Approach to a patient with fever

Ankara University School of Medicine

2019-2020 Y2C5 Lectures

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Learning objects

At the end of the course students,

- Define fever, understand its importance,
- List the causes of fever,
- Explain diagnostic approach of fever, and
- List what to do in the first application for the diagnosis and differential diagnosis of the febrile patient.

Fever

Body temperature (Bt) above the normal of 37°C (98.6°F) in the control of the central nervous system in response to a certain stimulus, especially infectious diseases, is called fever.

37-38°C (100 -100.4°F) ➔ mild or low-grade or "subfebris"

> 38°C - 40.5 °C (100.5 -105 °F) ➔ high grade

>40.5 °C (>106 °F)➔ hyperthermia (non-pyrogen mediated)

Circadian (diurnal) rythym

Body temperature gradually increases during the day

depending on metabolism

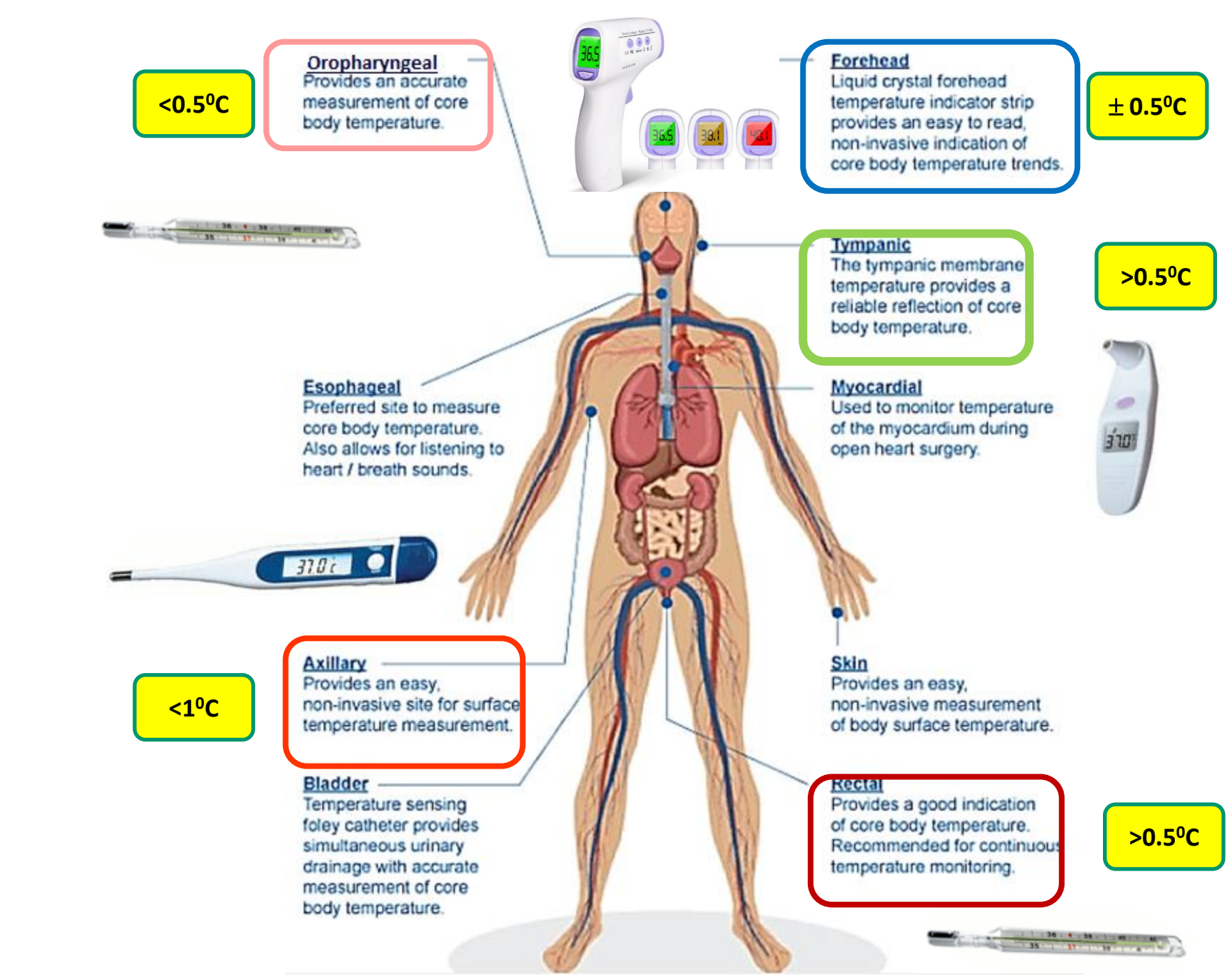
measured **physiologically**

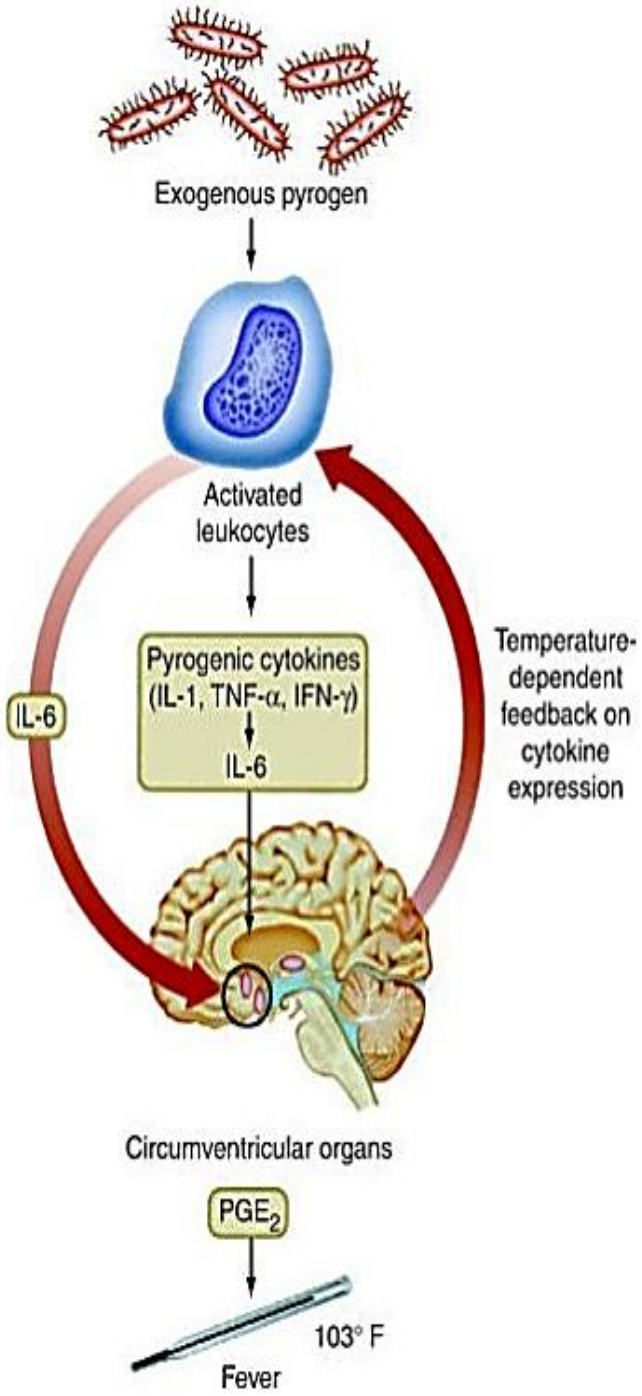
around 4 AM the lowest, around 4-6 PM the highest.

The difference between morning and evening is usually

no more than 1^0C in every day

Circadian rythym

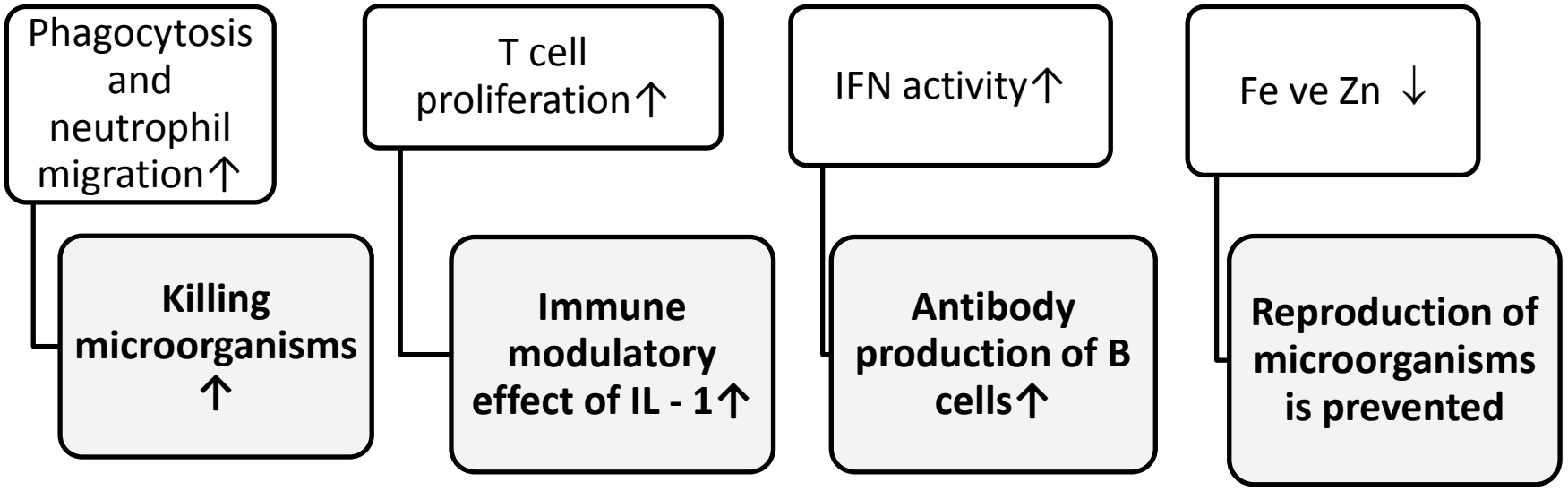

<0.5⁰C
Oropharyngeal
Provides an accurate measurement of core body temperature.
Forehead
Liquid crystal forehead temperature indicator strip provides an easy to read, non-invasive indication of core body temperature trends.
± 0.5⁰C
Tympanic
The tympanic membrane temperature provides a reliable reflection of core body temperature.
>0.5⁰C
Esophageal
Preferred site to measure core body temperature. Also allows for listening to heart / breath sounds.
Myocardial
Used to monitor temperature of the myocardium during open heart surgery.
<1⁰C
Axillary
Provides an easy, non-invasive site for surface temperature measurement.
Skin
Provides an easy, non-invasive measurement of body surface temperature.
Bladder
Temperature sensing foley catheter provides simultaneous urinary drainage with accurate measurement of core body temperature.
Rectal
Provides a good indication of core body temperature. Recommended for continuous temperature monitoring.
>0.5⁰C



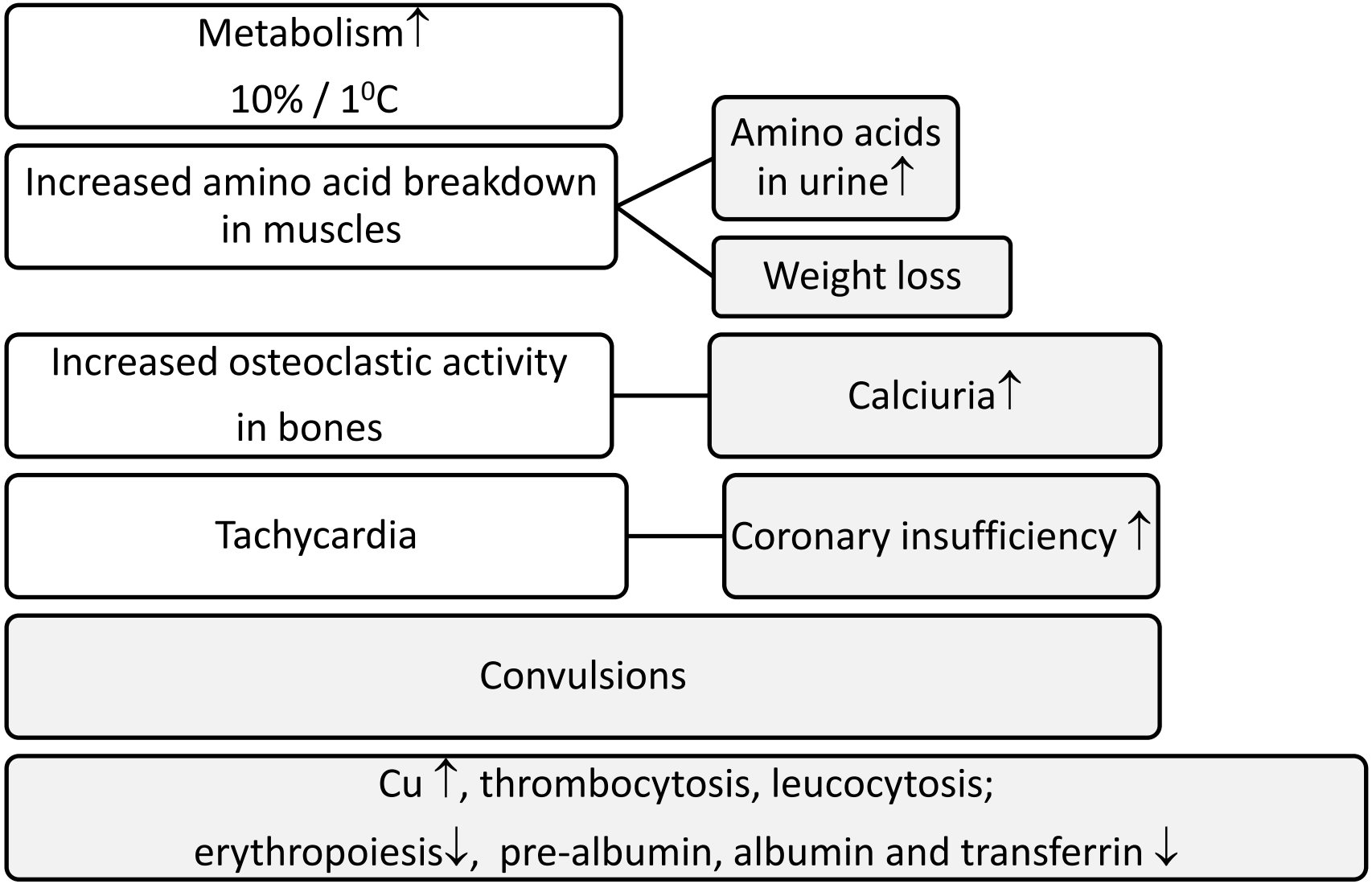
Fever stimulators and inhibitors

- Infectious agents
- Microbial products
- Tissue damage
- Tissue ischemia/necrosis
- Hypoxia
- TLR agonists
- Macrophages
- Endothelium
- RES
- Release of pyrogenic cytokines (IL-1, IL-6, TNF, IFN)
  - ← Inhibitory — Corticosteroids
- Transport via systemic circulation to preoptic area of hypothalamus
- Hypothalamic endothelium (cytokine receptors and TLR)
- PGE2
  - ← Inhibitory — Antipyretics
- Thermostat
- Vasomotor center
- Heat conservation (vasoconstriction)
- Heat production (shivering)
  - ← Inhibitory — Dantrolene
- **FEVER**

Benefits of fever to the body



Harmful effects of fever?



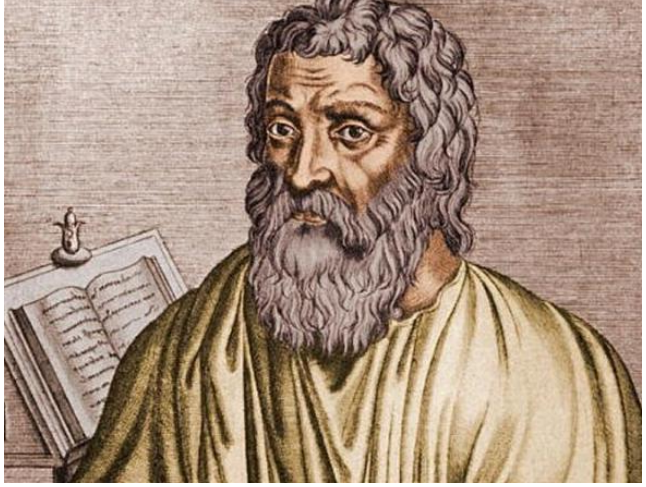
In <3ys or, elderly people there may be absent fever response

Therefore, sign and symptoms of the underlying disease may be atypical, or absent

Clinical condition may critically change immediately

Complications of the disease, or death may occur dramatically!

Hippocrates



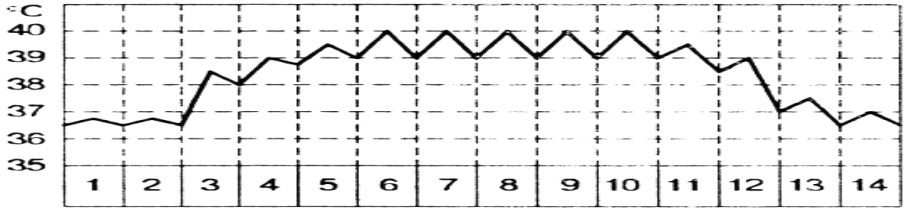
Says in relation to fever and the diseases that cause it;

- some fevers are continuous,
- some are night and day, and nighttime increase,
- some are daytime, and nighttime decrease,
- there is a fever every other day, or every 3-4 days,
- **the most severe, serious and troubled fatal illness has fever constantly**.

Patterns of fever

A. Regular

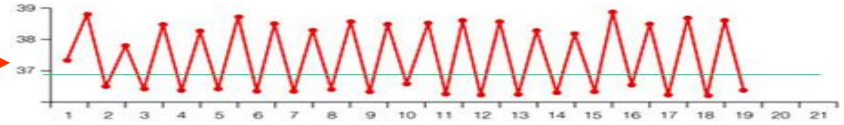
1. Subfebris(<38 C)
2. Continue (*Febris continua*)

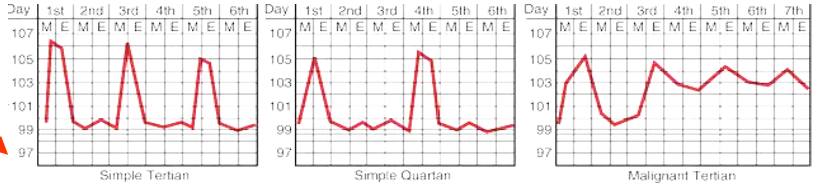


B. Irregular

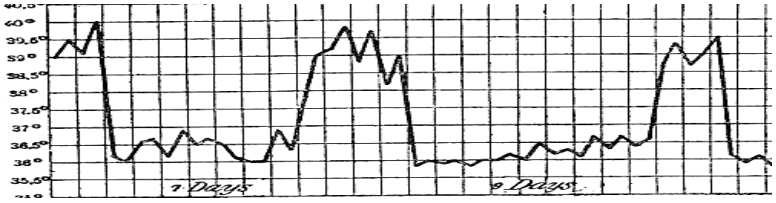
1. Remittan (Febris remittent)

2. Intermittan (Febris intermittent)





3. Recurrent-relapsing (Febris recurrens)

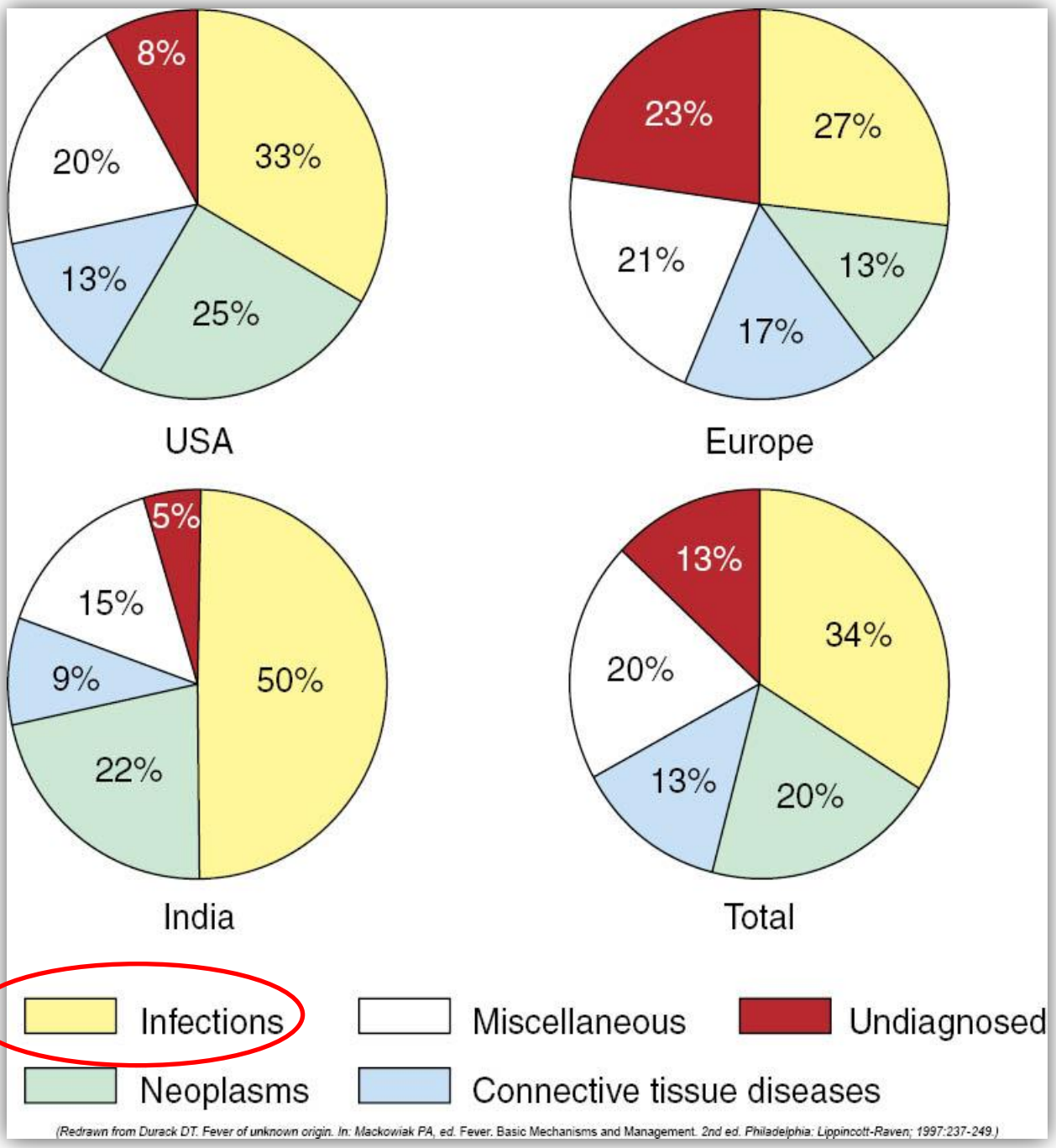


4. Undulent (Febris undulens)

Fever of unknown origin (FUO)

- Classical
- Healthcare-associated (nosocomial)
- Neutropenic (Immun-deficient)
- HIV-associated

Causes of FUO at worldwide



Causes of FUO

Classical	Healthcare-associated	Immun-Deficient	HIV associated
• Tuberculosis (Tb) • Endocarditis • Brucellosis • Osteomyelitis • Abcess • Adult Still's disease • Giant cell arteritis • Neoplasms	• Postoperative • Septic thrombophylebitis • Clostridium colitis • Drugs	• **>20% infectious** • Gram +ve, -ve bacterial infect. • Candida • Invasive aspergillosis • Herpes simplex	• Tb (typical, atypical) • Pneumocystis jirovecii infect. • Toxoplasmosis • Cryptococcus • Lymphoma • CMV, HIV • Drugs

Etiology of fever ➔ VINDICATEs

- ✓ **V**ascular disorders: Myocardium, lung, brain tissue infarctions, hematoma, dissecting aneurysms.
- ✓ **I**nfections (1/3): All local, general, septicemic infections with bacteria, viruses, ricketsia, chlamydia, mycoplasma, parasites and fungi
- ✓ **N**eoplastic diseases (1/5): Solid and metastatic tumors, hypernefroma, cancers in the lung, liver, pancreas, bone and other tissues, sarcomas and melanomas, Hodgkin and non-Hodgkin lymphomas of the reticuloendothelial system, histiocytosis, leukemias, acute hemolytic diseases.
- ✓ **D**rugs: Including antibiotics.
- ✓ **I**nflamatory conditions
- ✓ **C**ongenital: Familial Mediterranean Fever, Fabry's disease.
- ✓ **A**utoimmune diseases, immune mechanism disorders, connective tissue diseases, …
- ✓ **T**rauma and others: Medulla spinalis cuts, brain hemorrhages, pontine hemorrhages, thromboses, encephalitis, brain tumors.
- ✓ **E**ndocrine metabolic diseases: Porphyria, hyperglyceridemia, adison, hyperthyroidism.
- ✓ **S**omething else: Psychogenic (fever simulators ➔ Factitious Fever).

Approach

- **History**: detailed, recurrent 
  - Fever + accompanied sign and symptoms, epidemiological features.
- **Physical exam**: Whole body
  - Fever + pathological findings
- **Laboratory**
- **Radiographs**
- **…**

History

Features of fever

< 7 days	1-2 weeks	≥3 weeks
Acute	**Sub-acute**	**Prolonged or resistant / FUO**

- **Duration** (how many days?)
- The **highest value** measured
- **Beginning :**
  - **How it rises?** Slow, **sudden**; **whether** there is severe **chills**?
- **Termination:**
  - **How long it lasts** ? and **how it decreases?:** Suddenly, by sweating, slow falling, by itself, by medication such as antipyretics, by wet compress application or with water-bath

Algorythm for appr. fever

Acute fever (<1wk)

History

cont.

- How did fever **change in day?**
  - what is the difference between morning and evening measurement?

- How did it **change from the beginning** to the present.
  - **Has it been every day? Change in days. Hippocrates !**

Symptoms that accompany fever

- **Chills, shivering**
- **Sweating**
- Any **pain**: Throat ache,headache, myalgia, arthralgia, abdominal pain,…
- **Cough**
  - Dry or sputum with pus
- **Diarrhea** (watery, with pus and/or blood) or constipation
- **Nausea, vomiting**,
- **Confusion, dizziness, hallucinations, verbal changes**,…
- Malaise, fatigue

Changes in organ functions that can be observed during fever

- **Chills, shivering** → cold perception of the body according to the environment-**involuntary contractions in the muscles**
- **Myalgia, arthralgia** → accumulation of **lactic acid** and bradykinin
- **Palpitation** → For **oxygen and energy supplement** to vital organs (brain, heart, kidney, liver,...)
- **Headache** → cerebral **vasodilation**, muscle contractions
- **Malaise, fatigue, weakness → cytokines**

cont.

- **Sweating** ➔ sympathetic activity, decreasing fever, or underlying disease
- **Flushing** ➔ After the Bt raised to the set point, vasodilation of the skin vessels to decrease fever.
- **Oliguria** ➔ sweating and evaporation
- **Letargia** ➔ impaired brain function-low O_2&glucose
- **Hyperventilation** ➔ need for more O_2

cont.

- **Skin lesions**: Macules, papules, vesicles, pustulas, petechiae-purpura
- **Lymph node enlargement** texture, location, distribution, configuration, tenderness, redness of the skin on it, any drainage,…)
- **Weight loss**
- **Urinary symptoms**: such as dysuria, urgency, oliguria, pollakiuria,
- **Cardiovascular symptoms**: such as palpitation, malaise, headache, abdominal pain, dyspnea,
- **Endocrine system symptoms**: such as tremor, thristy, hungry, sweating

Additional questions including **epidemiological** features

- **Suspicious food** consumption?
- **Are there any similar patients around?** Persons who has contacted with the patient.
- **Travel story?**
- **Sexual contacts without condom?**
- **Any drug** usage (including antibiotics)?
- **Trauma -** history of **surgery, bites (**animals or insects**)?**
- **…**

Algorythm for appr. fever

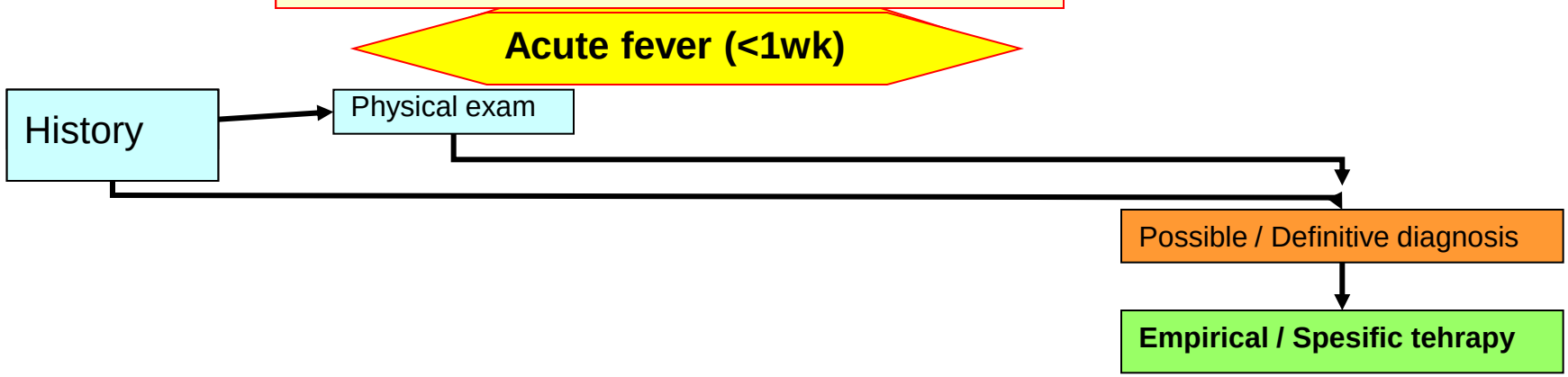
Acute fever (<1wk)

History

Possible / Definitive diagnosis

Empirical / Spesific tehrapy

Algorythm for appr. fever



Physical exam

Fever+

Chills, shivering	Pneumonia, sepsis, acute pyelonephritis, acute infective endocarditis, leptospirosis, malaria…
Sweating	Tuberculosis, brucellosis, lymphoma, malaria, pneumonia, hyperthyroidism
Headache/sore throath/ abdominal pain	Meningitis/ tonsillitis, sinusitis/ typhoid, intra abdominal infection,…
Cough, sputum, chest pain	Flu, pneumonia, pleuritis
Mental disorder+vomiting-nausea	Meningitis, meningoencephalitis
Urinary and gastrointestinal system complaints	Urinary and gastrointestinal infections

Fever + skin lesions

Texture, location, distribution, configuration

macules, papules	Enteroviral inf., typhoid, toxoplasmosis, rubella, measles, syphilis, gonorrhea, HIV, leptospirosis, Lyme disease, HBV, CMV, EBV
erythema	Scarlet fever, staphylococcal toxic shock syndrome, Kawasaki syndrome, Lyme disease
vesicles	Shingles , chickenpox, smallpox, *Herpes simplex*
petechiae-purpura	Meningococcemia, infective endocarditis, rickettsial infections
hemorrhagic bullae	Gas gangrene, anthrax, invasive group A streptococcal (GAS) infections

Fever - pulse discordance

Relative **bradycardia**	Relative **tachycardia**
• Typhoid • Typhus • Leptospirosis • Malaria • Legionaire disease • Haemorrhagic fevers • Drug fever • Simulation fever • Intracranial pressure increase syndrome • Heart conduction disorder	• Shock • Gas gangrene • Diphtheria • Anemia • Hypotiroidism • Pulmoner emboly • Supraventricular arythmia

Fever + lymphadenopathy

Texture, location, distribution, configuration, tenderness, redness of the skin on it, any drainage

Localized

- GAS tonsillitis
- Tuberculosis
- Rubella
- Tularemia
- Anthrax

Generalized

- Infectious mononucleosis
- Measles
- Toxoplasmosis
- HIV
- Secondary syphilis
- Typhoid
- Brucellosis
- Hematogenic bacterial infection

Neoplastic

Immunologic /autoimmune

Metabolic

Drugs

Miscellaneous

Fever +

Bleeding

- Viral hemorrhagic fevers:
  - Crimean Congo, Ebola Virus Disease,…
- Meningococcal disease,
- ….

Jaundice

- Hepatitis
- Leptospirosis
- Cholecystitis with stone
- Yellow fever
- Cholestasis,…

Fever +

- Hepatomegaly - splenomegaly
  - Hepatitis, infectious mononucleosis, Kala-azar, malaria, toxoplasmosis, typhoid, neoplasms…
- Abdominal tenderness, vomiting, diarrhea
  - Enteritis, colitis, enterocolitis
  - Intra abdominal abcess, UTIs, acute appendicitis, pancreatitis
  - Mesenteric adenitis, typhlitis
- Artritis
  - Acute rheumatic fever, septic artritis, osteomyelitis, Lyme artritis
  - Reactive artritis

Fever+ Neurological signs

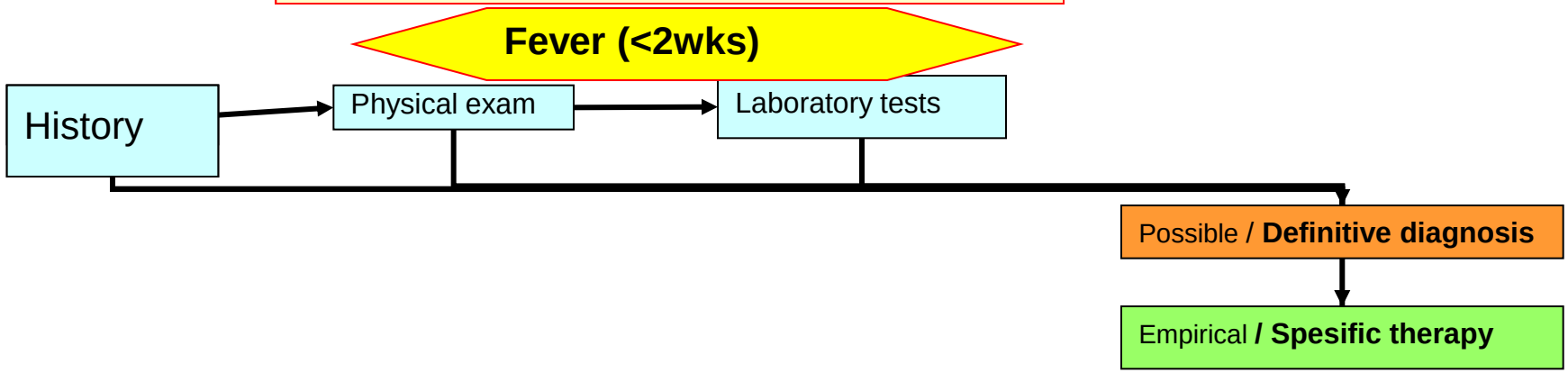
Meningeal irritation signs ➔ **Meningitis**

1. **Neck stiffness**
2. **Kernig's sign**
3. **Brudzinski's sign**

- *N. meningitidis*
- *S. pneumoniae*
- Malaria
- Syphilis
- Tb
- Anthrax
- Tularemia
- Brucellosis
- Rabies
- Lyme disease
- Schistosomiasis
- Trypanosomiasis
- Listeriosis
- Candida inf.

- HIV
- Rubella, rubeola
- Mumps
- Zona Zoster
- Influenzae
- Japan Ensefalitis
- *Herpes simplex 1, 2*
- Flaviviruslar
- *Mononucleosis*
- Histoplasmosis
- Toxoplasmosis
- *C. neoformans*
- Blastomycosis
- Coccioidosis

Algorythm for appr. fever



Labs in fever

1. **Complete blood count** ➔ incl. differential and platelet count
2. **Acute-phase reactants** ➔ Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
3. **Routine blood chemistries**➔ including liver enzymes and bilirubin
4. **Urinalysis** ➔ incl. microscopic exam, and urine culture
5. **Radiograph**s (chest ,…)
6. **Serologies** ➔ liver tests ↑ ➔hepatitis A, B, and C, and search for etiology
7. **Blood cultures** (three sets drawn from different sites with an interval of at least several hours between each set; in cases in which antibiotics are indicated, all blood cultures should be obtained **before administering antibiotics**).

Laboratory tests

CBC + Periferal blood smear

- **White blood cells (WBC: Leucocytes)**
  - **Neutrophils**
  - **Lymphocytes**
  - Monocytes
  - Eosinophils
  - Basophils
  - Microorganisms (protozoa, eg. malaria)
- **Red** blood cells (RBC: Erytrocytes)
- **Plateletes** (Thrombocytes)
- **Hemoglobulin**

Acute-phase reactants

ESR, CRP

Blood chemistry

- Na,K, Ca,
- Renal function tests (BUN, creatinin, GFR)
- ALT, AST, Bilirubin
- Albumin/Protein
- Glucose
- LDH

Urinalaysis

- Color, appearence, smell, density, pH
- Bilirubin, Glucose, Protein, Urobilinogen,
- **Nitrite**, **Leucocyte esterase**,
- **Microscopy (bacteria, …)**

Radiological imaging tests

X-Rays first line: **Chest**, dental, abdominal, sinuses

If necessary:

- Ultrasonography (USG)
- Digital and nuclear imaging techniques: CT, MR, Scintigraphy, PET…

Serology

Hepatitis A, B, E

Cultures

Blood, urine, feces, sputum, cerebrospinal fluid,…

Fever+

Neutropenia ➔ FN, Gram negative sepsis

Anemia ➔ Bleeding, destruction (malaria) or chronic inf. (tb)

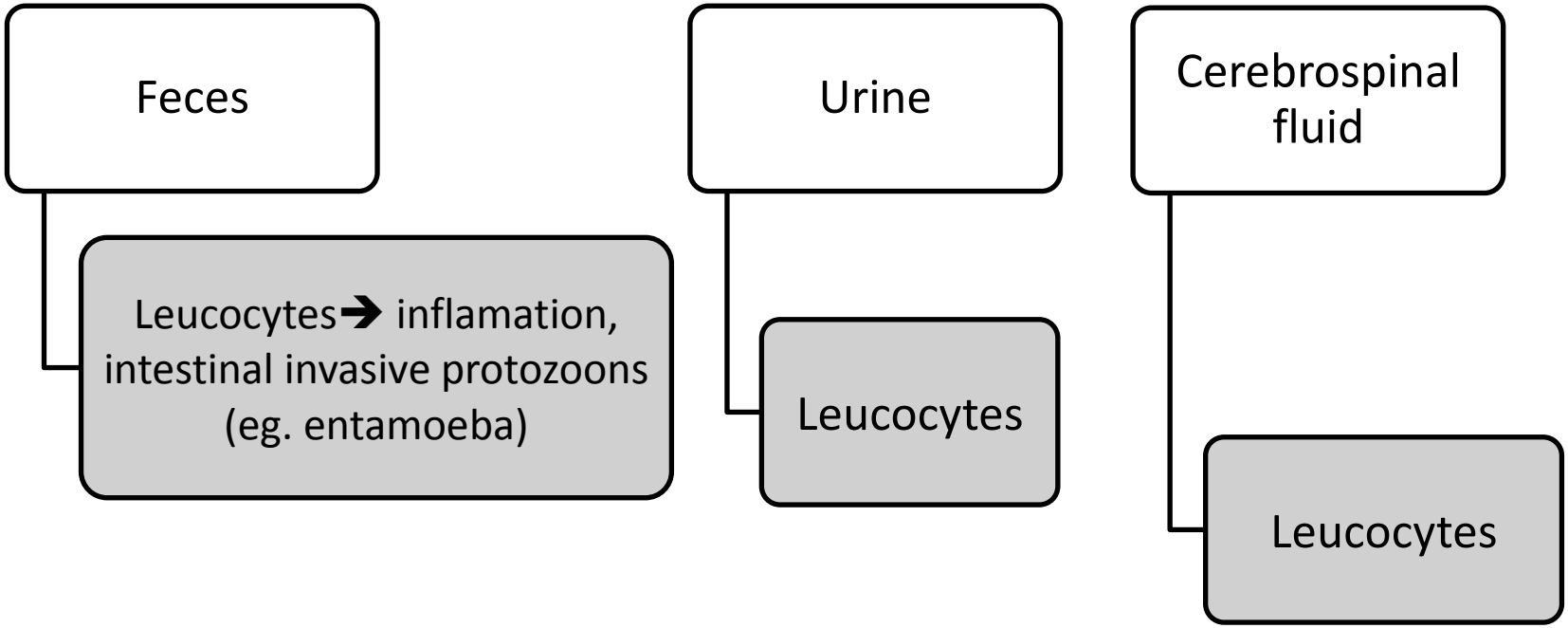
Thrombocytopenia ➔ Sepsis, viral infec.

ESR >100 mm/1h;
- Infection ➔ osteomyelitis, miliary tb, IE, intra abdominal abcess
- Connective tissue dis. ➔ Adult Still's dis., Giant cell arteritis
- Neoplasm ➔ carsinoma, lymphoma, multiple myeloma

CRP ➔ Invazive bacterial infec. ➔ **15-40 xN↑**
viral infec. ➔ **3-5 xN ↑**

Procalsitonin
<0.5ng/ml ➔ localized infections,
0.5-2ng/ml ➔ increased sepsis risk,
>2ng/ml ➔ severe sepsis/septic shock risk

Biological materials' fresh microscopic examination examples



Biological materials' staining examples

Peripheral blood smear
(Giemsa)

- Malaria, babesiosis

Sputum
(Gram, Giemsa, EZN)

- Pneumonia, Tb

Abcess, ulcer, aspirate
(Gram)

- Inflamation ± microorganisms

Agglutinations

Tube

- **Gruber Widal**
  Typhoid
- **Brucella (Wright)**
  Brucellosis
- **Paul Bunnel**
  Infectious mononucleosis
- **Cold Agglutination**
  Mycoplasmal pneumonia

Slide

- **Rose bengal**
  Brucellosis
  (screening)
- **Monospot test**
  Infectious
  mononucleosis

Cultures

Golden standard !

The method that finalizes the diagnosis and treatment decision of infectious diseases

Aims ➔ to isolate the disease-causing microorganism

demonstrate ➔ real disease factor

If possible, it should be taken immediately before administering antibiotics;

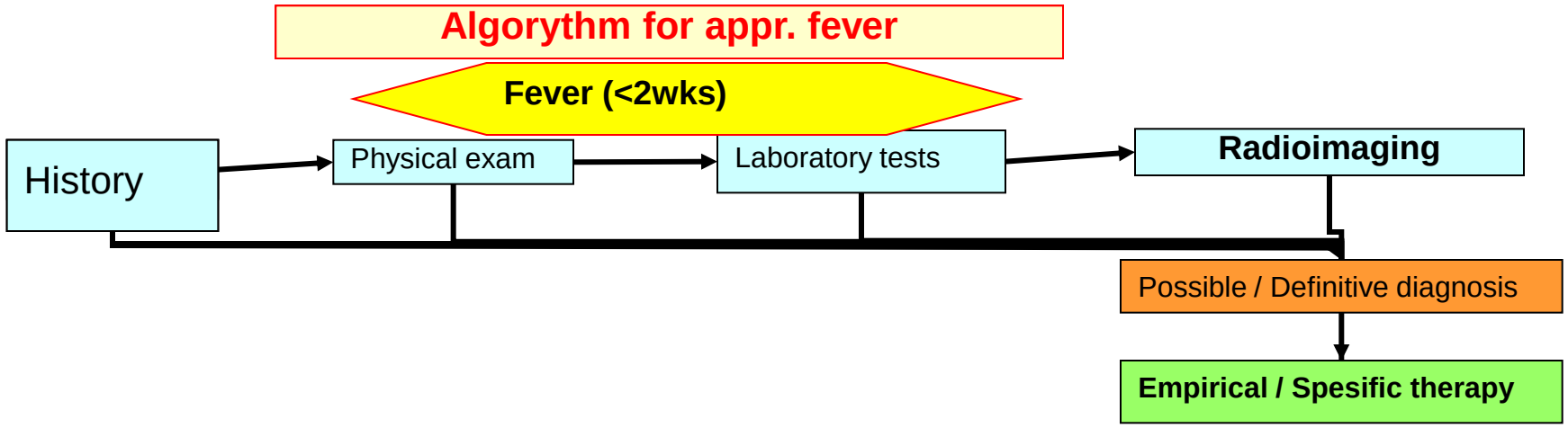
according to the method, as often as appropriate parts of the body or secretions should be taken from !!!

Blood

Three sets drawn from different sites with an interval of at least several hours between each set.

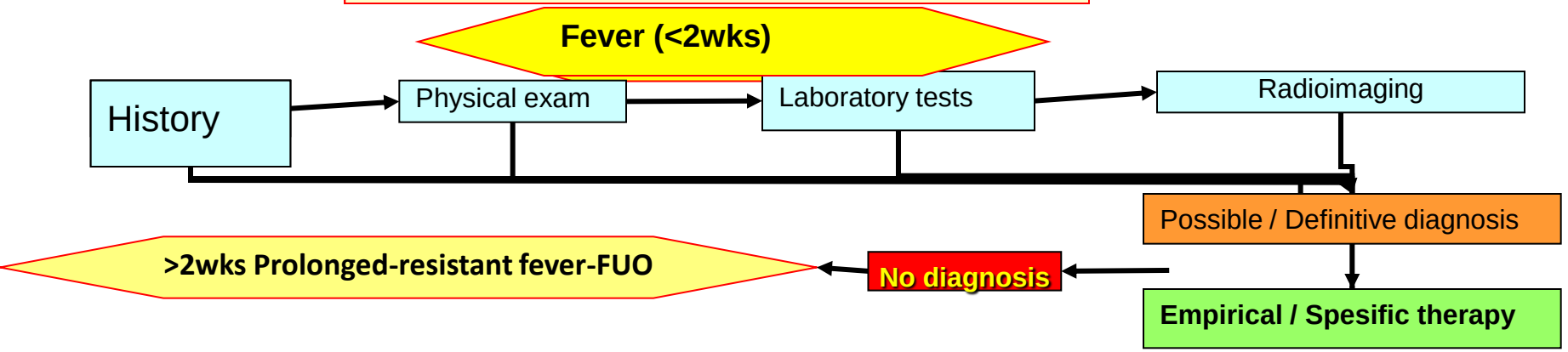
Cultures examples

Sypmtoms with fever	Possible site of infection	Culture material
Dysuria, urgency, frequent urination	Urinary tract infection	Urine, blood
Sore throat, extreme weakness	Tonsillopharyngitis	Throat swab
Cough, purulent sputum	Pneumonia	Sputum, blood
Blurring / closure of consciousness, vomiting, headache	Meningitis, encephalitis	CSF, blood
High / unknown fever	Abscess, tuberculosis, typhoid, brucellosis, sepsis	Blood



<u>Radiological imaging tests</u>
X-Rays first line: **Chest**, dental, abdominal, sinuses

Algorythm for appr. fever



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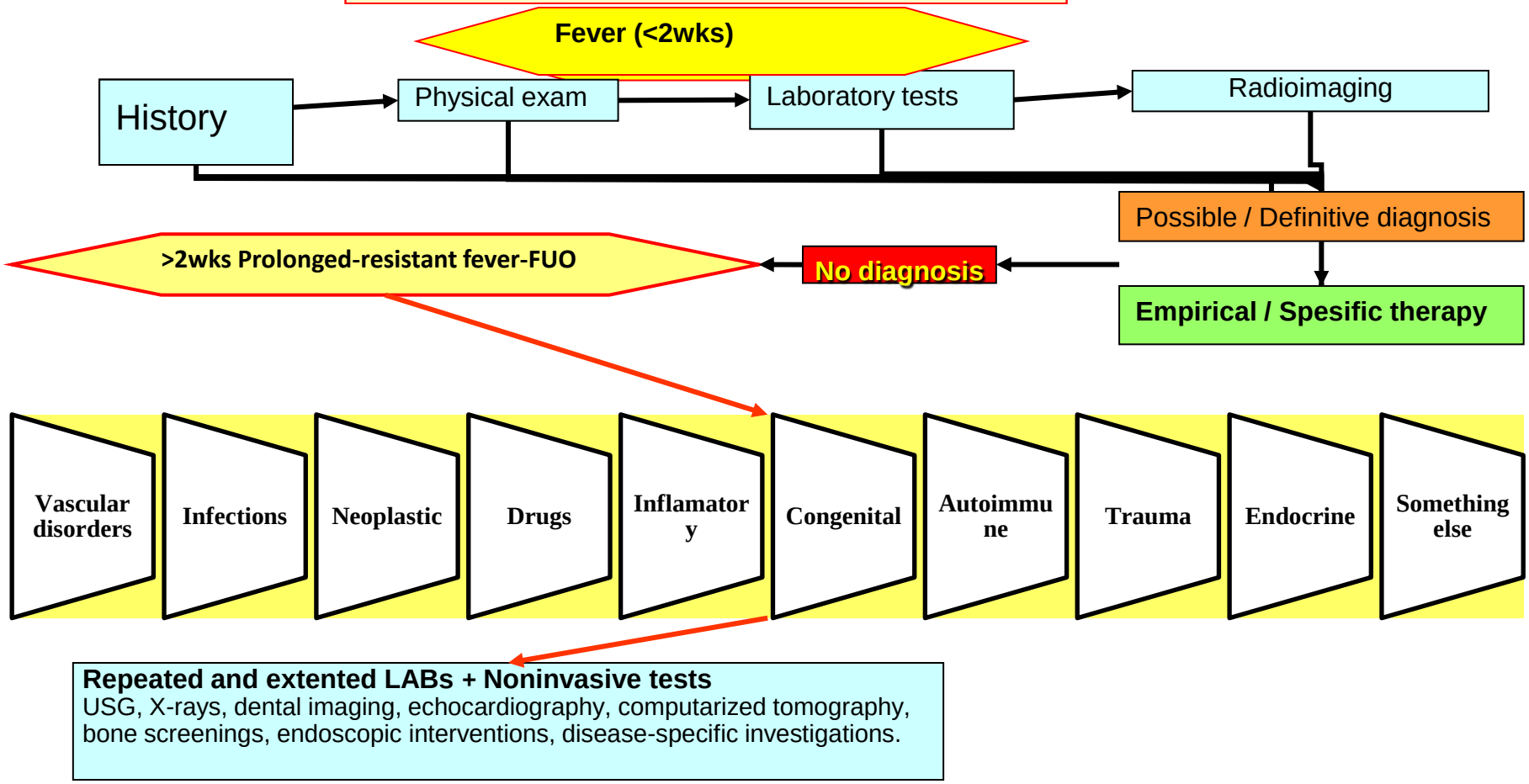

Repeated and extented LABs + Noninvasive tests
USG, X-rays, dental imaging, echocardiography, computarized tomography, bone screenings, endoscopic interventions, disease-specific investigations.

Laboratory tests

Whole Blood

White blood cells (WBC: Leucocytes)

- Red blood cells (RBC: Erytrocytes)
- Plateletes (Thrombocytes)
- Hemoglobulin

Periferal blood smear

Differantials:

- **Neutrophils**
- **Lymphocytes**
- Monocytes
- Eosinophils
- Basophils
- Microorganisms (protozoa, eg. malaria)

Acute-phase reactants

ESR, CRP

Blood chemistry

- Na,K, Ca,
- Renal function tests (BUN, creatinin, GFR)
- ALT, AST, Bilirubin
- Albumin/Protein
- Glucose
- LDH

Urinalaysis

- Color, appearence, smell, density, pH
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Radiological imaging tests

X-Rays first line: **Chest**, dental, abdominal, sinuses

If necessary:

- **Ultrasonography (USG)**
- **Digital and nuclear imaging techniques: CT, MR, Scintigraphy, PET…**

Serology

Hepatitis A, B, C, **EBV, CMV, HIV**

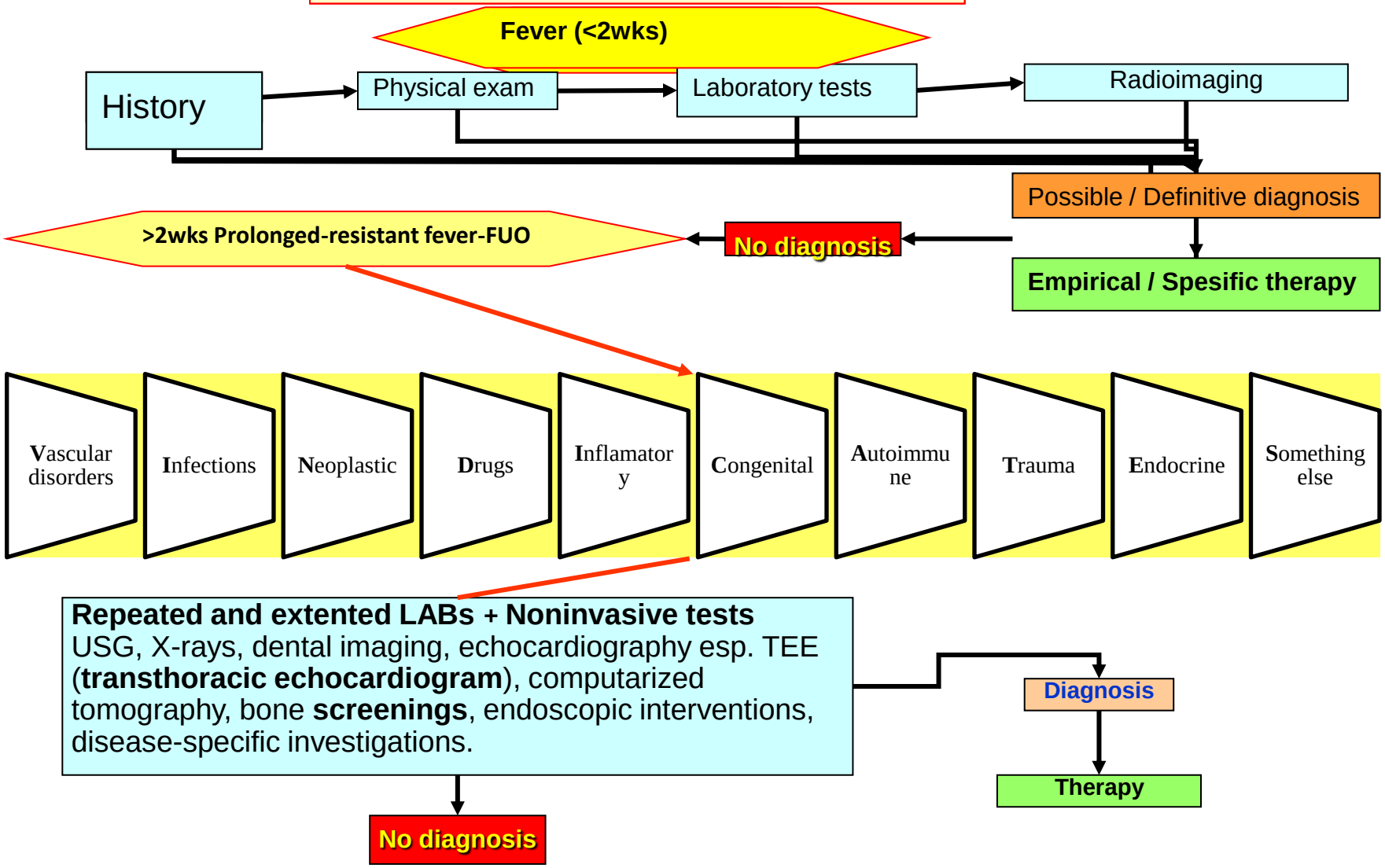
Cultures

Blood, urine, feces, sputum, cerebrospinal fluid,…

>2wks Prolonged-resistant fever or FUO

- Serum lactate dehydrogenase (**LDH**)
- Tuberculin skin test (**TST**) or interferon-gamma release assay (**IGRA**) (**Quantiferone**,TB-Gold,…)
- HIV serology (**AntiHIV**)
- Three routine **blood cultures** (drawn from different sites over a period of at least several hours without administering antibiotics, if not already performed)
- Rheumatoid factor (**RF**)
- Creatine phosphokinase (**CPK**)
- Heterophile antibody test (**mono/ Paul Bunnel**) in children and young adults
- Antinuclear antibodies (**ANA**)
- Serum protein electrophoresis (**PEF**)
- **CT** scan of abdomen, chest

Algorythm for appr. fever



Algorythm for appr. fever

Fever (<2wks)

History → Physical exam → Laboratory tests → Radioimaging

Possible / Definitive diagnosis

Empirical / Spesific therapy

No diagnosis

>2wks Prolonged-resistant fever-FUO

- **V**ascular disorders
- **I**nfections
- **N**eoplastic
- **D**rugs
- **I**nflamatory
- **C**ongenital
- **A**utoimmune
- **T**rauma
- **E**ndocrine
- **S**omething else

Repeated and extented LABs + Noninvasive tests
USG, X-rays, dental imaging, echocardiography esp. TEE (transthoracic echocardiogram), computarized tomography, bone screenings, endoscopic interventions, disease-specific investigations.

No diagnosis

Diagnosis

Therapy

Invasive tests: **Biopcies** (bone marrow, liver, spleen, skin, LAP, muscle, temporal arteria, etc. organs), **hystopatologic preparations, diagnostic laparotomy**

No diagnosis

Diagnosis

Evaluation ➔ **Empirical therapy**

If the fever still continues, plan again

Summary slides

Fever stimulators and inhibitors

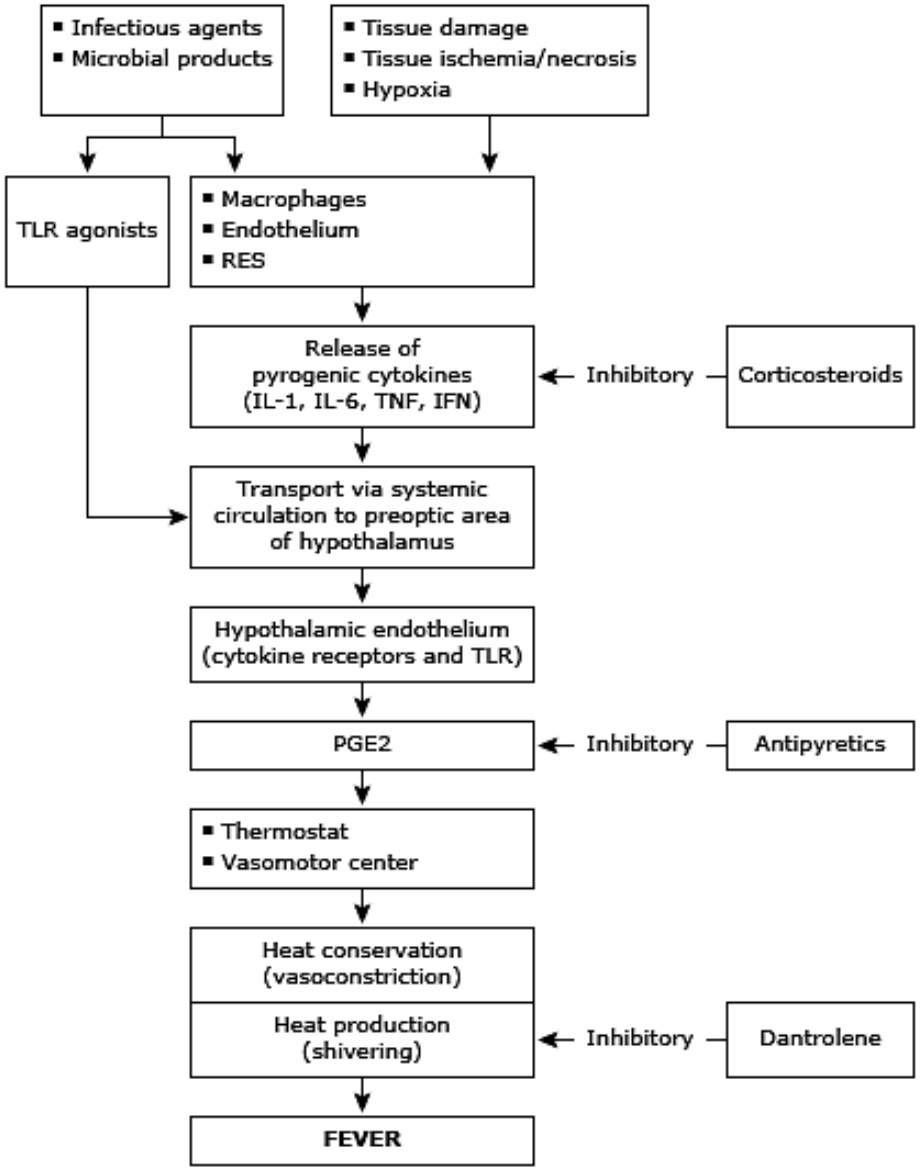


TABLE 44–1 Summary of Definitions and Major Features of the Four Subtypes of Fever of Unknown Origin (FUO)

	Classic FUO	Nosocomial FUO	Immune-Deficient FUO	HIV-Related FUO
Definition	>38.0°C, >3 wk, >2 visits or 3 d in hospital	>38.0°C, 3 d, not present or incubating on admission	>38.0°C, >3 d, negative cultures after 48 h	38.0°C, >3 w for outpatients, >3 d for inpatients, HIV infection confirmed
Patient location	Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital
Leading causes	Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia	Nosocomial infections, postoperative complications, drug fever	Majority due to infections, but cause documented in only 40–60%	HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower limb deep veins	Wounds, drains, devices, sinuses, urine	Skin folds, IV sites, lungs, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Months	Weeks	Days	Weeks to months
Tempo of investigation	Weeks	Days	Hours	Days to weeks

Abbreviations: CMV, Cytomegalovirus; CXR, chest radiograph; HIV, human immunodeficiency virus; IV, intravenous.
Adapted from Durack DT. Fever of unknown origin. In: Mackowiak PA, ed. Fever. Basic Mechanisms and Management. 2nd ed. Philadelphia: Lippincott-Raven; 1997:237–249.

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