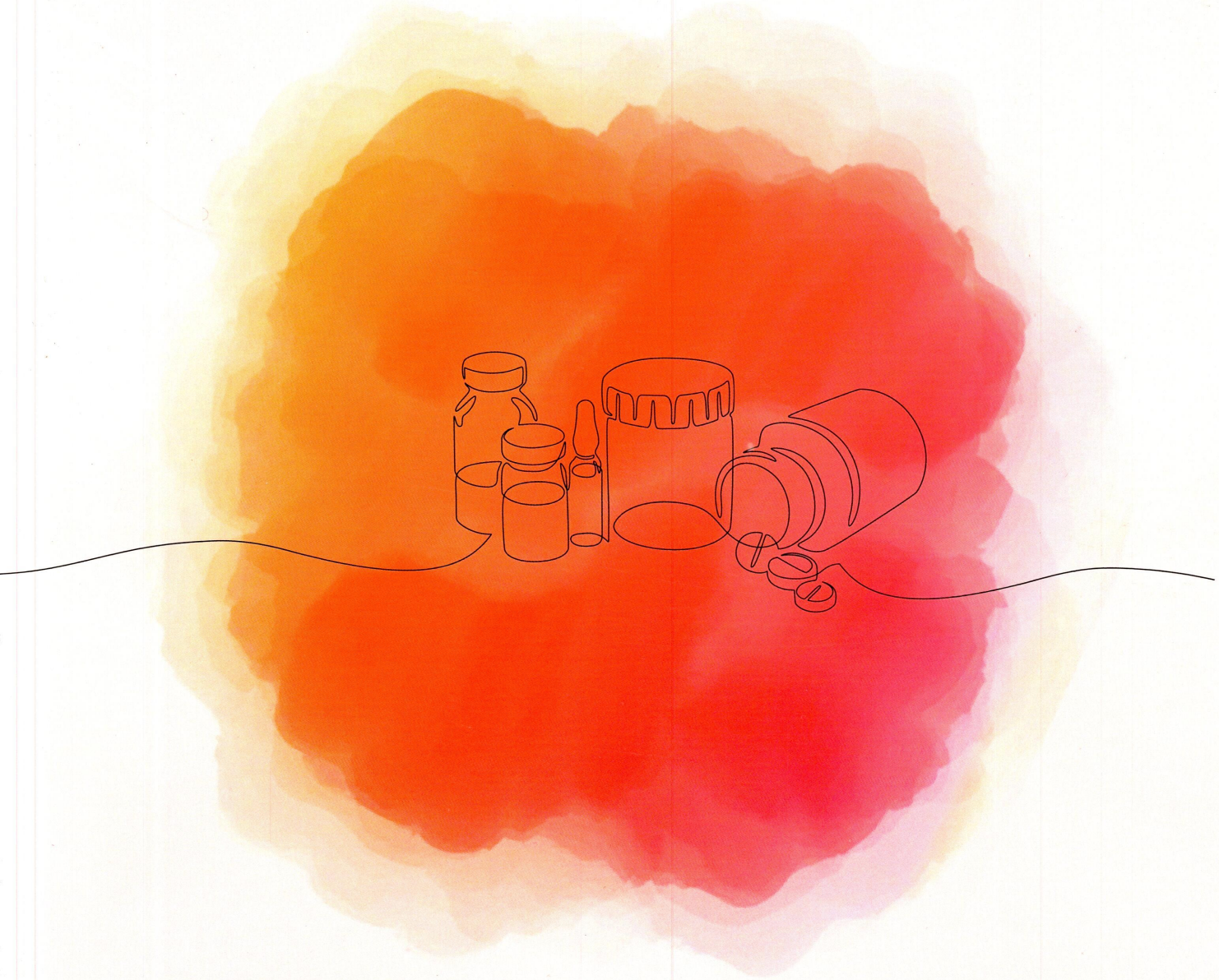
VOLUME-II

PrepLadder



MEDICINE

NEET SS VERSION 4.0

PREFACE

Dear Dreamer,

Pat your back and reward yourself, today you've taken an important step towards reaching your dream. Mark Twain said, "the secret of getting ahead is getting started". You have started in the right direction.

The next few months until your targeted exam or exams are crucial. Every moment counts and each step you take now, will help you reach your goal, your dream.

PrepLadder is your partner in this journey. We are in this together. So, don't worry, do not stress. Just focus on your preparation and stay positive. Set daily targets, achievable and realistic ones. If you pass the target, celebrate. However, if you miss a daily target, forgive yourself, move on and do better the next day.

Always remember that you are special and unique. Do not compare your preparation, your speed, your abilities with others. Believe us, it doesn't help.

Practice a lot. Solve the QBank. Take Grand Tests. Review your performance. But don't let ranks and results drag you down. Rather use them as a guiding light to know your strengths and weaknesses, to increase your speed and accuracy, and to get yourself ready for the exam day.

If you have a doubt or a question, ask us. We are here.

Lastly and most importantly. take care of yourself. You and your health are precious. So, keep up with exercise, eat healthy, get enough sleep and care for yourself.

We're behind you, cheering you on to the finish line. You might be feeling stressed, overwhelmed, and so tired, but you're nearly there. Give it everything you've got, and know that whatever happens next, you've got what it takes for the life you want. You are a Champion.

Own Your Dream
Team PrepLadder

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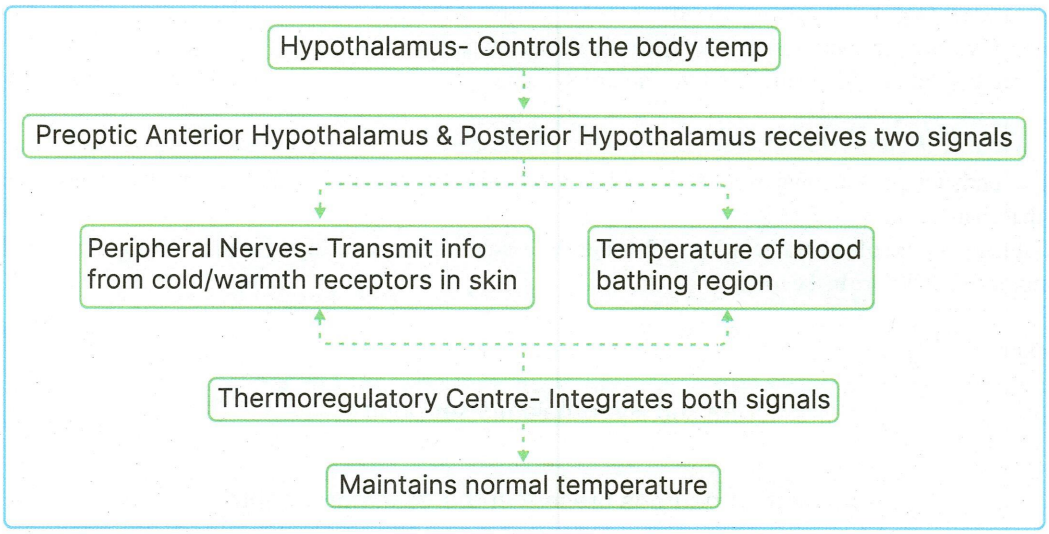
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GENERAL MEDICINE

1 FEVER PART-1

Anatomy and physiology

00:00:12



Normal Body Temperature Parameters

- In a scenario of neutral temp. environment- Human metabolic rate produces more heat than necessary and maintains the core body temperature
  - Normal Core Body Temperature- 36.5°C - 37.5°C or 97.7°F - 99.5°F
- Hypothalamic thermoregulatory centre
  - Normal body temp is maintained despite environmental variations (exposure of the body to extreme cold/heat)
  - Excess production by metabolic activity from muscle and liver and heat dissipation from skin and lungs

Definition of fever

- Observations made in a study involving >35000 individuals aged ≥18 yrs
  - Mean oral temperature 36.6°C
  - Temperature >37.7°C (>99.9°F) which represents 99th percentile for healthy individuals defines a Fever

Temperature variations

- Increased ambient temperatures are associated with elevated basal body temp
- Body temp have diurnal and seasonal variation
  - Low levels at around 8 AM
  - Higher levels at 4 PM

Factors Affecting Baseline Temperature

- Age- Reduced by 0.02°C for every 10yr increase in age
- Demographics- In African-American women have temperatures +0.052°C higher than white men
- Comorbidities- Cancer (+0.02°C), Hypothyroidism (-0.01°C)

Comparisons between sites of TEMPERATURE MEASUREMENT

- Rectal Temperature: +0.4°C (+0.7°F) higher than Oral temperatures
- Lower oral temperature is attributed to mouth breathing which is a factor in pt's with respiratory infections and rapid breathing
- Lower Esophageal temperature closely reflect core temperature
- Tympanic Membrane thermometers
  - Measures radiant heat
  - Also measure heat from nearby ear canal

- Display absolute value called as Unadjusted Mode (0.8°C/1.6°F lower than rectal)
- Maybe more variable than directly determined oral or rectal values
- Studies show readings are more with unadjusted mode compared to adjusted mode Tympanic Membrane thermometers

Menstrual Cycle Temperature Changes during Menstrual Cycle

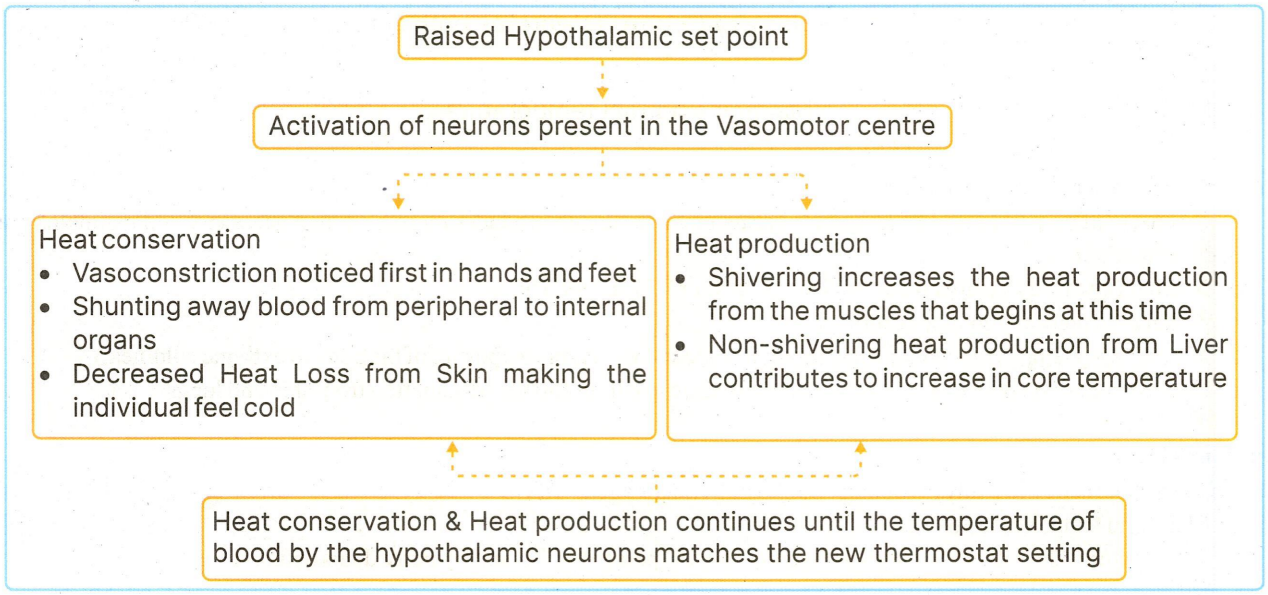
- AM temperature in menstruating women is lower for 2 weeks pre-ovulation
- Rises by 0.6°C with ovulation and stays elevated until menses occur
- Luteal Phase- Amplitude of Circadian rhythm remains the same

Fever

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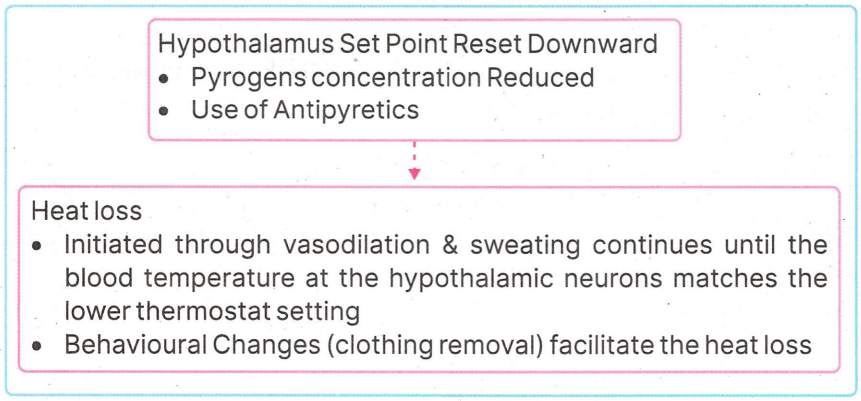
- Elevation of body temperature that exceeds normal daily variation occurring in conjunction with increase in the Hypothalamic set point that changes from 37°C to 39°C
  - Reset of temperature of normothermic to febrile level resembling the resetting of home thermostat to a higher level to raise the ambient temperature in the room

Fever Mechanism



- Most fevers body temperature increases by 1-2°C
- Behavioural adjustments (More clothing/bedding)- Increases the body temperature & decreases the heat loss
- Once the new thermostat setting point is reached Hypothalamus maintains the temperature at the febrile level by the same mechanism of heat-balance that functions in the afebrile state

Fever Resolution Mechanism



Hyperpyrexia

- Hyperpyrexia- Fever temperature >41.5°C (>106.7°F)
- Common Causes
  - Severe infections
  - M/c- CNS Hemorrhage
- Fever from variety of infections rarely exceeded >106.7°F in the pre-antibiotic era d/t natural thermal ceiling mediated by Neuropeptides functioning as central antipyretics

Hypothalamic Fever

- In rare cases the Hypothalamic set point is elevated d/t local trauma, hemorrhage, tumors or intrinsic hypothalamic functions
- Hypothalamic fever- Elevated temperature d/t abnormal hypothalamic function
- Most pt's with hypothalamic damage have sub-normal temperature but not Supra-normal

Hyperthermia

- Hyperthermia- Elevated body temperature without the elevation of pyrogens. This is commonly referred to as Heat stroke
- Characteristics of hyperthermia
  - Uncontrolled temperature increase that exceeds body's ability to lose the heat
  - Hypothalamic set point unchanged
  - No elevation of Pyrogens
- Mechanism by which hyperthermia results in dangerous high internal temperature
  - Exogenous heat exposure
  - Endogenous heat production
- Excessive heat production can easily cause hyperthermia despite physiologic & behavioural control of the body temperature
- E.g. Work/exercise in hot environment can produce heat faster than peripheral mechanism can lose it

Clinical Distinction between fever & Hyperthermia

- It is important to distinguish between the two as hyperthermia can be rapidly fatal and does not respond to antipyretics
- In systemic sepsis, fever can be rapid in onset and temperatures can exceed 40.5°C (104.4°F)
- Hyperthermia is diagnosed based on events preceding temperature rise
  - H/o heat exposure
  - Drugs interfering with thermoregulation
- In pt's with Heat stroke syndrome and pt's drugs that block sweating the skin is hot and dry
  - Antipyretics do not reduce elevated temperature in hyperthermia
- In fever the skin can be cold as a consequence of vasoconstriction
  - Antipyretics decrease body temperature to an extent

Pathogenesis of fever

00:53:53

Pyrogen Classification

- Pyrogen = Greek word used to describe "fever-causing substance"

Exogenous	Endogenous

• Derived from outside the pt
• Most are microbial products, microbial toxins or whole microorganism
• Examples
  ○ Lipopolysaccharide (produced by all Gram -ve bacteria)
  ○ Gram-Positive Pyrogenic Products
  → Staphylococcus aureus Enterotoxins
  → Group A & B Streptococcal Toxins (AKA Super antigens)
	• Highly pyrogenic molecule in humans
	• Injected IV into volunteers at 12-3 ng/kg is associated with development of fever, leucocytosis, increase in acute phase protein and generalised malaise

Important Information

Clinical importance

- Staphylococcal Toxin associated with isolates of Staphylococcus aureus causing Toxic Shock Syndrome
- Staphylococcal toxin IV at conc of 1-10 µg/kg associated with development of fever in experimental animals into

Pyrogenic cytokines

- Cytokines are small proteins with molecular mass of 10,000-20,000 Daltons
- Regulate immune, inflammatory and hematopoietic processes
- Neutrophilia occurring in majority of infections are attributable to IL-1 & IL-6
- Some cytokines also fever which were referred to as Endogenous pyrogens, but now called Pyrogenic Cytokines. E.g:
  - Interleukin-1 (IL-1)
  - Interleukin-6 (IL-6)
  - Tumor Necrosis Factor (TNF)
  - Ciliary Neurotropic Factor (Member of IL-6 Family)
- Fever caused by cytokines is a prominent side effect of Interferon-α therapy
- Each of these pyrogenic cytokines are encoded by a separate gene and each has known to cause fever in laboratory animals and humans
- Dosage at which Cytokine can induce fever
  - IL-1 & TNF- 10-100 ng/kg
  - IL-6- 1-10 µg/kg
- A wide spectrum of bacterial and fungal products induce synthesis and release of pyrogenic cytokines

Non-infectious Fever Causes

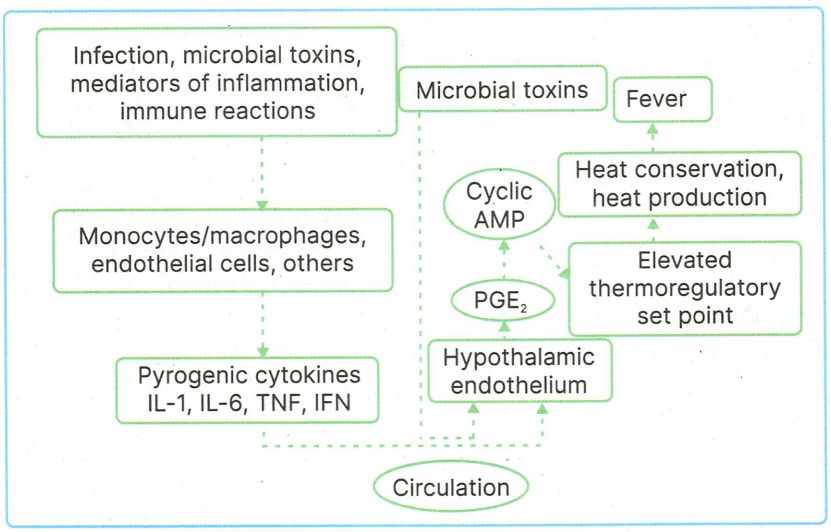
- Fever can be a manifestation of the disease in the absence of infection also
  - Inflammatory processes
  - Pericarditis
  - Trauma
  - Stroke
  - Routine Immunization

  }
  - All Induce Production of IL-1, IL-6, TNF
  - These pyrogenic cytokines, individually or in combination trigger Hypothalamus to raise the set point to febrile levels

Hypothalamic set point elevation

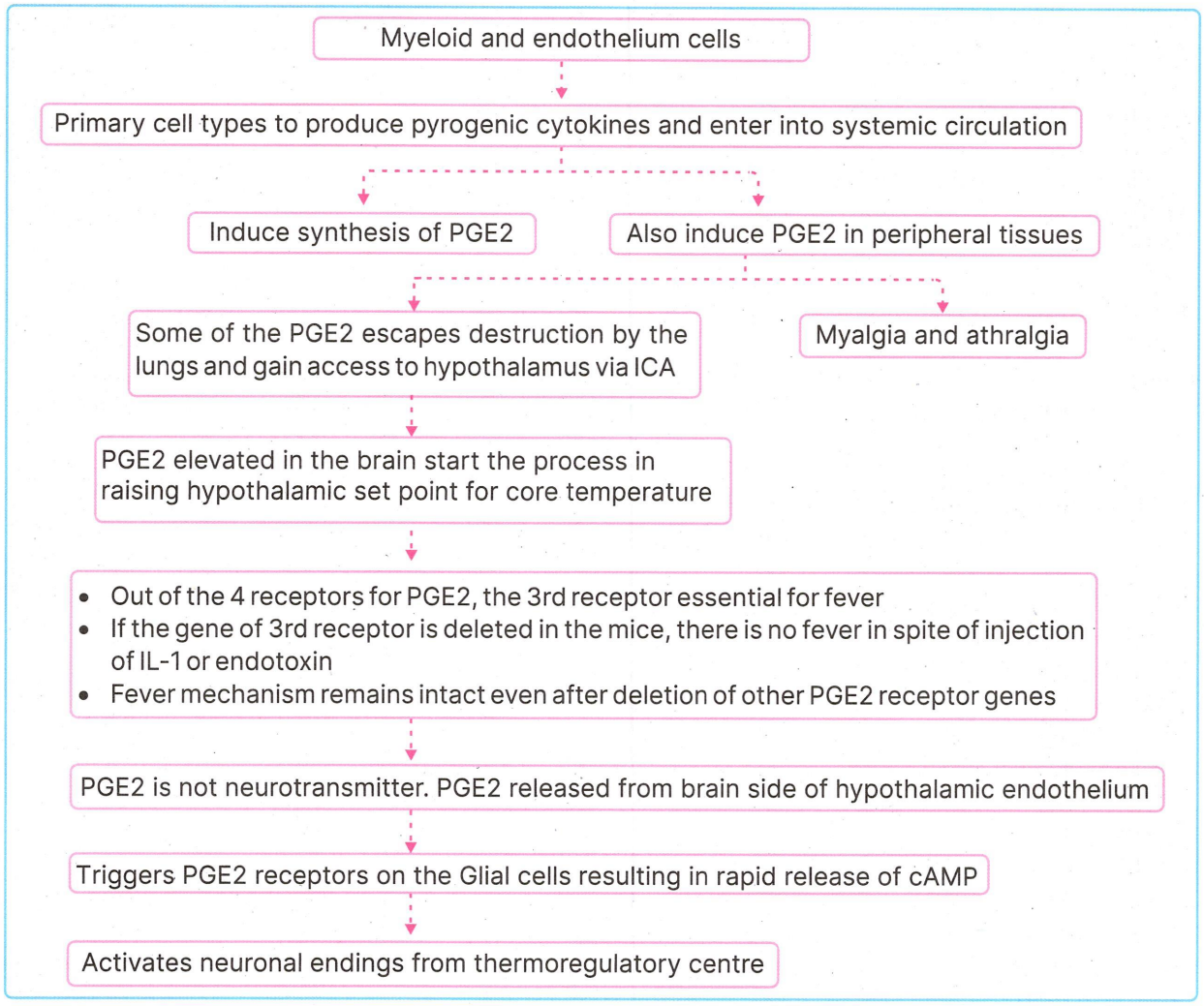
PGE2 Role in Fever

- During fever levels of PGE2 are elevated in hypothalamic tissue and 3rd cerebral ventricle
- Conc. of PGE2 are highest at Circumventricular Vascular Organs- Organum Vasculosum of Lamina terminalis
- Destruction of these organs reduce the ability of the pyrogens to produce fever
- Exogenous pyrogens & pyrogenic cytokines interact with endothelium of these capillaries which is the 1st step in initiating the fever



- Mechanisms involved
  - Peripheral vasoconstriction
  - Increased metabolism
  - Shivering

Cellular mechanisms involved in development of fever



- Distinct receptors for microbial products are located on Hypothalamic endothelium called Toll like receptors (similar to IL-1 receptors) share a signal transducing mechanism
- Direct Activation of Toll-Like Receptors or IL-1 Receptors results in PGE2 Production and development of fever

CNS cytokine production

- Cytokines Produced in brain accounts for Hyperpyrexia
- Seen in
  - CNS Hemorrhage
  - Trauma
  - CNS Infections
- Viral infections of CNS induce microbial and neuronal Production of IL-6, IL-1 and TNF
- In experimental animals the conc. of a cytokine required to cause fever is several orders of magnitude lower with direct injection into the brain than with the systemic injection
- Cytokines produced in CNS can raise the hypothalamic set point bypassing circumventricular organs

2 FEVER PART-2

Approach to Patient with Fever

00:00:23

History and Physical Examination

- Fever is a cardinal manifestation of a range of disease processes
- A thorough history helps distinguish between broad categories of diseases presenting with fever

Disease Categories with Fever as Cardinal Sign

- Infectious diseases
- Autoimmune and non-infectious inflammatory disorders
- Malignancy
- Medication-related (e.g., Vaccine)
- Endocrine disorders (e.g., Hyperthyroidism d/t to increased BMR)
- Intrinsic hypothalamic malfunction

Chronology of Events

- Ascertain chronology of events preceding fever, including exposure to symptomatic individuals or disease vectors

Temperature Measurement

- Electronic devices for oral, tympanic membrane, or rectal temperature are reliable
- Same site should be used consistently to monitor febrile disease

Absence of Fever (Blunted Febrile Response)

- New-born's
- Elderly patients
- Patients with chronic hepatic or renal failure
- Patients taking glucocorticoids
- Treatment with anti-cytokines

} May have active disease despite absence of fever

Laboratory Tests

00:06:50

Complete Blood Count (CBC)

- Should include a manual differential count or with an instrument sensitive to juvenile or band form
- Instrument should also identify toxic granulations and Döhle bodies, suggestive of bacterial infection
- Neutropenia may be present in viral infections

Circulating Cytokines

- Measurement of circulating cytokines (e.g., IL-1, TNF) is generally not helpful
- Levels are often below detection limits and do not coincide with fever

Low-Grade Fever or Suspected Occult Disease

- Most valuable measurements are CRP and ESR- Markers of inflammatory processes and helpful in detecting occult disease
- Measurement of circulating IL-6, which induces CRP, can be useful
- IL-6 levels may vary during febrile disease, while CRP levels remain elevated

Fever in Patients Receiving Anti-Cytokine Therapy

00:12:06

- Patients on long-term anti-cytokine regimens are at increased risk of infections because of lowered host defences
  - E.g., Latent Mycobacterium tuberculosis infection can disseminate in patients receiving anti-TNF therapy
- Increasing use of anti-cytokines to reduce activity of IL-1, IL-6, IL-12, IL-17, or TNF in conditions like Crohn's disease, Rheumatoid arthritis, and Psoriasis can blunt the febrile response

- Blocking cytokine activity lowers host defences against both routine bacterial and opportunistic infections (e.g., Mycobacterium tuberculosis, fungal infections)
- Use of monoclonal antibodies to reduce IL-17 in Psoriasis increases the risk of Systemic candidiasis
- Fever is among the presenting signs in nearly all reported cases of infection associated with anti-cytokine therapy. However, the extent to which the febrile response is blunted in these patients remains unknown
- Therefore, low-grade fever in these patients is of considerable concern, and the physician should conduct an early and rigorous diagnostic evaluation
- Febrile response is also blunted in patients receiving chronic glucocorticoid therapy or anti-inflammatory agents such as NSAIDs

Treatment of Fever

00:23:50

General Principles	• Fever itself is not an illness; it is an ordinary response to a perturbation of the normal host physiology • Most fevers are associated with self-limited infections such as viral diseases • Use of antipyretics is not contraindicated in these infections • Treatment of fever and its symptoms with routine antipyretics does no harm and does not slow the resolution of common viral and bacterial infections • In bacterial infections, withholding antipyretic therapy can be helpful in evaluating the effectiveness of a particular antibiotic,especially in the absence of positiveblood culture • Withholding antipyretics in some cases may facilitate the diagnosis of an unusual febrile disease
Phaget's Sign (Relative Bradycardia)	• Temperature-pulse dissociation occurs in Typhoid fever, Brucellosis, Leptospirosis, and some drug-induced fevers
Absence of Fever Despite Infection	• Observed in newborn's, elderly patients, patients with chronic liver or kidney disease, and patients taking glucocorticoids
Hypothermia	• Hypothermia can develop in patients with septic shock
Characteristic Fever Patterns	• Some infections have characteristic patterns in which febrile episodes are separated by intervals of normal temperature • Plasmodium vivax causes fever every third day • Plasmodium malariae causes fever every fourth day • Another relapsing fever is related to Borrelia infection, with days of fever followed by a several-day afebrile period and then a relapse • The Pel-Ebstein pattern of fever lasting 3 to 10 days followed by an afebrile period of 3 to 10 days is classic for Hodgkin's disease and Lymphomas • In Cyclic neutropenia, fever occurs every 21 days and accompanies the neutropenia
Periodic Fever Syndromes	• E.g. Familial Mediterranean Fever and TNF receptor-associated periodic syndrome (TRAPS) • They differ in their periodicity, duration of attack, constellation of clinical features, genetic causes, and therapies

Anti-Cytokine Therapy to Reduce Fever in Autoimmune and Auto-inflammatory Diseases

00:38:45

- Recurrent fever is documented in most autoimmune diseases and many auto-inflammatory diseases
- These include periodic fever syndromes and disorders of the inflammasomes (e.g., NLRP3, Pyrin) and other components of the innate immune system
- Recurring fevers are characteristic of auto-inflammatory diseases
  - E.g., Adult and juvenile Still's disease, Familial Mediterranean Fever, Hyper IgD syndrome, and common diseases like Idiopathic pericarditis and Gout
- In addition to recurrent fevers, neutrophilia and serosal inflammation characterize auto-inflammatory diseases

- Fevers associated with many of these illnesses are dramatically reduced by blocking IL-1 activity with Anakinra or Canakinumab
- Anti-cytokines therefore reduce fever in autoimmune and auto-inflammatory diseases
- Although fevers in auto-inflammatory disease are mediated by IL-1 β, patients also respond to antipyretics

Mechanisms of Antipyretic Agents

00:47:22

- Reduction of fever by lowering the elevated hypothalamic set point is a direct function of the reduction of PGE2 level in the thermoregulatory centre
- Synthesis of PGE2 depends on the constitutively expressed enzyme cyclooxygenase (COX)
- Arachidonic acid is the substrate for COX and is released from cell membranes; its release is a rate-limiting step in PGE2 synthesis
- Inhibitors of COX are potent antipyretics
- Antipyretic potency of various drugs is directly correlated with the inhibition of brain COX
- **Acetaminophen**
  - Poor COX inhibitor in peripheral tissue and lacks noteworthy anti-inflammatory activity
  - In the brain, Acetaminophen is oxidized by the P450 cytochrome system, and the oxidized form inhibits COX activity
  - Inhibition of COX-3 in the brain by Acetaminophen may account for its antipyretic effect. COX-3 is not found outside the CNS
- Oral Aspirin and Acetaminophen are equally effective in reducing fever in humans
- NSAIDs such as Ibuprofen and specific inhibitors of COX-2 are also excellent antipyretics
- Chronic high-dose therapy with antipyretics such as aspirin or NSAIDs does not reduce the normal core body temperature; PGE2 appears to play no role in normal thermoregulation
- **Glucocorticoids**
  - As effective antipyretics acting at two levels
    - → Similar to COX inhibitors, they reduce PGE2 synthesis by inhibiting the activity of phospholipase A2 (needed to release Arachidonic acid from the cell membrane)
    - → Block the transcription of mRNA for the pyrogenic cytokines
  - Individuals taking glucocorticoids have a blunted fever response
- **MOA of Ibuprofen & COX-2 inhibitors**
  - Experimental evidence indicates that ibuprofen and COX-2 inhibitors reduce IL-1 induced IL-6 production and may contribute to the antipyretic activity of NSAIDs

Regimens for the Treatment of Fever

01:00:52

Objectives

- To reduce the elevated hypothalamic set point
- To facilitate heat loss
- Reducing fever with antipyretics also reduces systemic symptoms such as headache, myalgia, and arthralgia

Choice of Medication

- Oral aspirin and NSAIDs effectively reduce fever but can adversely affect platelets and GIT
  - Therefore, Acetaminophen is preferred as an antipyretic
- In children, Acetaminophen or oral Ibuprofen must be used because Aspirin increases the risk of Reye's syndrome
- If the patient cannot take oral antipyretics, parenteral preparations of NSAIDs and rectal suppositories of various antipyretics can be used

Scenarios Treatment of Fever is Highly Recommended

- Fever increases the demand for O_2; for every 1°C increase over 37°, there is a 13% increase in O_2 consumption
- Fever can aggravate the condition of patients with pre-existing impairment of cardiac, pulmonary, or CNS function
- Children with h/o of febrile or non-febrile seizures should be aggressively treated to reduce the fever
- It is unclear what triggers febrile seizures, and there is no correlation between absolute temperature elevation and the onset of febrile seizure in susceptible children
- Hyperpyrexia

- In hyperpyrexia, the use of cooling blankets facilitates the reduction of temperature
- However, cooling blankets should not be used without oral antipyretics
- In hyperpyretic patients with CNS disease or trauma (especially causing CNS bleeding), reducing the core temperature mitigates the detrimental effect of high temperature on the brain

3 FEVER OF UNKNOWN ORIGIN PART-1

Introduction

- Older definition: Any febrile illness without any initial obvious aetiology
  - FUO is reserved for disorders with prolonged febrile illness without an established aetiology despite intensive evaluation and diagnostic testing
- Beeson & Petersdorf originally defined FUO in 1961
  - Duration of illness >3 weeks + Fever of ≥38.3°C on 2 occasions + uncertain diagnosis in spite of 1 week inpatient evaluation
- Hospitalisation is required if their clinical condition requires it
- Recent definition: In immunocompromised patients have been excluded whose workup requires and entirely different diagnostic & therapeutic approach

Definition of FUO

00:05:01

- Fever of ≥38.3°C on 2 occasions
- Duration of illness ≥3 weeks
- No known immunocompromised state
- Uncertain diagnosis after thorough history, physical examination and obligatory investigations
  - Obligatory investigations
    - → ESR, CRP, Platelet count, WBC count, Differential count, Electrolytes, RFT, Total proteins, AST, ALT, Alkaline PO4, LDH, Creatinine kinase, Ferritin, ANA, RA factor, Protein electrophoresis, Urine analysis and culture, Blood culture, Chest x-ray, USG, Tuberculin skin test/Interferon gamma release assay

Inflammation of Unknown Origin

- Closely related FUO
- Defined as the presence of inflammatory parameters - Elevated ESR/CRP for at least 3 weeks on multiple occasions in immunocompetent patients with normal body temperature
- Unable to make a final explanation despite history taking, physical examination and obligatory test

Important Information

- Etiology and work up of FUO and IUO are same for both of them

Note: For the convenience of this lecture, IUO and FUO will together be referred as **FUO**

Etiology

00:13:35

Geographic Area	No. of Cohorts (Inclusion Period)	No. of Pt's	Infections, Median % (Range)	Non-infectious Inflammatory Diseases, Median % (Range)	Malignancy, Median % (Range)	Misc. Median % (Range)	No Diagnosis, Median % (Range)
Western Europe	10 (1990–2014)	1820	17 (11–32)	25 (12–32)	10 (3–20)	10 (0–15)	37 (26–51)
Other European and Turkey	13 (1984–2015)	1316	38 (26–59)	25 (15–38)	14 (5–39)	6 (2–18)	16 (4–35)
Middle East	3 (2009–2010 and ?)	1235	66 (42–79)	15 (7–17)	7 (1–30)	1 (0–12)	8 (2–12)
Asia	20 (1994–2017)	3802	42 (11–58)	20 (7–57)	13 (6–22)	9 (0–15)	18 (0–36)

- This is a pooled result of large studies published in the past 20 years
- The range of FUO etiologies has evolved since its first definition as a result of changes in the spectrum of diseases causing FUO
- Proportion of cases caused by fever d/t intra-abdominal abscess and intra-abdominal tumours has decreased because of earlier detection by CT abdomen & USG
- Infective endocarditis is also a less frequent cause due to blood culture and echocardiographic techniques have improved the identification
- Non-western cohorts, infection was the common cause
- Half of all infections in FUO outside Western nations are commonly caused by M. tuberculosis
- Western cohorts, Non-infectious inflammatory diseases, including autoimmune, autoinflammatory, granulomatous disease, as well as vasculitides, are a common cause
- >1/3rd of western patients with FUO have a diagnosis that falls within the category of Non-infectious inflammatory diseases
- In almost 1/3rd of Western patients, FUO remains unexplained
- Only difficult-to-diagnose cases meet the criteria for FUO
- In patients with recurrent fever, aetiology can be made out in <50% of cases
  - Recurrent fever- Repeated episodes of fever interspersed with fever-free intervals of at least 2 weeks & apparent remission of underlying disease
- Differential diagnosis of FUO- Extensive
- FUO is far more often caused by an atypical presentation of a common disease rather than a rare disease

Reported causes of FUO

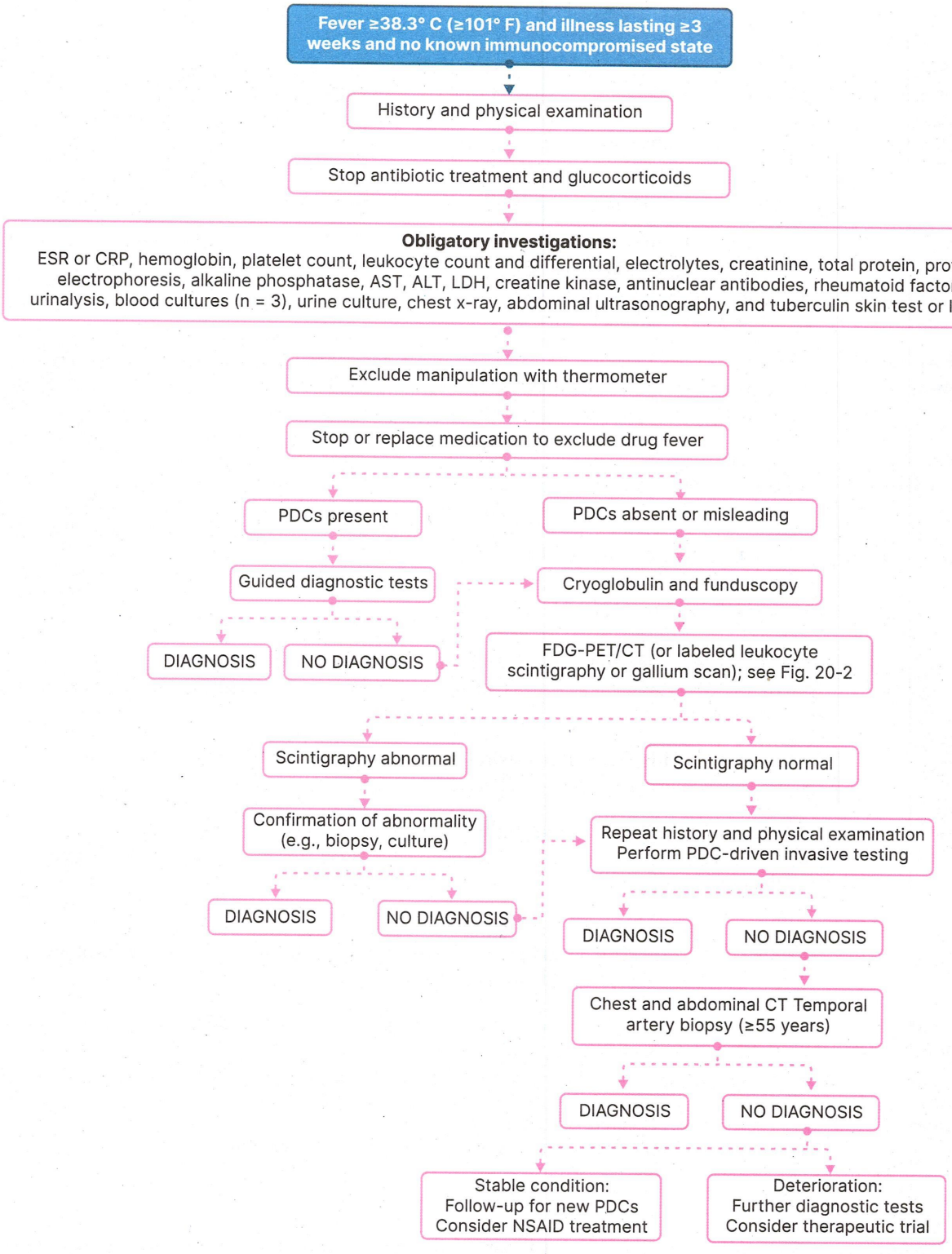
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Infections - Bacterial (Nonspecific)	• Abdominal abscess, Adnexitis, Apical granuloma, Appendicitis • Cholangitis, Cholecystitis, Diverticulitis, Endocarditis • Epidural abscess, Infected joint prosthesis, Osteomyelitis • Prostatitis, Pyelonephritis, Sinusitis, etc.
Infections - Bacterial (Specific)	• Actinomycosis, Bartonellosis, Brucellosis, Legionellosis • Listeriosis, Lyme disease, Leptospirosis, Tuberculosis • Tularemia, Typhoid fever, Whipple's disease
Infections - Fungal, Parasitic, Viral	• Fungal: Aspergillosis, Blastomycosis, Candidiasis, Histoplasmosis • Parasitic: Amebiasis, Babesiosis, Malaria, Schistosomiasis • Viral: Epstein-Barr virus, Hantavirus, Cytomegalovirus, West Nile virus
Non-infectious Inflammatory Diseases (NIID)	• Systemic Rheumatic Diseases: Lupus, Sjogren's syndrome, Vasculitis • Granulatomous diseases: Sarcoidosis, Idiopathic granulomatous hepatitis • Auto-inflammatory Syndromes: CAPS, PFAPA, Schnitzler syndrome **CAPS (Cryopyrin-associated periodic syndromes)** • A group of inherited autoinflammatory disorders caused by mutation in NLRP3 gene **PFAPA (Periodic Fevers with Aphthous stomatitis, Pharyngitis, and Adenitis)** • Non-hereditary, self-limiting autoinflammatory disorders commonly seen in children presenting with recurrent fevers, mouth ulcers, sore throat and swollen LN **Schnitzler syndrome** • Rare late-onset autoinflammatory disorders associated with chronic urticarial rash, recurrent fever, joint pains and monoclonal IgM/IgG gammopathy
Neoplasms	• Hematologic malignancies: Leukemia, Lymphoma, Multiple myeloma • Solid tumours: Breast, Lung, Pancreatic, Renal cell carcinoma • Benign tumors: Craniopharyngioma, Cavernous hemangioma
Miscellaneous Causes	• ADEM, Adrenal insufficiency, Aortic aneurysms, Aortic dissection • Atrial myxoma, Caroli disease, Cirrhosis, Cyclic neutropenia • Sweet syndrome, Thyroiditis, Thrombosis, Lead poisoning
Thermoregulatory Disorders	• Central: Brain tumor, Encephalitis, Hypothalamic dysfunction • Peripheral: Hyperthyroidism, Pheochromocytoma, Exercise-induced hyperthermia

- M/c infections disease for differential diagnosis of FUO- Atypical presentation of endocarditis, Diverticulitis, Osteomyelitis, Extra-pulmonary TB
- Q fever & Whipple's disease are rare, and the presenting symptoms are non-specific
  - Serological testing for Q fever should be performed by immunofluorescent assay in a pt living in a rural area, h/o heart valve disease, Aortic aneurysm or Vascular prosthesis
- In patients with unexplained symptoms localised to CNS, GIT and joints, PCR need to be performed for Tropheryma whipplei
- In patients with h/o travel to tropical countries or the American Southwest infectious diseases need to be considered
  - Malaria, Leishmaniasis, Histoplasmosis, Coccidiomycosis
- Fever with signs of endocarditis and negative blood culture are considered as culture-negative endocarditis, which is d/t difficult-to-culture bacteria (nutritional variant bacteria)
  - HACEK group
  - C. burnetti
  - T. whipplei
  - Bartonella species
- Marantic endocarditis- Sterile thrombotic disease occurring as a paraneoplastic phenomenon, especially with adenocarcinoma
  - Sterile thrombotic disease is also seen in SLE, Antiphospholipid antibody syndrome
- Adult-onset Still's disease, Large vessel vasculitis, Polymyalgia rheumatica, SLE, Sarcoidosis are common diagnoses in FUO
- Hereditary autoinflammatory syndromes are rare & usually present in young patients
  - Schnitzler syndrome- Can present at any age, uncommon, but easily diagnosed in pt's with FUO with urticaria, bone pain, monoclonal IgM/IgG gammopathy
- Among most tumours presenting with fever, malignant lymphoma is by far the most common diagnosis of FUO, and sometimes fever precedes lymphadenopathy detectable by physical examination

Miscellaneous causes of fever found in FUO 00:41:24

Drug-induced fever	• DRESS- Drug Reaction with Eosinophilia and Systemic Symptoms is often accompanied by Eosinophilia and extensive lymphadenopathy • Drugs contributing to fever o Allopurinol o Carbamazepine o Lamotrigine o Phenytoin o Sulfasalazine o Furosemide o Antibiotics- Sulphonamides, Minocycline, Vancomycin, β-lactam group, Isoniazid o Quinidine o Anti-retroviral drugs- Nevirapine
Exercise-induced hyperthermia	• Characterised by elevated body temperature associated with moderate to strenuous exercise • Temperature lasts from half an hour to several hours without an increase in CRP/ESR • Sweat during temperature elevation
Factitious fever	• Fever is artificially induced by pt. E.g. IV injection of contaminated water • Should be considered in all patients, but common in young women in healthcare professions
Fraudulent fever	• Pt is normothermic, but manipulated the thermometer • Overcome by simultaneous measurements at different body sites (Rectum, ear, mouth) • Dissociation between pulse rate and temperature is another clue
FUO in elderly	• Results from an atypical manifestation of a common disease • Giant cell arteritis and Polymyalgia rheumatica are most frequently involved • Among infections, TB is the most common disease in the elderly compared to younger patients


Fever ≥38.3° C (≥101° F) and illness lasting ≥3 weeks and no known immunocompromised state
History and physical examination
Stop antibiotic treatment and glucocorticoids
Obligatory investigations:
ESR or CRP, hemoglobin, platelet count, leukocyte count and differential, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, AST, ALT, LDH, creatine kinase, antinuclear antibodies, rheumatoid factor, urinalysis, blood cultures (n = 3), urine culture, chest x-ray, abdominal ultrasonography, and tuberculin skin test or IGRA
Exclude manipulation with thermometer
Stop or replace medication to exclude drug fever
PDCs present
PDCs absent or misleading
Guided diagnostic tests
Cryoglobulin and funduscopy
DIAGNOSIS
NO DIAGNOSIS
FDG-PET/CT (or labeled leukocyte scintigraphy or gallium scan); see Fig. 20-2
Scintigraphy abnormal
Scintigraphy normal
Confirmation of abnormality (e.g., biopsy, culture)
Repeat history and physical examination
Perform PDC-driven invasive testing
DIAGNOSIS
NO DIAGNOSIS
DIAGNOSIS
NO DIAGNOSIS
Chest and abdominal CT Temporal artery biopsy (≥55 years)
DIAGNOSIS
NO DIAGNOSIS
Stable condition:
Follow-up for new PDCs
Consider NSAID treatment
Deterioration:
Further diagnostic tests
Consider therapeutic trial

4 FEVER OF UNKNOWN ORIGIN PART-2

Causes of Recurrent fever in FUO

00:00:28

- Diagnostic work-up should include History taking, Physical examination & obligatory tests

Bacterial Causes (Nonspecific)	• Apical granuloma, Diverticulitis, Prostatitis • Recurrent bacteremia from Colonic neoplasia • Recurrent cholangitis, Cholecystitis, Pneumonia, Sinusitis, UTI
Bacterial Causes (Specific)	• Bartonellosis, Brucellosis, Chronic gonococcemia • Louse-borne relapsing fever (Borrelia recurrentis) • Melioidosis (Pseudomonas pseudomallei), Q fever (Coxiella burnetii) • Salmonellosis, Whipple's disease
Fungal, Parasitic, and Viral Causes	• Fungal: Coccidioidomycosis, Histoplasmosis, Paracoccidioidomycosis • Parasitic: Babesiosis, Malaria, Toxoplasmosis, Trypanosomiasis • Viral: Cytomegalovirus, Epstein-Barr virus, Herpes simplex
Non-infectious Inflammatory Diseases	• Systemic Rheumatic & Autoimmune Diseases: Lupus, Sjogren's, RA • Vasculitis: Churg-Strauss, Giant cell arteritis, Polyarteritis nodosa • Granulomatous Diseases: Sarcoidosis, Idiopathic granulomatous hepatitis
Autoinflammatory Syndromes	• Adult-onset Still's disease, Blau syndrome, CAPS • Familial Mediterranean fever, TRAPS, Schnitzler syndrome • SAPHO syndrome, PFAPA syndrome **TRAPS (Tumor Necrosis Factor (TNF) Receptor–Associated Periodic Syndrome)** • Hereditary autoinflammatory disordered characterized be recurrent episodes of fever, rash & inflammation **SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis)** • Chronic inflammatory disorders bones, joints & skin **PFAPA (Periodic Fevers with Aphthous stomatitis, Pharyngitis, and Adenitis)** • Common pediatric autoinflammatory syndrome that causes recurrent fever & inflammation of throat and LN **Schnitzler syndrome** • Rare autoinflammatory disorders characterized by chronic urticarial rash, recurrent fever, joint pains and monoclonal gammopathy (usually IgM type)
Neoplasms and Miscellaneous Causes	• Hematologic: Hodgkin's, Non-Hodgkin's lymphoma, Castleman's disease • Solid Tumors: Colon carcinoma, Craniopharyngioma • Miscellaneous: Adrenal insufficiency, Cyclic neutropenia, Drug fever
Thermoregulatory Disorders	• Central: Hypothalamic dysfunction • Peripheral: Anhidrotic ectodermal dysplasia, pheochromocytoma

Febrile period

- Pt with recurrent fever is asked to return during the febrile period to repeat history, physical examination and laboratory during the symptomatic phase
- Further diagnostic tests in FUO performed only during febrile period or inflammatory parameters are abnormal - PET/CT or Scintigraphy imaging

Recurrent fever >2 yrs

- Recurrent fever lasting for >2 yrs, then it is unlikely the fever is caused by infection or malignancy
- Further diagnostic test should be considered only when pathological diagnostic clues for infection, vasculitis syndrome, malignancy are present or when patient's clinical condition is deteriorating

Diagnostic modalities

FDG-PET

00:13:13

- 18F-FDG-PET has become an established imaging procedure in pt's with FUO
- FDG accumulates in the tissues with high glycolysis rate- High glycolysis rate occurs in malignant cells and also in activated leukocytes
  - Imaging of acute and chronic inflammatory processes can be done
- Advantage of FDG-PET over conventional Scintigraphy
  - Offers higher resolution
  - Has greater sensitivity in chronic low grade infections
  - Has higher degree accuracy in central Skelton
  - Vascular uptake of FDG is increased in patients with Vasculitis
- Mechanisms of FDG uptake do not allow differentiation among infections, sterile inflammation and malignancy
  - As all these are causes for FUO, FDG-PET CT can be used to guide additional diagnostic tests
  - E.g. Targeted biopsies
- Physiological uptake of FDG may obscure the pathological foci in Brain, Heart, Bowel, Kidneys, Bladder
- FDG uptake in the heart obscures Endocarditis
  - Prevented by reduced consumption of carbohydrates before the scan
- Bone marrow is uptake is frequently increased in a non-specific way in pt's fever d/t cytokine activation which upregulates the glucose transporter in the bone marrow cells
- Diagnostic yield of PET & PET-CT are highly variable in the selection of the pt's, follow-up and selection of gold standard reference
- FDG-PET CT outperformed the FDG-PET, Gallium Scintigraphy and Leukocyte Scintigraphy
- Correct timing of FDG-PET CT increases the diagnostic value in Pt's with FUO as they present with periodic fever
- Although PET CT and other Scintigraphy techniques do not provide directly provide definitive diagnosis, they often identify anatomic location of the particular ongoing metabolic process
  - With help of Biopsy and culture a timely diagnosis and treatment can be facilitated
- Pathological FDG uptake can be quickly eradicated by Glucocorticoids in may diseases like Vasculitis & Lymphoma
- FDG-PET CT is relatively expensive procedure- Limited availability
- FDG-PET CT in earlier stages of FUO- Cost effective as it helps in establishing early diagnosis, thereby reducing the days of hospitalization and avoid unnecessary investigations
- FDG-PET CT done under right conditions like elevated CRP/ESR, febrile period increases the diagnostic yield
- FDG-PET CT has not contributed to the final diagnosis

Conventional Scintigraphy

00:35:15

- Includes
  - 67GA- Citrate Scintigraphy
    → Diagnostic yield is ~24%
    → Can locate the site of the disease in 1/3rd of pt's
  - 111In or 99mTc-Leukocyte Scintigraphy
    → Diagnostic yield is 8-31%
- Have low Specificity and sensitivity

Later stage diagnostic tests

00:38:23

- In some cases, more invasive tests are appropriate

- Abnormalities found in imaging, confirmation should be done by pathology and culture of biopsy
  - LN biopsy is necessary in case of lymphadenopathy even when the affected LN's are hard to reach and when the previous biopsies are inconclusive
  - In case of skin lesions, skin biopsy should undertaken
  - 2nd stage screening diagnostic test- Performed if no diagnosis is reached despite imaging and pathologic diagnostic clue (PDC) driven histological investigation or culture
- In 3 studies the diagnostic yield of screening chest CT, abdominal CT in pt's with FUO was 20%
  - Specificity of chest CT was 80% and abdominal CT varied between 63-80%
  - Despite limited specificity abdominal CT and limited additional chest CT after FDG-PET CT, these modalities may used as screening procedures at later stages of diagnostic protocol
- Bone marrow aspiration- Seldom useful in the absence of PDC's for bone marrow disorders
  - Value of bone marrow biopsy has reduced d/t to the addition of FDG-PET CT which is highly sensitive in detecting in Lymphoma, Carcinoma & Osteomyelitis
- In case of Giant cell arteritis (large arteries are involved), most cases can be diagnosed by FDG-PET CT.
  - Temporal artery biopsy is recommended in patients >55yrs in later stages of diagnostic protocol
  - FDG PET CT is not useful in vasculitis limited to Temporal artery d/t the smaller diameter of these vessels and high levels of FDG uptake in brain
- Liver biopsy- Was a screening procedures in patients with FUO
  - Abnormal LFT is not predictive of diagnostic liver biopsy in FUO
  - Liver biopsy is not a screening test as it is a invasive procedures associated with complications and death until PDC's are present for liver or Miliary TB
- Diagnostic delay often occurs d/t failure to recognise PDC's

Treatment

00:56:43

Empirical therapy

- A trial of empirical therapeutic trial with antibiotics, Glucocorticoids or anti-tubercular agents should be avoided in FUO except when patient's condition is rapidly deteriorating after diagnostic tests
- Antibiotics or anti-tubercular agents therapy will diminish the ability to culture fastidious bacteria or mycobacteria
- Hemodynamic unstable or neutropenia is an indication for empirical antibiotic therapy
- Anti-tubercular empirical therapy- If Tuberculin skin test is positive or Interferon gamma radioimmune assay is positive or presence of granulomatous disease with allergic and sarcoidosis is unlikely
- In case of Miliary TB, there is spread of the organism to distant organs making it difficult to obtain rapid diagnosis.
- If fever does not respond to empirical ATT after 6 weeks another diagnosis should be considered

Familial Mediterranean fever (FMF)

- Colchicine helps in preventing attacks, but not always effective once the attack is underway
- Colchicine may tried in patients with features compatible with Familial Mediterranean fever especially when these pt's originate from high prevalence region
- If the fever persists and source remains elusive after the completion of later stage investigations, supportive treatment with NSAIDs can be helpful
- In case of Adult onset Still's disease, NSAID's response is dramatic in some cases
- In case of Polymyalgia rheumatica & Giant cell arteritis, the effect of Glucocorticoids are equally impressive
  - Glucocorticoids in early empirically decreases the chances of reaching a diagnosis

Interleukin-1 inhibitors

- IL-1 is key cytokine in local & systemic inflammation and also for febrile response
- Targeting IL-1 has revealed a pathological role of IL-1 mediated inflammation in a growing list of diseases
- Anakinra- Recombinant form of naturally occurring IL-1 receptor antagonist
  - Blocks the activity of IL-1α & IL-1β

- Extremely effective in treatment of many autoinflammatory syndromes - FMF, CAPS, TRAPS, Mevalonate kinase deficiency, Adult onset Still's disease, Schnitzler syndrome
- Anti-IL-1 is also highly effective in Chronic inflammatory disorders
- Therapeutic trail of Anakinra can be considered in cases of FUO is not diagnosed after later stage diagnostic tests
- Although most Chronic inflammatory disorders can be controlled by Glucocorticoids, monotherapy with IL-1 inhibition can provide improved control without metabolic, immunologic & GI side effects of Glucocorticoids

Prognosis

01:20:32

- FUO unexplained cases- Favourable prognosis
- 2 large studies were done on mortality in these patients.
  - The 1st study included 436 cases of which 168 remained without diagnosis. Of these only 4 died during follow-up. All the 4 patients died upon index admission and in 2 of them diagnosis was made upon autopsy where one had Intravascular lymphoma and the other had B/L pneumonia
  - 2nd study out of 131 pt's with unexplained FUO, 9 pt's died during the median follow up of 5 yrs. Out of these the cause of death was known in 6 pt's and in 5 of them the death was considered to unrelated to the febrile disease

5 CHEST DISCOMFORT PART-1

Chest Discomfort

Life-Threatening Conditions presenting with Chest Discomfort

- **Myocardial Ischemia**
- **Other Cardiopulmonary Causes:**
  - Myopericardial disease
  - Aortic emergencies (e.g., aortic dissection – tearing pain)
  - Pulmonary diseases (e.g., pneumothorax)
- **Non-cardiopulmonary causes**

Epidemiology & Natural History

00:02:45

- **Hospitalization**: Over 60% of patients are hospitalized for further testing.
- Less than 15% of evaluated patients are diagnosed with Acute Coronary Syndrome (ACS).
- **Other Common Causes:** Gastrointestinal causes are common.
- **Life-Threatening Cardiopulmonary Conditions** (excluding ACS)**:** Account for about 5% of cases.
- **Mortality rate:** Patients with a missed MI diagnosis have a 30-day risk of death that is double that of hospitalized counterparts.

Common Etiologies of Chest Discomfort

- Gastrointestinal: 42%
- Ischemic Heart Disease: 31%
- Chest Wall Syndromes: 28%
- **Other Causes:** Pericarditis, pleurisy, pulmonary embolism, lung cancer, aortic aneurysm, aortic dissection, aortic fibrosis.

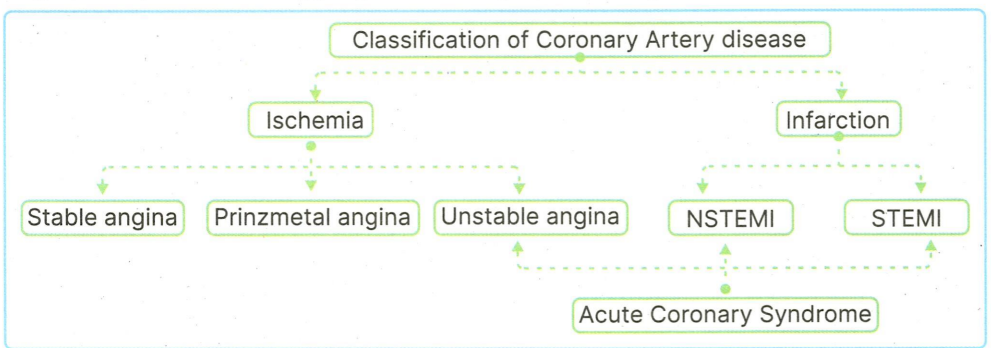
Ischemic Heart Disease (Myocardial Ischemia/Injury)

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- Chest discomfort due to myocardial ischemia is termed **angina pectoris**.

Etiology:

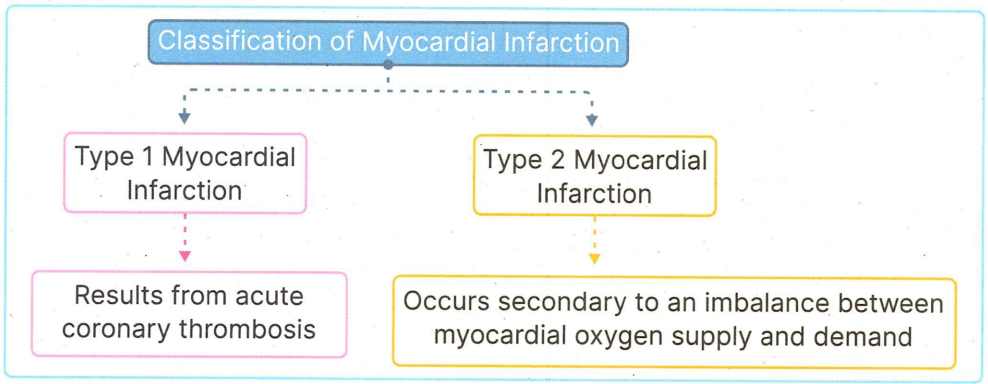
- Precipitated by an imbalance between myocardial oxygen requirement (demand) and myocardial oxygen supply → Insufficient oxygen delivery to meet the heart's metabolic demand.
- **Myocardial Oxygen Consumption (Demand) is elevated by:**
  - Increase in heart rate (e.g., tachyarrhythmias)
  - Ventricular wall stress
  - Increased myocardial contractility
- **Myocardial Oxygen Supply is determined by:**
  - Coronary blood flow
  - Coronary arterial oxygen content
- If myocardial ischemia is sufficiently severe and prolonged (as little as **20 minutes**), it leads to **irreversible cellular injury** and results in myocardial infarction.
- Most commonly caused by **atheromatous plaque** obstructing one or more epicardial coronary arteries.



- **Stable Ischemic Heart Disease / Stable Angina**
  - **Cause:** Results from gradual atherosclerotic narrowing of coronary arteries.
  - **Precipitating Factors:** Ischemic episodes typically precipitated by a superimposed increase in oxygen demand during physical exertion.
  - **Relief:** Angina gets relieved upon **resting** or with nitroglycerin.
  - **Onset:** Usually begins gradually, reaching maximum intensity over minutes, then dissipates.
  - Occurs predictably at characteristic levels of exertion or psychological stress.
- **Unstable Ischemic Heart Disease / Unstable Angina**
  - **Manifestation:** Angina occurs at **rest** or exhibits an **escalating pattern** of pain.
  - **Cause:** Most commonly occurs with rupture or erosion of one or more atherosclerotic lesions, triggering coronary thrombosis → 100% occlusion
  - **Classification:** Further classified by presence or absence of detectable acute myocardial injury.

Type	Cardiac Biomarkers	ECG Findings	Pathophysiology
Unstable Angina	Not elevated	No ST elevation	No detectable acute myocardial injury; partially obstructing thrombus
NSTEMI	Elevated	ST depression	Acute myocardial necrosis due to partially occlusive thrombus
STEMI	Elevated	ST elevation	Acute and completely occlusive thrombus leading to transmural ischemia

  - **Etiology:**
    → **Increased myocardial oxygen demand:** During fever, intense psychological stress.
    → **Decreased oxygen delivery:** Due to anemia, hypoxia, hypotension.
- **Acute Coronary Syndrome (ACS)**
  - Encompasses **Unstable Angina, NSTEMI, and STEMI**.
  - Generally reserved for ischemia precipitated by **acute coronary atherothrombosis**.



- Non-ischemic cause of ischemic heart disease: Myocarditis

Other Contributors to Ischemic Heart Disease

- Endothelial dysfunction (common in diabetic patients).
- Microvascular diseases.
- Vasospasm: Typically seen in Prinzmetal (variant) angina.

Non-Atherosclerotic processes causing Coronary Obstruction/Myocardial Injury:

- Congenital abnormalities of coronary vessels:
  - Myocardial bridging

- Coronary arteritis: Kawasaki disease.
- Radiation-induced coronary disease.

Conditions Associated with Extreme Myocardial Oxygen Demand & Impaired Endocardial Blood Flow

- Aortic valve diseases (e.g., aortic stenosis, aortic regurgitation).
- Obstructive pathologies (e.g., hypertrophic obstructive cardiomyopathy - HOCM).
- Dilated cardiomyopathy.

Characteristics of Ischemic Chest Discomfort (Angina Pectoris)

00:35:50

- Clinical characteristics are similar across stable angina, unstable angina, and MI; the **duration of symptoms** differs.
- **Heberden's describes as** sense of strangling and anxiety.
- **Pain:**
  - **Description:** Aching, heaviness, squeezing, crushing, constricting.
  - In a minority, discomfort is vague, described as mild tightness, an uncomfortable feeling, numbness, or burning sensation.
- **Site of Discomfort:** Most commonly retrosternal.
- **Radiation:**
  - Common, typically down the ulnar surface of the left arm
  - Also, radiates to right arm, neck, jaw, and shoulders.

Stable Angina	Unstable Angina	Myocardial Infarction (MI)
• Begins gradually, reaches max intensity over minutes. • Characteristic level of exertion or psychological stress. • Relieved upon resting or with nitroglycerin.	• Occurs with progressively lower intensity of physical activity or at rest. • Occurs at rest or with escalating pattern (lower activity).	• More severe, prolonged (typically >30 minutes). • Not relieved by resting or nitroglycerin.

Mechanisms of Cardiac Pain (Neural Pathways)

00:44:02

- **Ischemic episodes** excite local **chemosensitive and mechanoreceptive receptors**.
- This stimulates the release of mediators like **adenosine and bradykinin**.
- These mediators activate sensory ends of **sympathetic and vagal afferent fibers**.
- **Sympathetic Afferents:**
  - Travel via nerves connecting the upper five thoracic sympathetic ganglia and the upper five distal thoracic roots of the spinal cord.
  - Impulses are transmitted to the thalamus, where pain is perceived.
  - Within the spinal cord, cardiac sympathetic afferent impulses converge with impulses from somatic thoracic structures, → **referred cardiac pain**.
- **Vagal Afferents:**
  - Synapse in the nucleus tractus solitarius of the medulla oblongata, then descends to the upper cervical spinothalamic tract.
  - This route may contribute to angina pain experienced in the neck and jaw.

Other Cardiopulmonary Causes for Chest Discomfort

00:52:06

- **Pericardial Diseases (Pericarditis)**
  - Inflammation of the pericardium due to infectious or non-infectious cause.
  - Most of the visceral and parietal pericardium is pain-insensitive. Pain usually arises from associated pleural inflammation → pleuritic pain.
  - **Exacerbating Factors:** Exacerbated by breathing, coughing, or changes in position.
  - **Referred Pain:**
    - → Central diaphragm's sensory supply overlaps with somatic fibers from C3-C5 cervical segments.
    - → This overlap causes pain from pleural and pericardial inflammation, often referred to the shoulder and neck (as these cervical segments also supply these areas).

→ Involvement of the pleural surface of the lateral diaphragm can lead to pain in the upper abdomen.

- **Acute Myocarditis**
  - Inflammatory injury of the myocardium.
  - Severe increase in wall stress related to poor ventricular performance.
- **Takotsubo Cardiomyopathy**
  - Stress-Related Cardiomyopathy
  - **Onset:** Abrupt, with sudden onset of chest pain and dyspnea.
  - **Trigger:** The most recognizable form is triggered by an emotionally or physically stressful event.
  - **Mimics Acute MI:**
    - → Often presents with ST-segment elevation.
    - → 2D echo shows hypokinesia of the apex.
    - → Cardiac biomarkers are elevated.
  - **Differentiation from MI:** Normal coronaries ón coronary angiogram.
  - **Predilection:** Commonly observed in females > 50 years of age.

6 CHEST DISCOMFORT PART-2

Other Cardiopulmonary Causes for Chest Discomfort

Diseases of the Aorta

- **Acute Aortic Dissection:**
  - Though less common, it's critical due to potential catastrophic outcomes if unrecognized or untreated.
- **Acute Aortic Syndromes (AAS):**
  - Encompasses aortic diseases involving disruption of the tunica media of the aortic valve.
  - Involves a tear in the aortic intima, leading to tunica media separation and formation of a **false lumen**.
  - **Penetrating Ulcer:** An ulceration of an aortic atheromatous plaque extending through the intima into the aortic media, potentially even adventitial rupture → leading to vascular collapse).
- **Intramural Hematoma:**
  - An aortic wall hematoma without a demonstrable intimal flap, intimal tear, or false lumen on imaging.
  - Primarily **results** from **rupture of vasa vasorum**; less commonly from a penetrating ulcer.
- **Chest Discomfort in Aortic Disorders:**
  - Very severe
  - Sudden in onset
  - Described as tearing
  - Can involve any part of the aorta
- **Chest Discomfort in Acute Aortic Syndromes (AAS):**
  - **Ascending aorta:** Pain typically in the midline of the anterior chest.
  - **Descending aorta:** Pain most often in the back.
  - **Dissection extending from ascending to descending aorta:** Pain starts anteriorly, then moves to the back (between shoulder blades).
- **Stanford Type A Aortic dissection:** Proximal Aortic Dissections
  - Involving the ascending aorta carries a **high risk for major complications** due to **proximity** to vital structures.
  - **Complications:**
    - → If dissection compromises coronary ostia → Myocardial Infarction
    - → If dissection disrupts the aortic valve → Insufficiency/Regurgitation.
    - → If the hematoma ruptures into the pericardial space → Cardiac Tamponade
- **Non-Traumatic Aortic Dissections (Rare):**
  - **Occurs** mainly due to the deterioration of elastic or muscular components of the aortic media without hypertension
  - **Associated Conditions:**
    - → Pregnancy
    - → Bicuspid aortic disease
    - → Inherited connective tissue diseases (e.g., Marfan syndrome, Ehlers-Danlos syndrome).
- **Aortic Aneurysms:**
  - Most often asymptomatic.
  - Thoracic aortic aneurysms can cause chest pain by compressing adjacent structures.
  - **Pain Character:** Tends to be steady, deep, and occasionally severe.
- **Aortitis:**
  - Non-infectious or infectious etiology; a **rare cause** of chest or back discomfort in the absence of **dissection**.

Pulmonary and Pulmonary Vascular Conditions

00:18:37

- Presentation: Chest discomfort with dyspnea.
- Chest pain is often **pleuritic**.

Pulmonary Embolism (PE):

- Produces sudden onset dyspnea and chest discomfort, typically pleuritic.
- **Mechanisms of Chest Discomfort:**