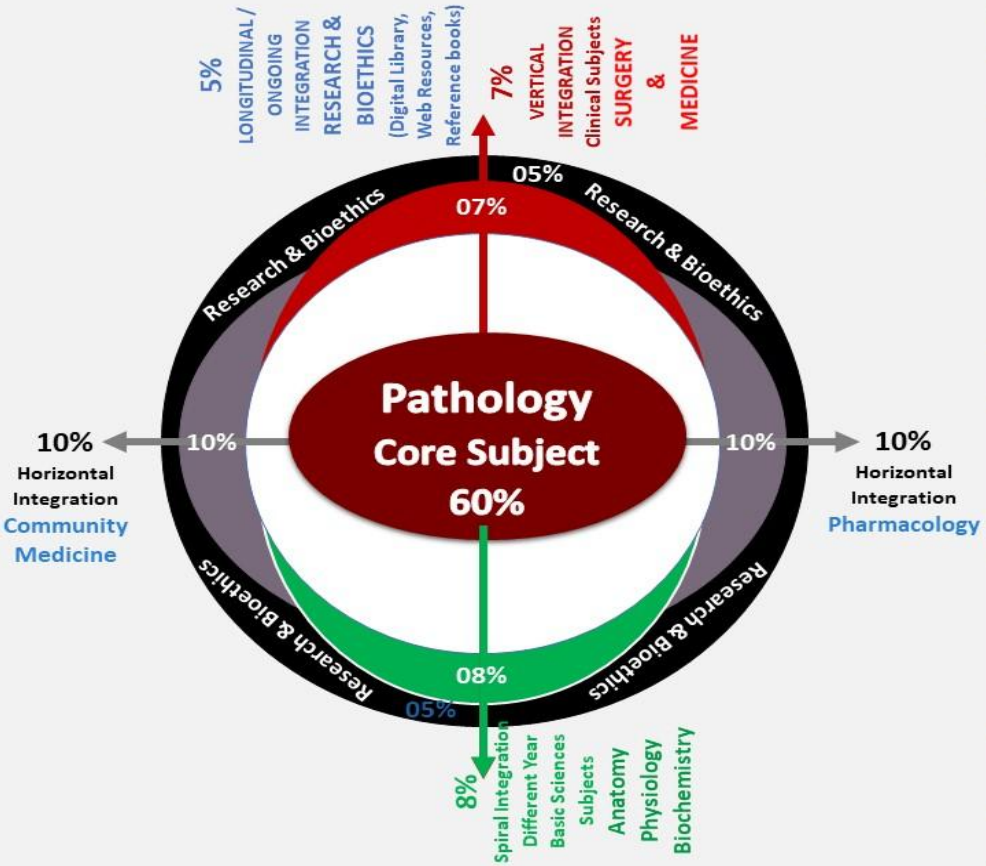

بسم الله الرحمن الرحيم

Prof. Umar, LGIS (Lecture) Model

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



Model 3rd Year Pathology LGIS (≈30 slides)	
Core Subject – 60% (≈ 18-20 slides)	
Pathology (≈ 18-20 slides)	
Horizontal Integration – 20% (≈ 5-6 slides)	
Same Year Subjects	• Pharmacology (10%) (≈ 2-3 slides) • Community Medicine (10%) (≈ 2-3 slides)
Vertical Integration – 07% (≈ 2-3 slides)	
Clinical Subjects	• Medicine (3-5%) (≈ 1-2 slides) • Surgery (3-5%) (≈ 1-2 slides)
Spiral Integration – 08% (≈ 2-3 slides)	
Different Year Basic Sciences Subjects	• Anatomy (1-3%) (≈ 1-2 slides) • Physiology (1-3%) (≈ 1-2 slides) • Biochemistry (1-3%) (≈ 1-2 slides)
Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides)	
Research & Bioethics (≈ 1-2 slides)	

RMU is thriving to upgrade the Integrated Clinical Oriented Modular Curriculum and Teaching. There are many deficiencies in this system which RMU has learned with five year experience of real ground experience. We have designed the teaching (lecture) model of integration, covering all components of vertical and horizontal and clinical integration along with continuous step ladder pattern of research, professionalism and ethic. This teaching strategy is in alignment with assessment principles of integrated modular curriculum.

Approach to Patient with Fever of Unknown Origin

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LEARNING OBJECTIVES

- DEFINE PUO
- ENUMERATE CAUSES / ETIOLOGY OF PUO
- DESCRIBE INVESTIGATIONS AND MANAGEMENT PLAN OF PUO

DEFINITION OF PUO

- Fever higher than 38.3C on several occasions
- Duration of fever of at least 3 weeks
- Failure to reach diagnosis after on week of in- patient investigation

CORE CONCEPT

ETIOLOGIES OF PUO

- Infections
- Malignancies
- Systemic rheumatic diseases

CORE CONCEPT

FUO is Classified as

- Classic FUO
- Nosocomial FUO
- Neutropenic FUO
- Associated with HIV

CORE CONCEPT

Remember!

Fever of unknown origin is more often caused by an atypical presentation of a common disease rather than a rare disease.

Infections	
Most common Mycobacterial infections, MAC, atypical mycobacteria Q fever Brucellosis	**Rickttsial infecions** Ampalasmosis, q-fever, ehriliosis,
Less common HIV infection, abscesses (Cholangitis, liver abscess, pancreatic, subphrenic, osteomyelitis, sinusitis.) EBV, CMV, ENTERIC fever, toxoplasma	**Fungal infections** Aspergilliosis, blastomycosis, candidasis, histoplasmosis
Least common SBE, tooth abcess, chronic sinusitis, Chronic prostitis, discitis, cholecystitis.	**Parasitic infecctions** Amebiasis, chagas disease, malaria, toxoplasmosis, leishmaniasis,

NEOPLASM

malignant	Benign
Colon cancer	Atrial myxoma
Gall bladder cancer	Renal angiomuolipoma
Hepatoma	
Hodgikins lymphoma, non-hodgkins lymphoma	
Leukemia, malignant histiocytosis	
Pancreatic carcinoma Renal cell carcinoma	
sarcoma	

CORE CONCEPT

Other causes

Collagen vascular diseases	Granulomatous diseases	Inherited and metabolic disease	Miscellaneous conditions
Most common Adult still disease Giant cell artritits	crohn's disease,	Cyclic neutropenia	Aortic dissection
Less common SLE, PAN,RA	Granulomatous liver disease	Type 5 hypertriglyceridemia	Drug fever Gout Post MI
Least common Anti-phosholipid syndrome,	sarcoidosis	Fabry disease	hemoglobinopathies
Hypersensitivity pneumonitis		Adrenal insufficiency	Recurrent pulomanry embolism
Mixed connective tissue disease			Hematomas

CORE CONCEPT

CENTRAL	PERIPHERAL
Brain tumor	Hyperthyroidism
Cva, encephalitis	pheochromocytoma
Hypothalamic dysfunction	

CORE CONCEPT

RULE OUT;

- Habitual fever (exaggerated circadian rhythm)
- Factitious fever
- Thermoregulatory disorders

Case studies of fever of unknown origin: prevalent diagnoses

Diagnosis	Case study					
	Alt 1913 to 1930 n = 23	Petersdorf 1952 to 1959 n = 93	de Kleijn 1992 to 1994 n = 117	Vanderschueren 1990 to 1999 n = 192	Miller 1989 to 1993 n = 72	Knockaert 1980 to 1989 n = 41
Location	Boston, United States	Seattle, United States	Netherlands	Belgium	London, United Kingdom	Belgium
Rheumatic fever	2	6	0	0	0	0
Abdominal abscess	1	4	4	5	0	5
Endocarditis	0	5	4	11	0	2
Syphilis	1	1	1	0	0	0
Mycobacterial	6	12	3	8	57	15
Lymphoma	2	8	11	14	7	5
Solid tumor	3	10	7	7	1	7
Sarcoid	0	2	2	10	0	2
Lupus	0	5	2	8	0	0
Rheumatoid arthritis	0	0	2	2	0	5
Giant cell arteritis	0	2	4	11	0	19
Drug fever	0	1	3	4	0	7
Factitious fever	0	3	2	1	3	0

Case studies of fever of unknown origin

Author	Alt	Petersdorf	Vanderschueren	Miller	Knockaert	Bleeker-Rovers	Fusco
Years	1913 to 1930	1952 to 1959	1990 to 1999	1989 to 1993	1980 to1989	2003 to 2005	2005 to 2015
Location	Boston, United States	Seattle, United States	Belgium	London, United Kingdom	Belgium	Netherlands	Asia, Europe, Middle East
Subpopulation	Adults	Adults	Adults	AIDS	Elderly	Adults[¶]	Adults
Case definition*	1	2	2	2	2	2	Varies[Δ]
Number of cases	101	100	290	79	47	73	3164
Diagnostic categories[◊]							
Infections	11	36	20	80	25	16	38
Neoplasms	6	19	10	8	12	7	12
Multisystem[§]	0	17	24	1	31	22	21
Miscellaneous	6	21	13	2	20	4	6
No diagnosis	78	7	34	9	12	51	23

* 1: no diagnosis at time of hospital discharge; 2: temp >101°F (38.3°C), duration >3 weeks, undiagnosed >1 week; 3: temp >101.3°F (38.5°C), duration >2 weeks, undiagnosed.

VERTICAL INTEGRATION

DIAGNOSTIC APPROACH TO FEVER OF UNKNOWN ORIGIN

Establishing FUO

- History
- Physical examination
- Complete blood count, including differential counts
- Blood cultures
- Routine blood chemistry
- Hepatitis A, B, C serologies
- Urinanalysis including microscopic examination and culture
- Chest radiograph

VERTICAL INTEGRATION

REMEMBER!

- There is no standard algorithm for evaluating FUO
- Best guided by clues in history, physical exam, and baseline labs.
- Beginning with least invasive avoids harm and cost to patient
- FUO that remain undiagnosed despite long term evaluation have good long term prognosis (25-30% of cases)

History

- Fever Pattern
- Localizing symptoms
- Immunosuppression
- Drugs and toxins
- Immunization status
- Nutrition and weight loss
- Dental history
- Occupational history
- Travel history
- Sexual history
- Recreational history
- Animal exposure (pets, occupational farms)
- Family history

Remember! Revisiting the history at different times may provide new clues

Fever Pattern

- Tertian fever: *Prolonged malaria*
- Undulant fever: *Brucellosis*
- Tick-borne relapsing fever: *Borelliosis*
- Pel-Ebstein fever: Hodgkin's lymphoma
- Double quotidian fever: *adult still disease, typhoid, malaria*
- Morning fever: *PAN, TB, Typhoid*

HORIZONTAL INTEGRATION

Historical Clues in Non-infectious Inflammatory Diseases

- Headache, jaw claudication, vision disturbances:

  Giant cell artritis /temporal artritis

- Symmetrical pain, stiffness of large proximal muscles and lumbar spine:

  Polymyalgia rheumatic

- High spiking fever, rash that follows the fever curve, arthralgias: *adult onset still disease*
- Facial rash: *SLE,dermatomyositis*
- RUQ pain,diarrhea: *Crohn disease, Yersinia*
- Erythema nodosum: sarcoidosis, Ucerative colitis
- CNS disorders: *SAH, cerebral trauma, CVA*

HORIZONTAL INTEGRATION

Historical Clues to Some Infectious Causes of FUO

- Previous abdominal surgery, trauma, endoscopy urologic or gynecologic procedures:
  Intra abdominal abscess
- Animal and animal product Exposure
- to unpasteurized dairy:
  Brucellosis, Coxiella, Burnetii (Endocarditis, Q Fever), Yersinia enterocolitica
- Expoure to birds: *Chlamydia psittaci*
- Cats: *Toxoplasmosis*
- Undercooked meat: *Trichinosis*

HORIZONTAL INTEGRATION

Travel Related

- Desert areas of USA: *Coccidioides immitis*
- Caves: *Histoplasma*
- Swimming in rivers: *Leptospirosis*
- Rural Areas of Africa and Asia: *Malaria*
- Tropics: *Visceral leishmaniasis*
- Uncertain Sanitation, adventurous eating: *Salmonella typhi*

Other Causes of FUO

- Painless Lymphadenopathy: *Malignancy*
- Weight loss with anorexia: *Malignancy, chronic infections*
- Prolonged immobility, car trips, flights: *Thromboembolic disease*
- Prolonged treatments: *drug fever*

HORIZONTAL INTEGRATION

Physical Examination Clues

- Pulse temperature deficit: *Typhoid fever, Q fever, Psittacosis, lymphoma*
- Unequal pulses: *Takayasu arteritis*
- Eyes-Roth spots: *SLE, Vasculitis, bacterial endocarditis*
- Oral Ulcers: *SLE, Behcet* dz
- Tender tooth on percussion: *Dental abscess*
- Enlarged or tender thyroid: *Thyroiditis*
- Lymphadepathy: *Sarcoidosis, SLE,Malignancies*

HORIZONTAL INTEGRATION

- Cardiac murmur:
  SLE, Bacterial Endocarditis
- Hepatomegaly without splenomegaly:
  primary liver cancer, granulomatous hepatitis
- Splenomegaly without hepatomegaly: *Bacterial Endocarditis, EBV/CMV, Typhoid, TB, Q fever, Cirrhosis*
- Tenderness of sternum:
  Hematological malignancy

Clues in Labs

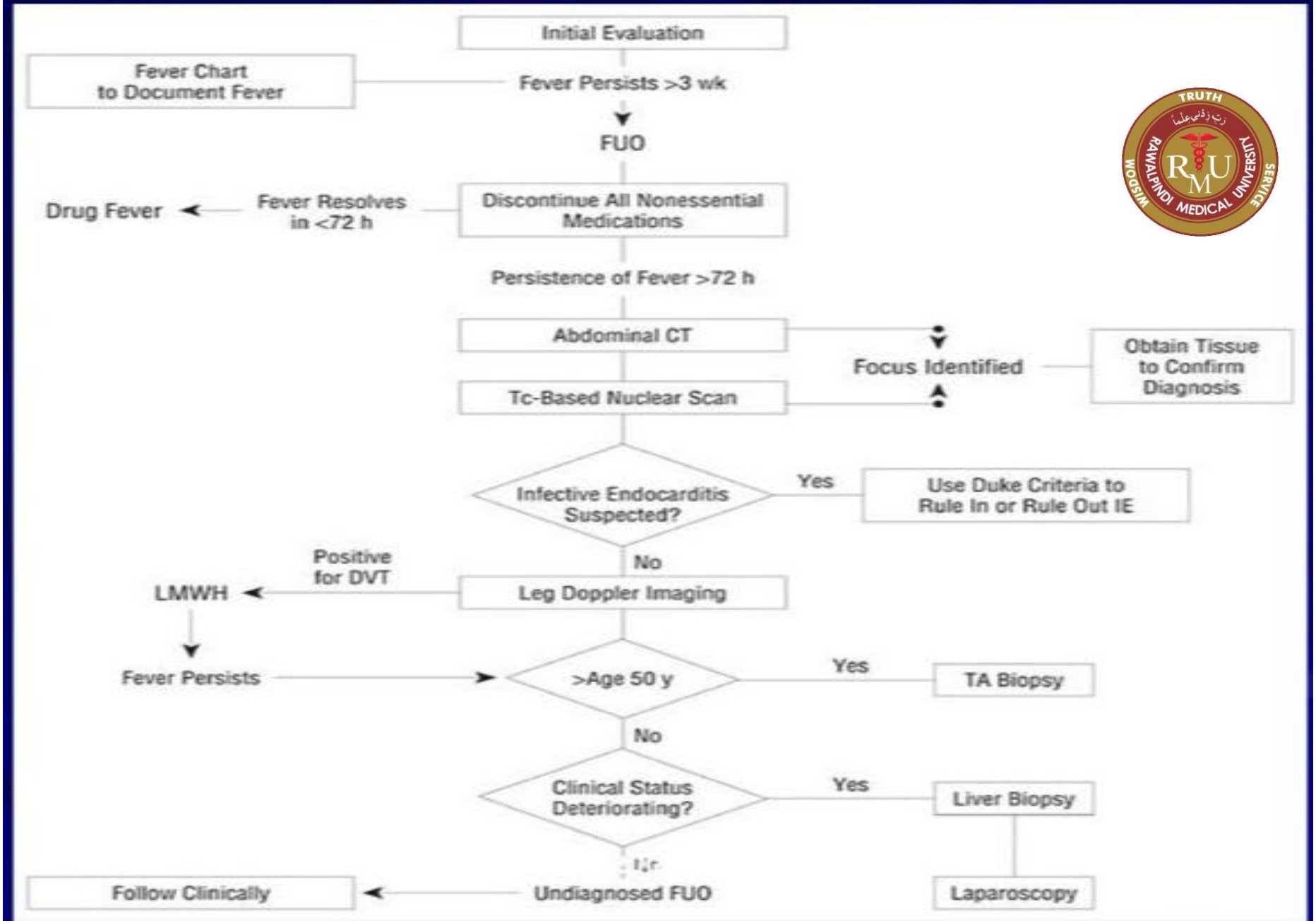
- ESR>100 Consider malignancy, or infection(Endocarditis, TB, Osteomyelitis)

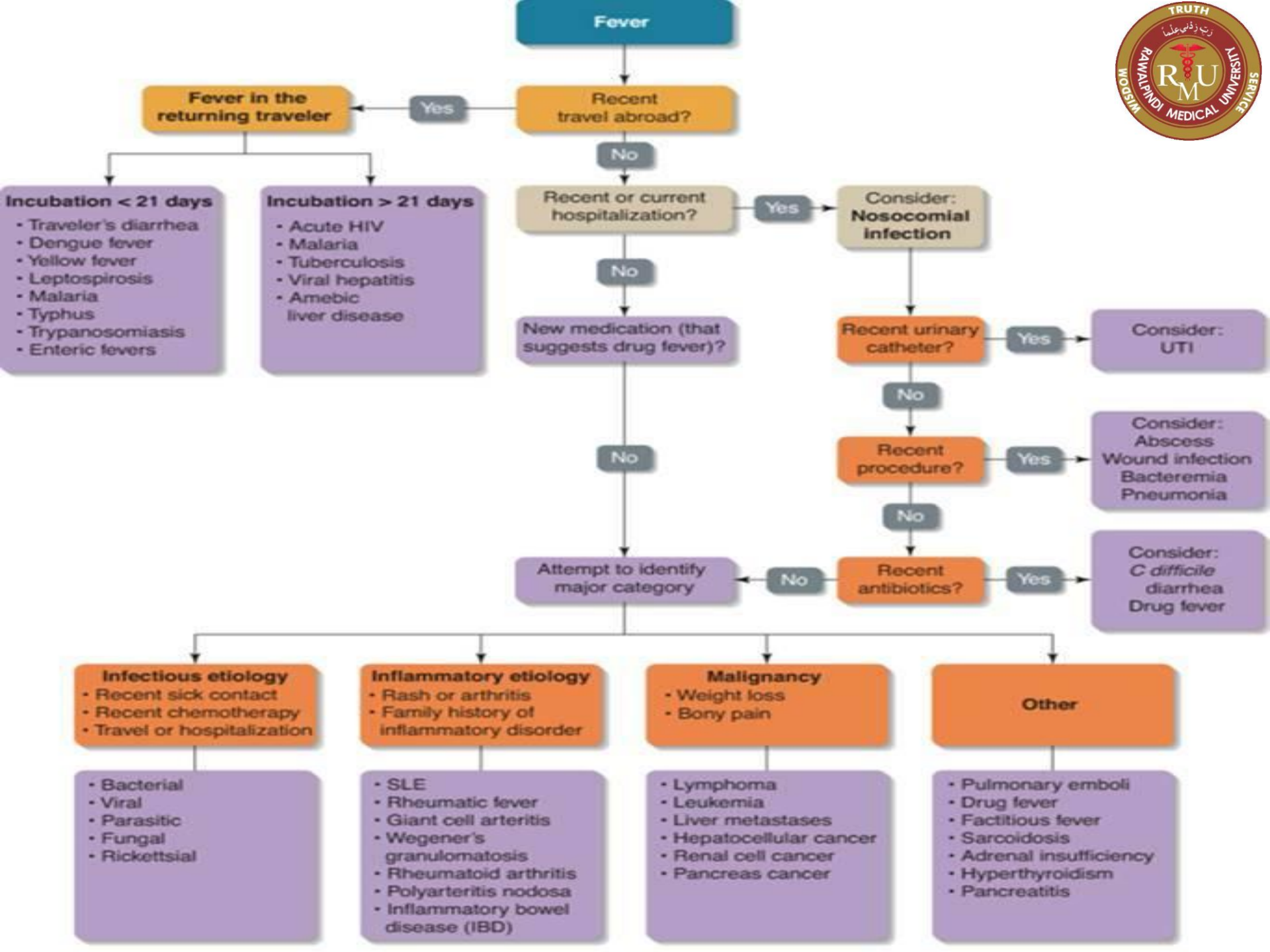
VERTICAL INTEGRATION

Table 1. Potential second-line investigations for pyrexia of unknown origin

Infection	Inflammatory	Neoplastic	Miscellaneous
Echocardiogram, preferably TOE	ANA	Colonoscopy	Pituitary screen
Line cultures if the patient has an intravascular device	ANCA	CT chest, abdomen and pelvis	Synacthen test
Lumbar puncture	Anti-CCP	Echocardiogram, preferably TOE	Thyroid function tests
Lymph node biopsy	Antiphospholipid antibodies (lupus anticoagulant and anticardiolipin)	LDH	
Malaria screen (RDT and three malaria films on consecutive days)	Complement levels	PET-CT	
PET-CT	Cryoglobulins	Serum calcium	
Serology for viral hepatitis	CT chest, abdomen and pelvis	Serum electrophoresis	
Specialised serological or molecular tests	Ferritin	Tissue, lymph node and/or bone marrow biopsy for histology	
Spinal MRI	Joint aspiration to detect crystals	Urine for Bence Jones protein	
Sputum test for culture (consider an induced sputum test if the patient is not expectorating)	LDH		
Stool samples for culture, PCR and OCP	MR or CT angiography		
Syphilis serology	PET-CT		
Two to three peripheral blood cultures	Rheumatoid factor		
Urine culture, plus three early morning urines for TB culture in sterile pyuria	Serum ACE level		
Wound swabs	Serum electrophoresis		
	Serum urate		
	Temporal artery biopsy		
	Urine for Bence Jones protein		

Note: This is not a comprehensive list of investigations to be carried out in every patient with PUO but instead a list of tests that should only be performed when there is a reasonable pretest probability of the condition investigated being present.
ACE = angiotensin converting enzyme; ANA = anti-nuclear antibodies; ANCA = antineutrophil cytoplasmic antibody; Anti-CCP: anti-cyclic citrullinated peptide; CT = computed tomography; LDH = lactate dehydrogenase; MR(I) = magnetic resonance (imaging); OCP = ova, cysts and parasites; PET-CT = positron emission tomography–computed tomography; PCR = polymerase chain reaction; RDT = rapid diagnostic test; TB = tuberculosis; TOE = transoesophageal echocardiogram


Initial Evaluation
Fever Chart to Document Fever
Fever Persists >3 wk
FUO
Drug Fever
Fever Resolves in <72 h
Discontinue All Nonessential Medications
Persistence of Fever >72 h
Abdominal CT
Focus Identified
Obtain Tissue to Confirm Diagnosis
Tc-Based Nuclear Scan
Infective Endocarditis Suspected?
Yes
Use Duke Criteria to Rule In or Rule Out IE
No
Positive for DVT
LMWH
Leg Doppler Imaging
Fever Persists
>Age 50 y
Yes
TA Biopsy
No
Clinical Status Deteriorating?
Yes
Liver Biopsy
Follow Clinically
Undiagnosed FUO
Laparoscopy


Fever
Recent travel abroad?
Yes
Fever in the returning traveler
No
Recent or current hospitalization?
Yes
Consider: Nosocomial infection
No
New medication (that suggests drug fever)?
Recent urinary catheter?
Yes
Consider: UTI
No
Recent procedure?
Yes
Consider: Abscess Wound infection Bacteremia Pneumonia
No
Recent antibiotics?
Yes
Consider: C difficile diarrhea Drug fever
No
Attempt to identify major category
Incubation < 21 days
- Traveler's diarrhea
- Dengue fever
- Yellow fever
- Leptospirosis
- Malaria
- Typhus
- Trypanosomiasis
- Enteric fevers
Incubation > 21 days
- Acute HIV
- Malaria
- Tuberculosis
- Viral hepatitis
- Amebic liver disease
Infectious etiology
- Recent sick contact
- Recent chemotherapy
- Travel or hospitalization
- Bacterial
- Viral
- Parasitic
- Fungal
- Rickettsial
Inflammatory etiology
- Rash or arthritis
- Family history of inflammatory disorder
- SLE
- Rheumatic fever
- Giant cell arteritis
- Wegener's granulomatosis
- Rheumatoid arthritis
- Polyarteritis nodosa
- Inflammatory bowel disease (IBD)
Malignancy
- Weight loss
- Bony pain
- Lymphoma
- Leukemia
- Liver metastases
- Hepatocellular cancer
- Renal cell cancer
- Pancreas cancer
Other
- Pulmonary emboli
- Drug fever
- Factitious fever
- Sarcoidosis
- Adrenal insufficiency
- Hyperthyroidism
- Pancreatitis

LONGITUDINAL INTEGRATION

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

JANUARY 17, 2013

Fever of Unknown Origin or Fever of Too Many Origins?

Harold W. Horowitz, M.D.

Petersdorf and Beeson's classic articles cataloguing the causes of fever of unknown origin (FUO) have framed the way generations of physicians think about fevers whose source is not readily explainable.[1] FUO as they define it — a temperature rising above 38.3°C (101°F) on several occasions over a period of more than 3 weeks, for which no diagnosis has been reached despite 1 week of inpatient investigation — is considered classic FUO. In the past 60 years, clinician-scientists have tracked the changing causes of

were caused by infection (in 36% of patients), malignancy (19%), collagen vascular diseases (19%), and miscellaneous other causes (19%), such as drug fever.[1] No cause was determined in 7% of patients. It is paradoxical that despite the introduction of computed tomography (CT), magnetic resonance imaging, improved cul-

As an infectious-disease physician who has practiced at academic, tertiary care facilities in the metropolitan New York area for nearly three decades, I've been struck by the fact that traditionally caused FUOs are now rarer than the FUOs that I'm increasingly asked to evaluate. The new FUOs are often found in patients in the intensive care unit (ICU) who have traumatic brain injury, other neurologic events, or dementia; are mechanically ventilated; have some combination of urethral, central, and peripheral catheters placed;

LONGITUDINAL INTEGRATION

Royal College of Physicians

Pyrexia of unknown origin

Authors: Cristina Fernandez[A] and Nick J Beeching[B]

ABSTRACT

The syndrome of pyrexia of unknown origin (PUO) was first defined in 1961 but remains a clinical challenge for many physicians. Different subgroups with PUO have been suggested, each requiring different investigative strategies: classical, nosocomial, neutropenic and HIV-related. This could be expanded to include the elderly as a fifth group. The causes are broadly divided into four groups: infective, inflammatory, neoplastic and miscellaneous. Increasing early use of positron emission tomography–computed tomography (PET-CT) and the development of new molecular and serological tests for infection have improved diagnostic capability, but up to 50% of patients still have no cause found despite adequate investigations. Reassuringly, the cohort of undiagnosed patients has a good prognosis. In this article we review the possible aetiologies of PUO and present a systematic clinical approach to investigation and management of patients, recommending potential second-line investigations when the aetiology is unclear.

MCQ # 1

A 30-year-old male known IV drug abuser presented with a history of fever for 2 weeks. On examination he was pale, emaciated and had IV injection site marks over his arms. Precordial examination revealed a pansystolic murmur over tricuspid area.

What is the likely cause of fever in this patient.

a) ENTERIC FEVER

b) MALARIA

c) BRUCELLOSIS

d) INFECTIVE ENDOCARDITIS

ANSWER # 1

INFECTIVE ENDOCARDITIS

MCQ # 2

A 36-year-old female presented with small joint pains in wrist for past 6 months. On further enquiry she had history of three miscarriages.

On examination, she had a butterfly rash over her face, was pale and had evidence of ascites.

She also complained of low-grade intermittent fever for past 3 months off and on.

What is the likely cause of fever in this patient.

a) RHEUMATOID ARTHRITIS

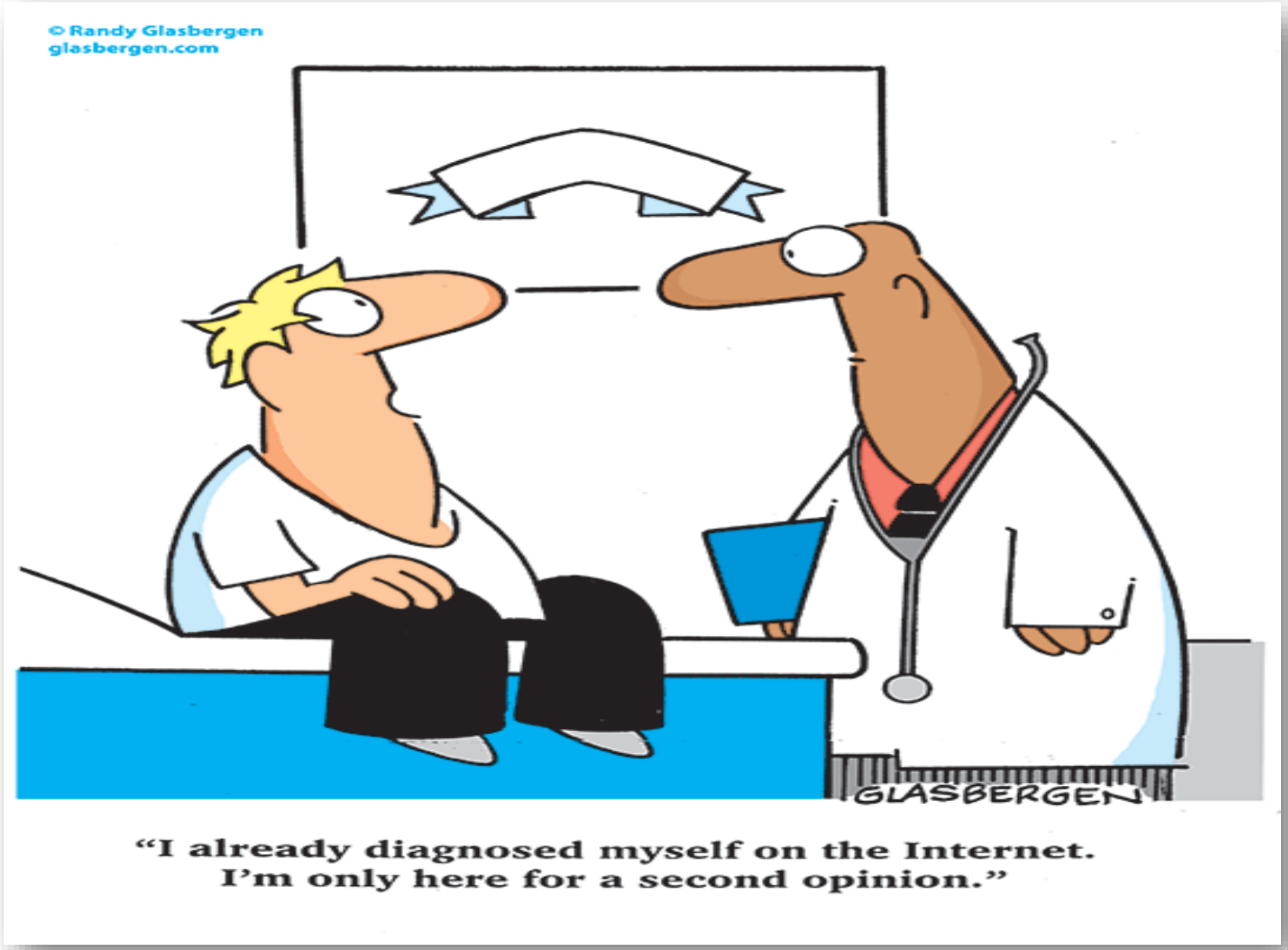
b) SYSTEMIC LUPUS ERYTHMATOSIS

c) FACTITIOUS FEVER

d) SPONTANEOUS BACTERIAL PERITONITIS

ANSWER # 2

SYSTEMIC LUPUS ERYTHMATOSIS



"I already diagnosed myself on the Internet.
I'm only here for a second opinion."


THANK
YOU!