

Fever of Unknown Origin

MARIA SONIA S. SALAMAT, M.D.

U.P. COLLEGE OF MEDICINE

Learning Objectives

By the end of the learning activity, the students should know the:

- Definition of fever of unknown origin (FUO)
- Categories of FUO
- Common causes of classic FUO

Learning Objectives

By the end of the learning activity, the students should:

- Be able to explain the approach to classic FUO
 - Algorithm of the approach to classic FUO
 - Important points in the history and physical exam of a patient with FUO
 - Laboratory exams important in the investigation of possible causes of classic FUO
- Know when empiric treatment is warranted in individuals with FUO
- Be able to apply the approach to classic FUO

Deuteronomy 28:22

The Lord will smite you with wasting disease, and with fever and with inflammation, with scorching heat and drought, with blight and with mildew, which will plague you until you perish.

Try this case:

I.C., 67/M, consults for fever for the past 3 weeks associated with substernal chest pain. I.C. has been on DM treatment for the past 3 years.

The patient has undergone the following tests:

CBC: Hb 12.5 g/dl, WBC 12.5 (segmenters 80), platelet = 405

Chest CT scan: infiltrates on the middle lobe of the right lung, minimal pericardial effusion

Abdominal CT scan: normal

The patient was treated for pneumonia with piperacillin-tazobactam. Anti-TB and steroids were also started for a presumptive diagnosis of pericardial TB. The fever lysed but recurred after 8 days.

Try this case:

M.T., 19/F consults for fever for the past 7 days accompanied by headache. She also has a 3-day history of watery stools. She lives in Manila but travels to Bataan every weekend to visit her family.

- Hgb: 11.2 g/dl Peripheral WBC: 6,000, neutrophils 65%, platelets 243
- Urinalysis: normal
- Chest x-ray: normal

M.T. is able to perform her usual activities despite the symptoms.

A case of FUO?



What is the definition of fever of unknown origin (FUO)?

Petersdorf and Beeson, 1961

- Temperatures of $>38.3^{\circ}\text{C}$ ($>101^{\circ}\text{F}$) on several occasions
- A duration of fever of >3 weeks
- Failure to reach a diagnosis despite 1 week of inpatient investigation

Durack and Street – Classic FUO

Temperatures of $>38.3^{\circ}\text{C}$ ($>101^{\circ}\text{F}$) on several occasions

A duration of fever of >3 weeks

3 outpatient visits or 3 days in the hospital without elucidation of cause or
1 week of “intelligent and invasive” ambulatory investigation



Knowledge is
having the right
answer.

Intelligence is
asking the right
question.

How do we investigate invasively AND intelligently?

What are the common causes of classic FUO?

Infections are the leading diagnosable causes of FUO.

- Extrapulmonary TB
- Intra-abdominal abscesses which may be poorly localized
- Hepatobiliary infections
- Infective endocarditis
- Osteomyelitis
- Cryptococcal meningitis
- Parasitic infections

What are the common causes of classic FUO?

Neoplasms

- Colon cancer
- Lymphoma
- Pancreatic cancer
- Renal cell cancer
- Hepatoma

What are the common causes of classic FUO?

Collagen vascular disease

- Systemic lupus erythematosus (SLE)
- Adult Still's disease
- Giant cell arteritis
- Rheumatic fever

What are the common causes of classic FUO?

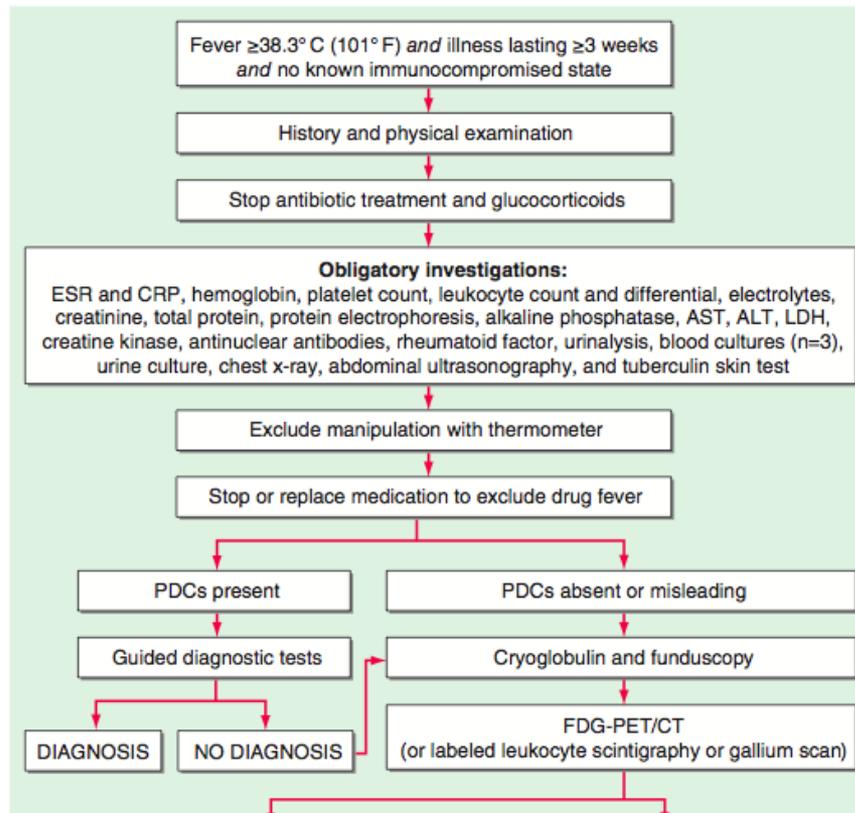
Miscellaneous diseases

- Drug fever
- Gout
- Sub-acute thyroiditis

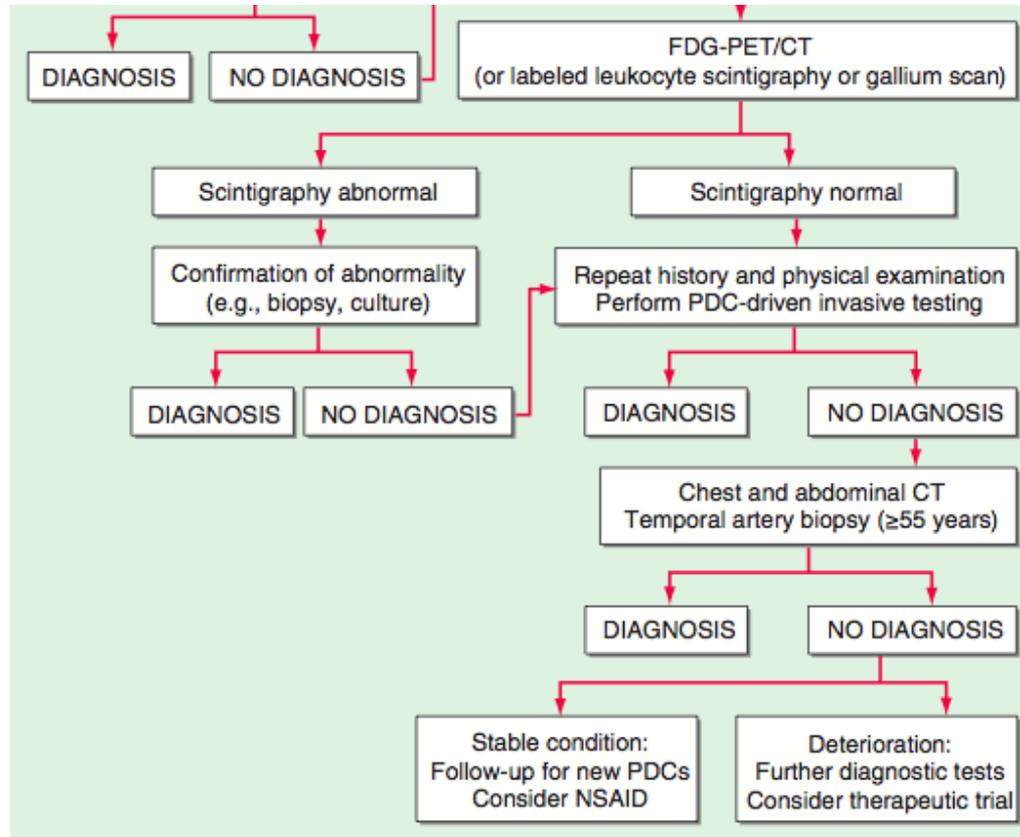
Granulomatous diseases

- Crohn's disease
- Sarcoidosis
- Granulomatous hepatitis

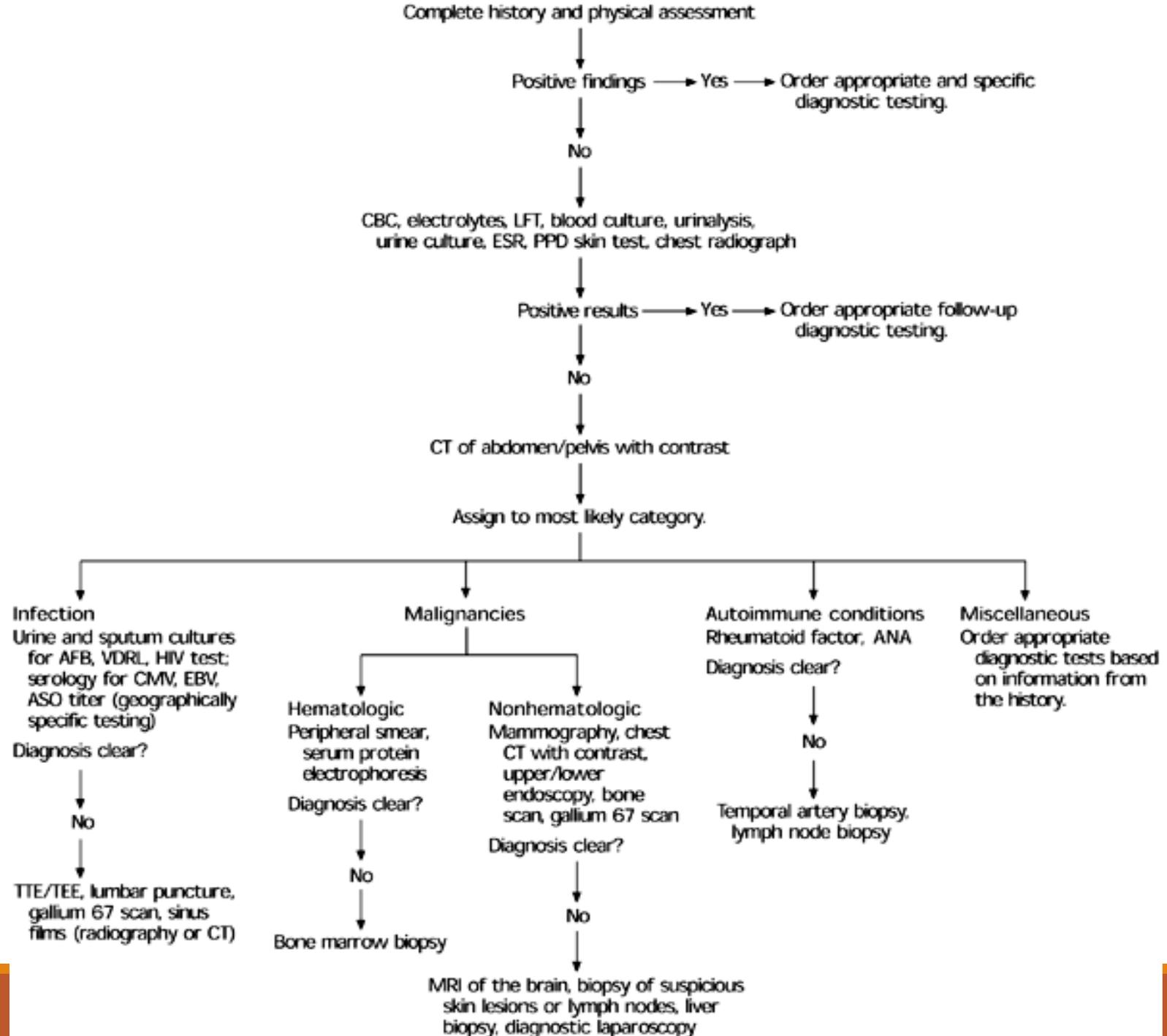
Approach to the patient with classic FUO (Harrison's 19th, C26,p139)



Approach to the patient with classic FUO (Harrison's 19th, C26,p139)



Roth and
Basello
2003.
American
Academy of
Family
Physicians.



The Clinical History

Careful review of symptoms

History of travel, adventure travel; diseases endemic in the places visited

Immunosuppression

Drug intake

Exposures

The Physical Exam

Routine P.E.

Rash, other skin lesions

Oral cavity, throat

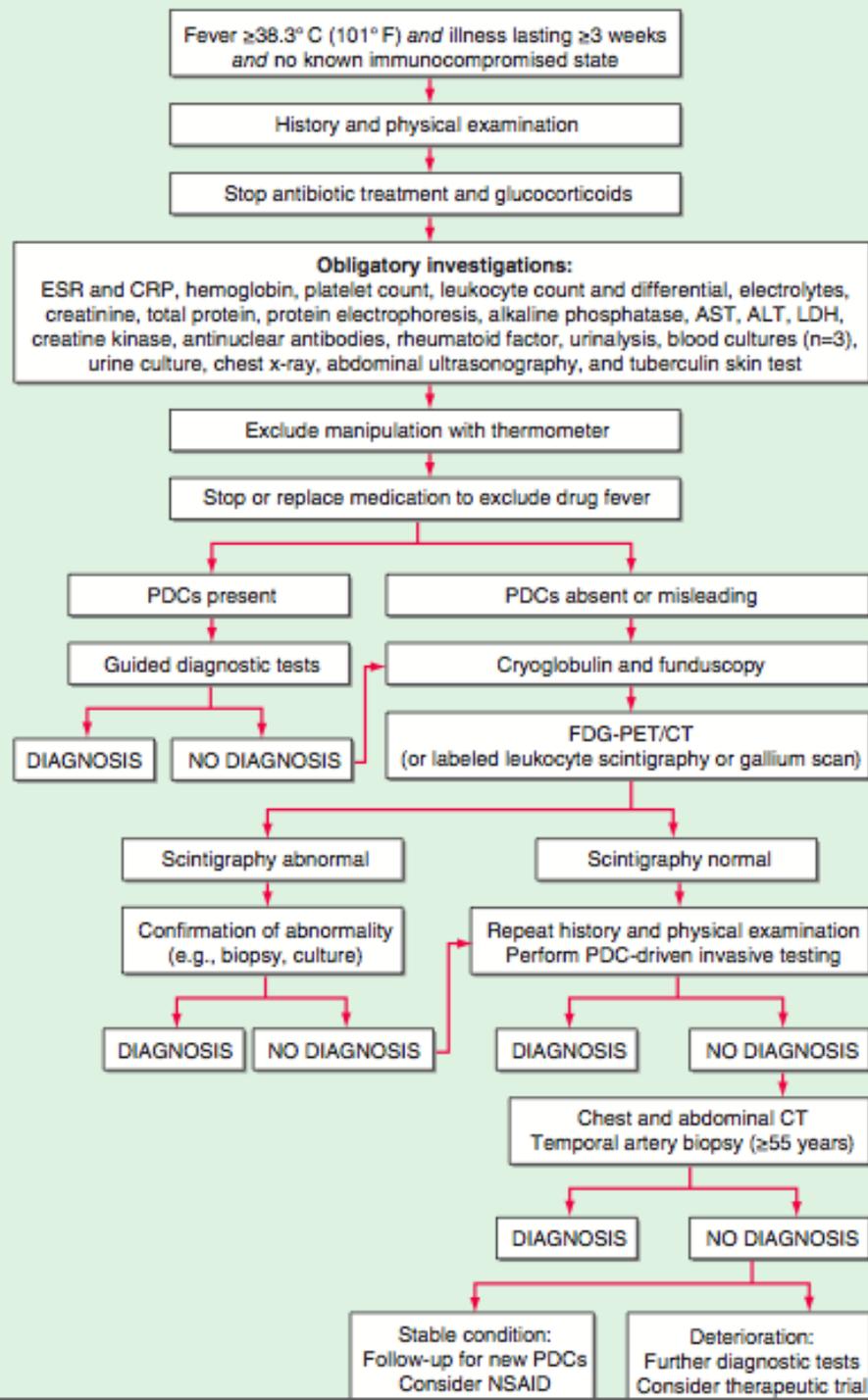
Lymph nodes: cervical, supraclavicular, axillary, femoral

Joint pain and swelling

Genitalia, perineum

Approach to the patient with classic FUO

Harrison's 19th ed., Figure 26



How can the recommended tests in the algorithm help us?

CBC and differential count

Creatinine

Anti-nuclear antibody

Procalcitonin

PPD

Biopsy

How can the recommended tests in the algorithm help us?

We need to send specimens for culture when investigating classic FUO.

- Blood
- Urine
- Sputum
- Tissue
- Other fluids as appropriate

How can the recommended tests in the algorithm help us?

Computed tomography (CT) scan

Magnetic resonance imaging (MRI)

Gallium scan, Indium scan, PET scan

Biopsy of liver and bone marrow should be considered if other tests are unrevealing.

Procalcitonin

Peptide precursor or procalcitonin, synthesized by parafollicular C cells of the thyroid

Acute-phase reactant

- Mildly elevated (0.15-2 ng/ml) in localized mild-to-moderate bacterial infection, non-infectious SIRS, untreated end-stage renal failure
- Markedly elevated (>2 ng/ml) in bacterial sepsis, severe localized bacterial infection, severe non-infectious inflammation, some carcinomas
- Levels fall with successful treatment of severe bacterial infection and severe non-infectious inflammation

Not useful in the assessment of fungal and viral infections



Source: South Med J © 2002 Southern Medical Association

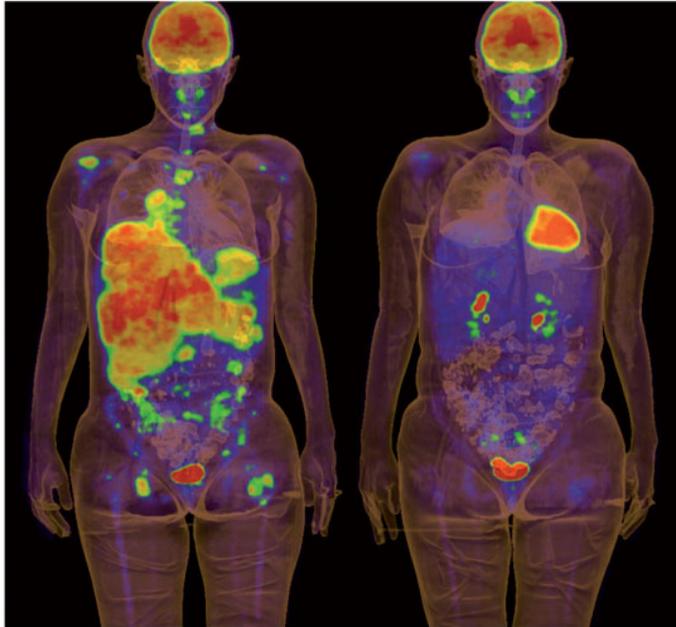
Intra-abdominal abscess

Positron emission tomography (PET) scan

a Patient 1

Pre-treatment

2 weeks vemurafenib



b Patient 2

Pre-treatment

2 weeks vemurafenib



Nature Reviews | **Drug Discovery**

From www.nature.com

Some Causes of Fever in the Returned Traveler (from Mandell's Principles and Practice of Infectious Diseases)

Malaria

Hepatitis

Enteric fever

Tuberculosis

Dysentery

Dengue fever

Do you agree?

Remember:

As the duration of fever increases, the likelihood of an infectious cause of FUO decreases.



Durack and Street – Nosocomial FUO

Temperature of $\geq 38.3^{\circ}\text{C}$ ($>101^{\circ}\text{F}$) develops on several occasions in a hospitalized patient who is receiving acute care and in whom infection was not manifest or incubating on admission

3 days of investigation, including at least 2 days' incubation of cultures

Healthcare-associated FUO: How do we approach it?

Begin at the original surgical or procedural field.

(“Go where the surgeon has been.”)

Infection is still the most common cause.

- IV lines
- Septic phlebitis
- Prostheses, devices
- Catheters
- *C. difficile* colitis



www.svcontinuum.blogspot.com









Non-infectious causes of healthcare-associated FUO

Deep vein thrombosis

Pulmonary embolism

Drug/alcohol withdrawal

Pancreatitis

Gout

Durack and Street – Neutropenic FUO

Neutropenic FUO

- Temperature of $\geq 38.3^{\circ}\text{C}$ ($>101^{\circ}\text{F}$) on several occasions in a patient whose neutrophil count is $<500/\mu\text{L}$ or is expected to fall to that level in 1 to 2 days
- 3 days of investigation, including at least 2 days' incubation of cultures

Who are at high risk for neutropenia?

Individuals who have recently received chemotherapy for cancer

Individuals receiving medications (aside from chemotherapy) that can result in neutropenia

Individuals with hematologic conditions e.g., aplastic anemia

Durack and Street – HIV-associated FUO

- Temperature of $\geq 38.3^{\circ}\text{C}$ ($>101^{\circ}\text{F}$) on several occasions over a period of >4 weeks for outpatients or >3 days for hospitalized patients with HIV infection
- 3 days of investigation, including 2 days' incubation of cultures

What is the approach to the empiric treatment of FUO?

The emphasis in the approach to FUO is on observation and examination.

Empiric antibiotics are started in patients with unstable vital signs or neutropenia.

NSAIDs and glucocorticoids must be used with caution because they can mask fever while permitting the spread of infection.

What is the approach to the empiric treatment of FUO?

When no underlying source of FUO is identified after prolonged observation (6 months), prognosis is generally good.

Up to 15% of FUOs will defy diagnosis.

Try this case:

I.C., 67/M, consults for fever for the past 3 weeks associated with substernal chest pain. I.C. has been on DM treatment for the past 3 years.

The patient has undergone the following tests:

CBC: Hb 12.5 g/dl, WBC 12.5 (segmenters 80), platelet = 405

Chest CT scan: infiltrates on the middle lobe of the right lung, minimal pericardial effusion

Abdominal CT scan: normal

The patient was treated for pneumonia with piperacillin-tazobactam. Anti-TB and steroids were also started for a presumptive diagnosis of pericardial TB. The fever lysed but recurred after 8 days.

Try this case:

M.T., 19/F consults for fever for the past 7 days accompanied by headache. She also has a 3-day history of watery stools. She lives in Manila but travels to Bataan every weekend to visit her family.

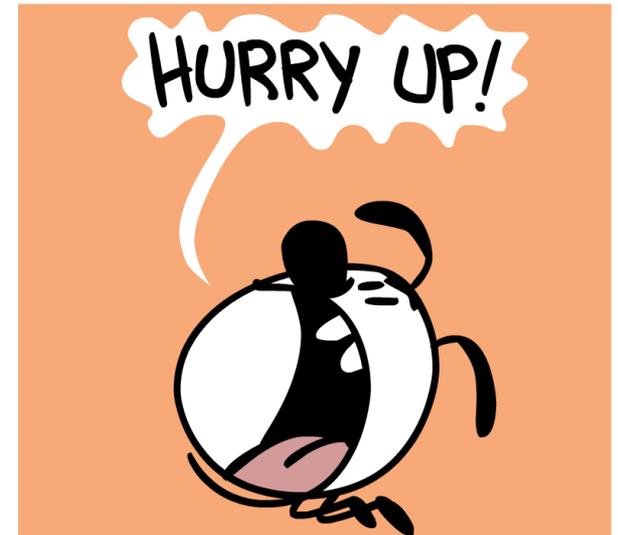
- Hgb: 11.2 g/dl Peripheral WBC: 6,000, neutrophils 65%, platelets 243
- Urinalysis: normal
- Chest x-ray: normal

M.T. is able to perform her usual activities despite the symptoms.

When dealing with FOU,

Patience, compassion, equanimity and intellectual flexibility are indispensable.

Patience



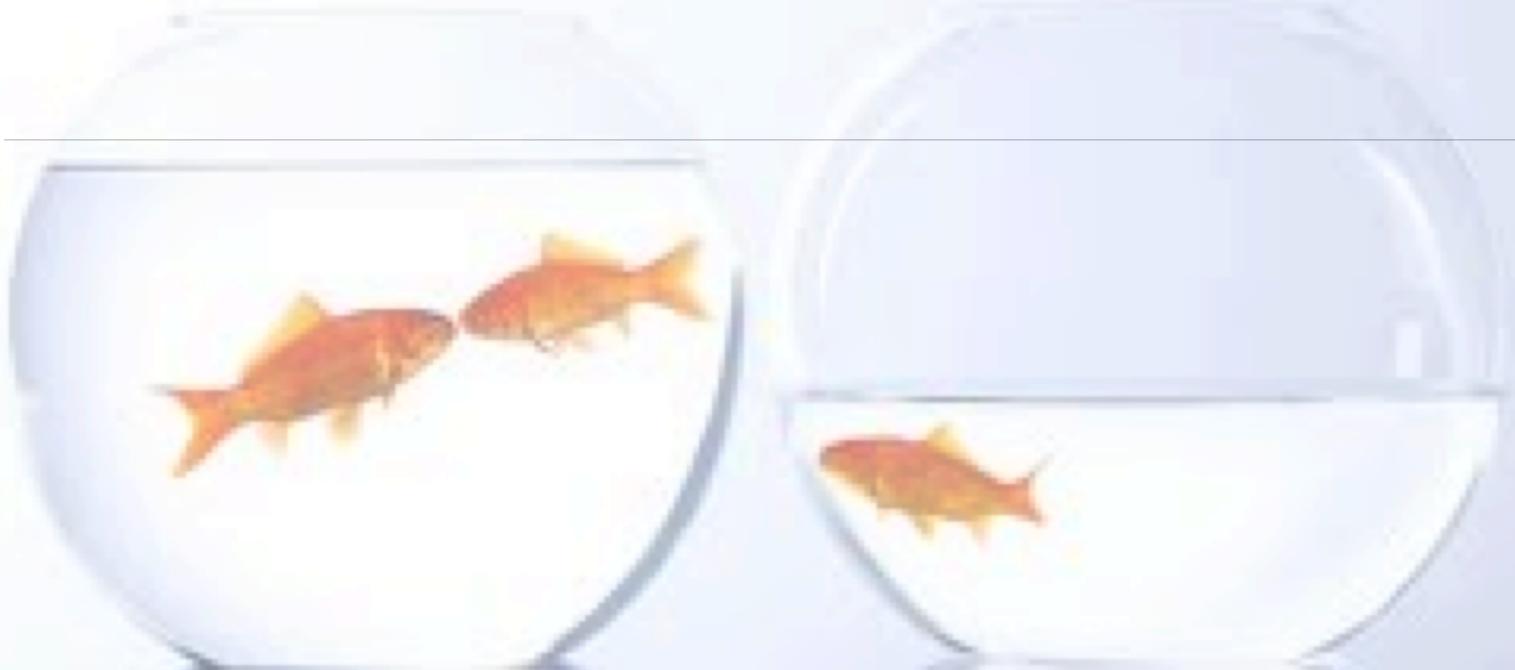


How Isaac Newton Discovered Gravity



“Invention and discovery emanate from being able to try seemingly wild possibilities and work in the unknown; **to be comfortable being wrong before being right...**”

- Peter Sims



“If envy were a fever, all the world would be ill.”

- Danish proverb