causes of fever in the general population

• Respiratory tract infections
• Gastrointestinal infections
• Urinary tract infections
New onset fever in the hospitalized patient
General considerations

• A very common clinical problem
• Causes are myriad
• Patients frequently have several medical and surgical conditions at a time
• Patients may be severely ill
• A complete present and past medical history and physical exam are key to determine the cause
Postoperative patient

- Wound infection (purulent discharge, erythema, edema, and tenderness) must first be excluded
- **Immediate** postoperative period (24-48 hours), *Streptococcus pyogenes*, severe bacteremia and septic shock, with minimal purulence at the wound
- **Later** postoperative period, *Staphylococcus aureus*, including MRSA, and nosocomial pathogens such as *Pseudomonas* spp., *Klebsiella* spp., and *Escherichia coli*
Surgical wound infections
Patient who has suffered bowel perforation

- Development of intra-abdominal abscess is a common cause of fever
- Frequently multibacterial:
  - Gram-positive cocci
  - Gram-negative rods
  - Anaerobes, especially *Bacteroides fragilis*
- Abdominal ultrasound, and particularly computerized tomography (CT) scan should be ordered to exclude this possibility
Abdominal abscesses
Chronically ill patient

- **Decubiti ulcers** need to be considered as a source of infection.
- Full examination of the **back** and **buttocks** regions should be performed for tissue breakdown and purulent discharge.
- Organisms associated with deep decubiti ulcers include those responsible of late postoperative infection and anaerobes, including *Bacteroides fragilis*. 
Decubiti ulcers
Respiratory infections in intensive care patients and other debilitated patients - Pathogenesis

- Bacteria colonizing the nasopharynx can readily gain entry to the bronchi and pulmonary parenchyma, causing bronchitis and pneumonia.
- Factors favoring:
  - Tracheal intubation
  - Sedatives
  - Stroke and other diseases
- Differential of infection and colonization difficult
Respiratory infections in intensive care patients and other debilitated patients - Diagnosis

- **Sputum tests:**
  - Presence of at least one organism on gram stain, combined with **more than 10 neutrophils per high-power field**, strongly suggests infection
  - Culture identifies the offending organism and sensitivities to antibiotics
- **Chest X-ray**, a new infiltrate suggests pneumonia
- **Arterial blood gases**, reduction in arterial Pa O₂, suggests pneumonia
Ventilator associated pneumonia
Line related fever – Prevalence and management

• Most hospitalized patients have one or more of these venous (and arterial) catheters or lines in place
• They are always at risk of becoming infected, and they are a common cause of fever in hospitalized patients
• At onset of fever, all venous (and arterial) lines should be examined for erythema, warmth, and exudate
• Particularly in the patient who has developed shock, all lines should be removed and appropriate empiric antibiotic coverage instituted immediately
Line infection
Line related fever - Causes

• *Staphylococcus aureus*, *Staphylococcus epidermidis*, and gram-negative rods

• *Candida* spp., in patients who
  • have been in the hospital for prolonged periods
  • have received multiple antibiotics
Bladder catheter related fever

- A major infectious cause of fever in hospitalized patients
- **Nearly all** patients with bladder catheters develop urinary tract infections within 30 days, despite the use of closed urinary collecting systems
- **Urinalysis** and **urine culture** need to be part of the fever workup in all patients with urinary catheters
Sinusitis

- Nasogastric and other tubes placed through the nasal passage, may occlude the ostia draining the air sinuses which can lead to sinusitis and fever
- Fever workup in these patients must include sinus films
- If sinusitis is discovered:
  - The tube must be removed from the nasal passage
  - Appropriate antibiotic coverage must be instituted
Maxillary sinusitis

Normal
Noninfectious causes of fever

• Pulmonary emboli
• Drugs, almost any of them, including antibiotics, may cause it
• Undrained collections of blood
• Inflammatory diseases
• Other
Antibiotic therapy

- Empiric antibiotic coverage must be individualized to take into account:
  - The patient **history, physical exam, test results**, etc.
  - The prevailing bacterial flora in each hospital unit
  - The history of antibiotic use in the patient

- Generally guided by **gram stain**, if gram unavailable, antibiotics should be active against gram-positive and gram-negative bacteria

- Empiric antibiotic coverage needs to be **streamlined** once culture data are available
Antibiotic related problems

- Selection of highly resistant bacterial pathogens
- Candidemia
- *Clostridium difficile* colitis
- Side effects

Hospitalized patient requires a systematic diagnostic approach and the judicious use of antibiotics. Too often, patients are covered unnecessarily for prolonged periods, using broad-spectrum antibiotics.
Fever of undetermined origin
Approach of the problem

- Remains one of the great challenges in infectious diseases
- Requires a thoughtful diagnostic approach by a highly experienced clinician
- Requires a team approach in which all caregivers repeatedly share their daily findings and continually generate and test new hypotheses
Definition

• The name “fever of undetermined origin” (FUO) carries with it specific criteria and should not be loosely applied

• As first defined in 1961, FUO requires that the patient have all the following:
  • An illness that has lasted at least 3 weeks
  • Fever of more than 38.3°C (101 °F) on several occasions
  • No diagnosis after routine workup for 3 days in hospital or after 3 or more outpatient visits
Before diagnosing FUO ...

• Carefully document that the patient fulfills the criteria

• The patient should be instructed to measure both 6-AM and 6-PM temperature to rule out an exaggerated circadian rhythm

• An electronic thermometer should always be used to exclude the possibility of factitious fever
Pattern of fever

• Generally **not helpful** in identifying the fever’s cause

• Patients with daily fever are more likely to be diagnosed as compared to those with intermittent or periodic fever

• Fever repeatedly highest in the early morning suggests:
  • Miliary tuberculosis
  • Typhoid fever
  • Periarteritis nodosa
Groups of causes of FUO

- Infections
- Neoplasms
- Autoimmune disorders
- Miscellaneous
Infections causing FUO - I

- **Abscesses**, particularly abdominal abscesses that may persist for prolonged periods before being diagnosed
- **Osteomyelitis**, particularly of the vertebral bodies, mandible, and air sinuses
- **Subacute bacterial endocarditis**, less common now with improved Micro and Echo tests
- **Biliary system infections**, sometime with no right upper quadrant pain or tenderness
- **Subacute pyelonephritis**, can present with absence of dysuria, frequency, or flank pain
Osteomyelitis
Subacute bacterial endocarditis
Infections causing FUO - II

• **Miliary tuberculosis**, in elderly and immunocompromised, such as patients with HIV, on high-dose glucocorticoids or a tumor necrosis factor (TNF) inhibitor

• Spirochetal diseases, such as **leptospirosis**, **Lyme disease** and **relapsing fever**

• **Brucellosis**, by eating unpasteurized cheese

• **Rickettsial** infections, history of tick bite

• **Chlamydia psittaci**, contracted from birds
Normal

Miliary tuberculosis
Miliary tuberculosis
Normal

Miliary tuberculosis
Normal

Miliary tuberculosis
Normal  

Miliary tuberculosis
Infections causing FUO - III

- Epstein–Barr virus and cytomegalovirus can both cause a mononucleosis syndrome
- Cryptococcosis and histoplasmosis being the two most common fungal diseases reported
- Parasites, such as malaria (nonfalciparum forms), leishmaniasis, toxoplasmosis, and trypanosomiasis
Infections and FUO

- Infection is the most common cause of FUO in patients under 65 years of age
- Helpful epidemiology circumstances: animal exposure, insect bites, outdoor camping, travel, and exposure to infected humans
- Useful clues that may provide physical exam: cardiac auscultation, and inspection of skin, nail beds, and fundi
- Prior antibiotic administration interferes with diagnosis
Neoplasms causing FUO

- **Hodgkin’s lymphoma**, intermittently produce pyrogens: the patient may be afebrile, and then may have hectic fevers, known as Pel-Ebstein fever
- Non-Hodgkin lymphoma
- Leukemia
- Renal cell carcinoma (formerly hypernephroma)
- Hepatocarcinoma
- Atrial myxoma
- Neoplasms are the most common cause of FUO in patients over 65 years of age
Hodgkin’s lymphoma
Cervical lymphadenopathies
Autoimmune Disease causing FUO

- **Still’s disease**: evanescent macular rash, arthralgias, sore throat, leukocytosis, etc.; no specific diagnostic test
- Systemic lupus erythematosus
- Polymyalgia rheumatica and temporal arteritis, old patients
- Polyarteritis nodosa, hypersensitivity angiitis and other vasculitis
- Mixed connective tissue disease
- Subacute thyroiditis
- Kikuchi’s disease, or histiocytic necrotizing lymphadenitis
Still’s disease, evanescent macular rash
Miscellaneous causes of FUO

- Drug fever
  - Phenytoin
  - Quinidine sulfate and procainamide
  - Sulfonamides and beta-lactams
- Familial mediterranean fever, lack of pyrin or marenostrin, a cytokine inhibitor
- Pulmonary emboli
- Factitious fever
- No cause found in some cases, but generally fever spontaneously subsides
Diagnostic Workup of FUO
General approach

- Laboratory tests, imaging studies and other tests should be guided by history and physical exam.
- Because each case is different, a series of yes-or-no branch points or diagrams are not useful for guiding diagnosis.
- An **iterative** approach to testing and analysis is most effective.
- The clinician must review each new potential diagnostic clue and assess its significance in relationship to the patient’s other positive findings.
History

• Present and past history
  • Play a critical role in narrowing the differential diagnosis and deciding on the most appropriate diagnostic tests
  • A review of symptoms needs to be periodically updated

• Family history

• Medications and other substances taken

• Social history
  • Pets, insect bites
  • Travel, hobbies
Physical examination

• Careful physical examination is frequently helpful
• Must be repeated regularly
• Particular attention should be paid to:
  • Skin: embolic or vasculitic lesions
  • Nail beds: small emboli
  • Joints: motion and effusions
  • Eyes: conjunctival petechiae, uveitis, choroidal tubercles, etc.
• Lymph nodes
Splinter hemorrhages
Choroidal tubercles: A) ophthalmoscopic pictures, black arrows; B) fluorescein angiogram, white arrows.
Common laboratory tests

- Complete blood count with differential
- C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)
- Liver function tests, lactic dehydrogenase (LDH), creatine phosphokinase (CPK)
- Antinuclear antibodies and rheumatoid factor
- Serum protein electrophoresis
- Urinalysis and urine culture
- Blood cultures ×3, held for three weeks
Imaging studies

- **Chest** and other radiographs
- **Abdominal**, cardiac and other ultrasound
- Computed tomography (CT) scan of chest and abdomen
- Magnetic resonance imaging (MRI)
- Positron emission tomography (PET) / CT scan with $^{18}$F fluorodeoxyglucose
- Radionuclide scans: Ga, In tagged white blood cells
Other studies - I

- Tuberculin skin test or interferon γ release assay
- Sputum: gram, acid fast, and culture
- Biopsy and culture * of bone marrow, lymph nodes or other tissues
- Viral cultures or quantitative polymerase chain reaction (PCR) may also be considered in specific cases, such as cytomegalovirus or Epstein-Barr virus suspected infections

* Aerobic, anaerobic, mycobacterial, and fungal
Other studies - II

- Peripheral blood smears with Giemsa and Wright stains
- Stool smears for ova and parasites
- **HIV antibody**, and HIV viral load
- Serologies, generally two samples
- Laparoscopic guided biopsy
- Temporal artery biopsy

- At times the wisest course of action is to wait
Treatment of FUO

• Antipyretics can be administered, in most cases on a regular schedule
• Antibiotics are generally contraindicated until a specific diagnosis is made
• Glucocorticoids best avoided until a specific diagnosis is made
Prognosis of FUO

- Delay in diagnosis may worsen the outcome in
  - Intra-abdominal abscess
  - Miliary tuberculosis
  - Pulmonary emboli
- If these diseases are carefully excluded, lack of a diagnosis after an extensive workup is associated with a 5-year mortality of only 3%
- Prognosis is somewhat worse in elderly patients because of their increased risk of malignancy
FUO in the HIV-infected patient

- Primary HIV infection can present with prolonged fever, diagnosis: HIV viral load
- In the later stages prolonged fever is common:
  - Bacterial and **mycobacterial** infections
  - Cytomegalovirus
  - *Pneumocystis jiroveci*
  - Toxoplasmosis and cryptococcosis
  - Leishmaniasis
  - Lymphoma
  - Drug fever
Key messages
To remember...

- Fever is a very common clinical presentation in most clinical settings.
- Causes of fever are myriad, but a clinical history and a physical exam allow a quick diagnosis in most cases and guides about further testing in all other cases.
Further reading
Used references


Preparing the exam

- These slides