Fever of unknown origin

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Definition

- AD 1961, Petersdorf, et al
  - Undiagnosed intermittent fever 3 wks, IPD work up 1 wk
- AD 1991, D. T Durack and A.C. street

Classical FUO
- Fever ≥38.3 °C on several occasions
- Duration ≥3 weeks
- Diagnosis uncertain after 3 days despite appropriate in-hospital investigation or three out-patient visits

Nosocomial FUO
- Hospitalized patients
- Fever ≥38.3 °C on several occasions
- Infection not present or incubating on admission
- Diagnosis uncertain after 3 days despite appropriate investigations (including at least 48-h incubation of microbiological cultures)

Neutropenic FUO
- Less than 500 neutrophils mm^{-3}
- Fever ≥38.3 °C on several occasions
- Diagnosis uncertain after 3 days despite appropriate investigations (including at least 48-h incubation of microbiological cultures)

HIV-associated FUO
- Confirmed HIV infection
- Fever ≥38.3 °C on several occasions
- Duration of ≥4 weeks (outpatients), or ≥3 days in hospitalized patients
- Diagnosis uncertain after 3 days despite appropriate investigations (including at least 48-h incubation of microbiological cultures)

Knockaert D.C, et al. Journal of internal medicine 2003; 253: 263-275

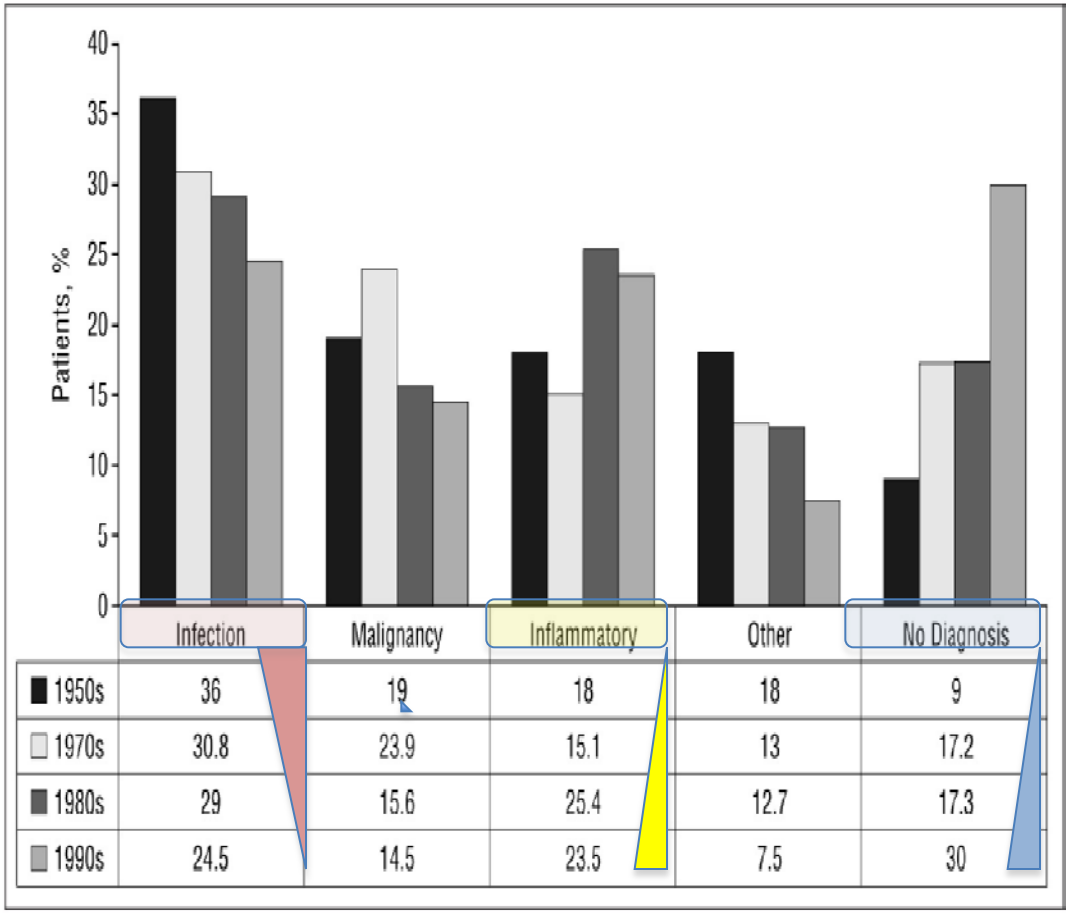
Definition

- Why to change
  - Difference on spectrum of underlying diseases
  - Alteration of immune system
  - Duration of investigations
    (depend on the type of investigations)

Knockaert D.C, et al. Journal of internal medicine 2003; 253: 263-275

Epidemiology

The percentage of patients with fever of unknown origin by causes over the past 40 year



	Infection	Malignancy	Inflammatory	Other	No Diagnosis
1950s	36	19	18	18	9
1970s	30.8	23.9	15.1	13	17.2
1980s	29	15.6	25.4	12.7	17.3
1990s	24.5	14.5	23.5	7.5	30

- Systematic review
- Jan 1966 – Dec 2000
- Petersdorf and Beeson criteria
- Exclude immunocompromised and younger than 18 yr
- N-US, W-EU, Scandinavia
- Most common cause
  - ID; Tuberculosis, intraabdominal abscess
  - CA; Hodgkin disease and non Hodgkin lymphoma
  - Temporal arteritis 16-17%

Mourad O, et al. ARCH INTERN MED. 2003 Mar vol 163:545-551

Epidemiology

- Case review 1990-Mar 2002
- New diagnostic tools; U/S, CT abdomen (1980s)
- AD 1961-1990 infection 34%, neoplasm 22.1%, NIID 12.5%, other 15%, undiagnosed 15% from 692 patient by Knockaert DC, 1992

Distribution of diagnostic categories in series with fever of unknown origin

			Causes (%)				
Publication year	Number	Author	Infections	Tumour	NIID	Miscellaneous	Undiagnosed
1992	85	Barbado	13	29	30	9	17
1992	86	Kazanjian	33	24	17	17	9
1992	199	Knockaert	23	7	23	22	26
1994	153	Iikuni	29	16	30	14	12
1994	80	Shoji	53	8	15	5	17
1997	167	De Kleyn	26	13	24	8	30

*Slightly rearranged based on the proposed classification system [22, 31–35]. NIID, noninfectious inflammatory diseases.

Knockaert D.C, et al. Journal of internal medicine 2003; 253: 263-275

Etiology

Common etiology in patients with fever of unknown etiology

Infections	Neoplastic disorders	Rheumatic inflammatory disorders	Miscellaneous disorders
Miliary TB	Lymphomas (HD-NHL) hypernephromas	Adult onset Still's disease	Drug fever
Subacute bacterial endocarditis	Hepatomas/liver metastases Myeloproliferative disorders (CML-CLL)	Polymyalgia rheumatica/temporal arteritis	Alcoholic cirrhosis
Intra-abdominal abscesses	Preleukemias (AML)	Rheumatoid arthritis Systemic lupus erythematosus Periarteritis nodosa/microscopic polyangiitis	Crohn's disease
Pelvic abscesses	Colon cancer		Subacute thyroiditis Factitious fever
Renal-perinephric abscesses			

Abdurrahman K, et al, Ecpert Rev Anti Infect Ther. 2013;11(8):805-815

Future change of epidemiology

- Decline of infectious cause
  - Widespread available of antibiotic
  - Reduction of poverty-related infection
- Antimicrobial resistance
  - Empirical treatment related
  - eg MDR-TB, GNB, STI
- Technology innovation for diagnose
  - Make shift to non-ID
  - Drug induced fever, adult-onset Still's disease, periodic fever syndrome
- Health systems; Specialty care or generalist

Brown M. Postgrad Med J 2015;91:665-669

Approach to Classic FUO

1. Meets the definition of FUO
2. Categorized group by history and PE hallmarks
   - CA; significant weight loss, early anorexia
   - NIID; + synovitis, x rigors
3. Organized organs involvement
   - SLE; x liver
   - IE; x hepatomegaly, + splenomegaly

Cunha, et al, The american Journal of medicine(2015) 128, 1138

History

- Significant clues from hitory and PE give 62% diagnosed. However, they could be found in 97% of patients[1]

Historical		Medical history	
Exposures		Abdominal disorders	Alcoholic hepatitis, cirrhosis, Crohn disease
Fresh water exposure	Leptospirosis		
Living conditions (e.g., homeless shelter)	Tuberculosis	History of transfusions	Hepatitis B or C, HIV
		Malignancy	Metastatic disease
Occupational exposures/sick contacts (e.g., with hospitalized patients, children)	Cytomegalovirus, Epstein-Barr virus, tuberculosis	Psychiatric illness	Factitious fever
		Recent hospitalization	Nosocomial infection
Pets, wild animals	Brucellosis	Risk-taking behaviors	
Recent travel, especially to areas with endemic diseases (domestic and abroad)	Region specific (e.g., Q fever for parts of Europe)	Intravenous drug abuse	Abscess, endocarditis, osteomyelitis
		Sexually transmitted infection exposure	HIV
Family history		Surgical history	
Hereditary febrile conditions	Familial Mediterranean fever	Presence of prostheses	Osteomyelitis

1. Elizabeth C, et al, American Family Physician, 2014, Vol 90;91-96

History

- **Infectious cause**

  - Dentition: apical abscess, subacute IE

- **Neoplasm**

  - Significant weight loss, post-hot bath pruritus, adenopathy

- **NIID**

  - Prominent arthralgias/myalgias ,
  - Oral ulcer(Bechet's diseases, SLE),
  - Joint symptoms+ generalized lymphadenopathy (Still's disease),
  - Acalculous cholecystitis (SLE, PA)
  - x chill

- **Miscellaneous**

  - Periodicity fever (cyclic neutropenia)
  - Neck/jaw pain (subacute thyroiditis)
  - Medications (Drug fever)

Cunha, et al, The american Journal of medicine(2015) 128, 1138

Drugs fever

Medications that can cause fever of unknown origin

Anticonvulsants
Barbiturates*
Carbamazepine (Tegretol)
Phenytoin (Dilantin)

Antihistamines
Cimetidine (Tagamet)
Ranitidine (Zantac)

Antimicrobials
Carbapenems*
Cephalosporins*
Erythromycin
Isoniazid
Minocycline (Minocin)
Nitrofurantoin (Furadantin)
Penicillins*
Rifampin
Sulfonamides*

Cardiovascular drugs
Captopril (Capoten)
Hydralazine
Hydrochlorothiazide
Methyldopa
Nifedipine (Procardia)
Procainamide
Quinidine

Nonsteroidal anti-inflammatory drugs
Ibuprofen
Salicylates
Sulindac (Clinoril)

Others
Allopurinol (Zyloprim)
Heparin
Meperidine (Demerol)
Phenothiazines

* The literature does not identify individual drugs in these classes

1. Elizabeth C, et al, American Family Physician, 2014, Vol 90;91-96

Physical examinations

- **More attention on eyes, skin, nodes, liver, and spleen**
- **Infectious cause**

  - Fever pattern analysis

  - Relative bradycardia; enteric fever, leptospirosis

  - Fundoscopic exam: Toxoplasmosis, tuberculosis

  - Isolated splenomegaly: miliary TB, EBV, CMV, enteric fever, histoplasmosis, malaria, subacute IE

  - Epididymo-orchitis: EBV, renal tuberculosis

- **Neoplasms**

  - Eyes; Roth spots (lymphoma, atrial myxoma) Retinal hemorrhages (preleukemia)

  - Isolated hepatomegaly: hepatoma, liver metastasis

- **NIID**

  - Morning temperature spikes: PA

  - Double quatidian fever: Still’s disease

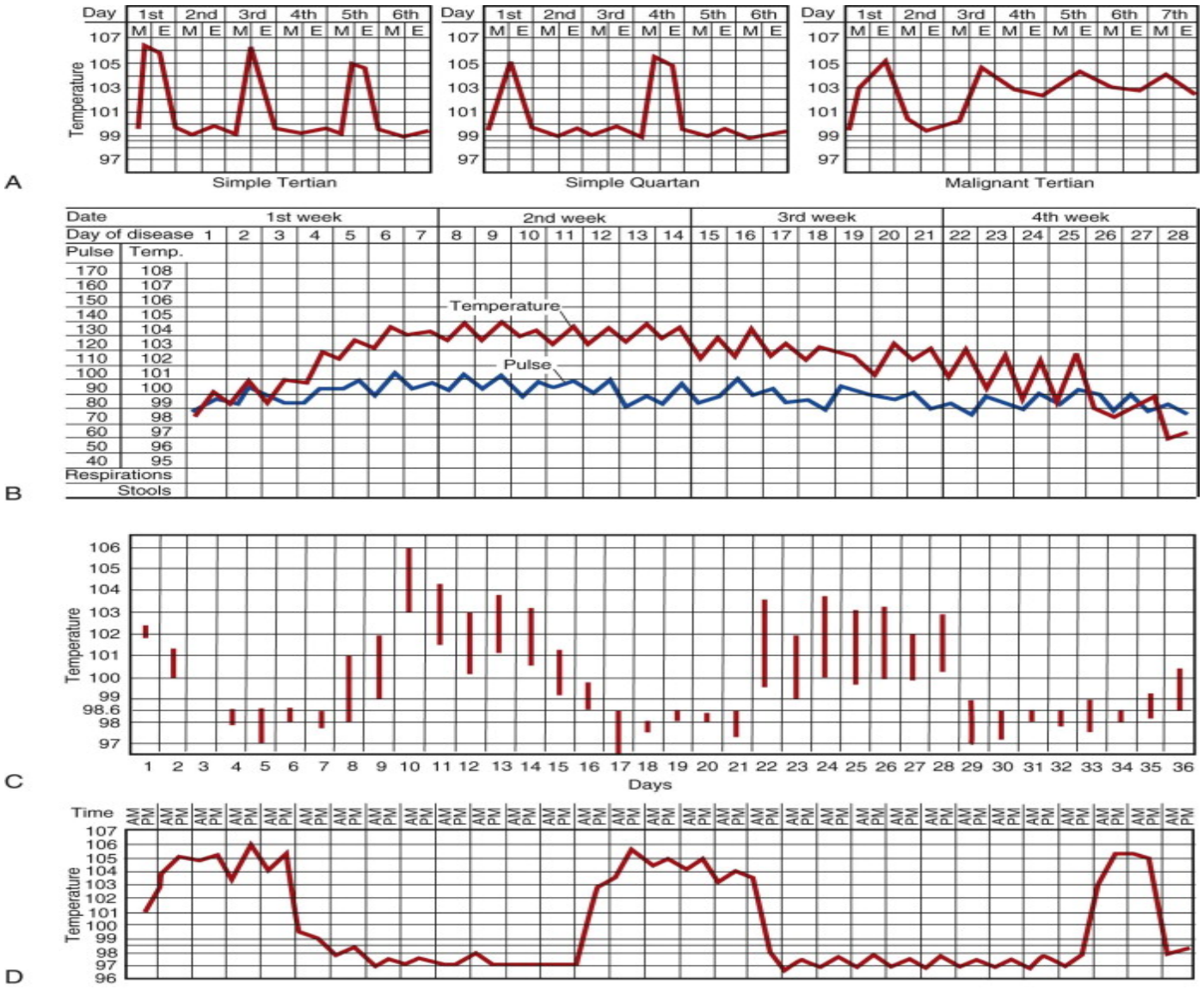
  - Unequal pulsatile: Takayasu’s arteritis

  - Lacrimal gland enlargement: late RA, sarcoidosis, SLE

  - SLE+ murmur+ neg H/C: Libman-Sacks endocarditis

Cunha, et al, The american Journal of medicine(2015) 128, 1138

Fever pattern



malaria

Typhoid fever

Hodkin's disease
(Pel-Ebstein pattern)

Relapsing fever
(Borreliosis)

William F W, Philip AM, Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 56, 721-731.e1

Investigations

- No specific guideline developed, but classified to non-specific, and specific tests
- Investigations driven by clinical clues, local epidemiologic data, and tests availabilities
- Petersdorf required several investions;[1]
  - Bacteriological and serological tests
  - Skin tests
  - Radiographs of chest and IVP
- Ultrasound and CT scan are significant role since 1980s[2]

1.Petersdorf RB, et al, Medicine 1961; 40: 1-30 2. .Knockaert D.C, et al. Journal of internal medicine 2003; 253: 263-275

Initial investigations 2003

Minimum diagnostic evaluation required for a case to qualify as classical fever of unknown origin

- Comprehensive history (including travel history, risk for venereal diseases, hobbies, contact with pet animals and birds, etc.)
- Comprehensive physical examination (including temporal arteries, rectal digital examination, etc.)
- Routine blood tests (complete blood count including differential, ESR or CRP, electrolytes, renal and hepatic tests, creatine phosphokinase and lactate dehydrogenase)
- Microscopic urinalysis
- Cultures of blood, urine (and other normally sterile compartments if clinically indicated, e.g. joints, pleura, cerebrospinal fluid)
- Chest radiograph
- Abdominal (including pelvic) ultrasonography
- Antinuclear and antineutrophilic cytoplasmic antibodies, rheumatoid factor
- Tuberculin skin test
- Serological tests directed by local epidemiological data
- Further evaluation directed by abnormalities detected by above test; e.g.
  - HIV antibodies depending on detailed history
  - CMV-IgM and EBV serology in case of abnormal differential WBC count
  - Abdominal or chest helical CT scan
  - Echocardiography in case of cardiac murmur
  - etc.

Knockaert D.C, et al. Journal of internal medicine 2003; 253: 263-275

Initial investigations 2014

Minimum diagnostic evaluation to qualify as fever of unknown origin[1]

1. Comprehensive history [including accompanying symptoms, travel history, sexual risk behaviour, profession, hobbies, contact with animals (pets, birds, insects) and ill persons, family history, use of medications and illicit drugs, past medical and surgical history, presence of foreign material]
2. Meticulous physical examination (eyes, mucosal surfaces, temporal arteries, skin, hands and nails, lymph nodes, thyroid, heart, lungs, abdomen, rectal examination, musculoskeletal system, neurological examination, vascular examination)
3. Erythrocyte sedimentation rate, C-reactive protein, protein electrophoresis
4. Complete blood count, including differential and platelet count;
5. Routine blood chemistry, including creatinine, sodium, potassium, enzymes (lactate dehydrogenase, bilirubin, liver enzymes, and creatine kinase)
6. Antinuclear and antineutrophil cytoplasmic antibodies, angiotensin-converting enzyme
7. Urinalysis, including microscopic examination
8. Routine blood and urine cultures while not receiving antibiotics, cultures of other otherwise sterile fluids (e.g. from joints, pleura, or cerebrospinal space) whenever appropriate
9. Tuberculin skin test or interferon-gamma release assay
10. Chest X-ray
11. Abdominal ultrasonography (including pelvis)
12. Further evaluation of any abnormalities detected by above tests (e.g. HIV testing in case of suspicious exposure, echocardiography in the case of cardiac murmur, blood smear for malaria in the traveller, cytomegalovirus serology in case of reactive lymphocytosis)

Using of interferon-γ release assay (IGRA) has limited sensitivity and specificity for diagnose TB[2]
Tuberculin skin test perhaps used for diagnose sarcoid[2]

1.Vanderschueren S, et al Acta Clinica Belgica 2014; Vol69,no 6;pages 412-417 2. Brown M. Postgrad Med J 2015; 91:665-669

Secondary evaluations

- Non invasive methods provided the most diagnoses, while invasive procedure gave the highest diagnostic yield[1]
- Blind pursuit of diagnostic approach, eg. bone marrow, liver biopsy, or lumbar puncture, rarely rewards for making diagnosis[2]
- ALP, SPEP, Serum ferritin are the common neglect tests[3]
- Ferritin level is specific to Still's diseases, or Hemophagocytic syndrome, but confused by infection[4]
- Temporal biopsy on unexpained fever and inflammation in elderly pt (age ≥55)[1]is the probably exception[2]
- Serology tests are also helpful when clues exit[2]
- Thyroid function test, cryoglobulins, complement studies, SPEP might be optional[2]
- Imaging study; CT, PET, PET-CT[1,2]

1. Elizabeth C, et al, American Family Physician, 2014, Vol 90;91-96
2. Vanderschueren S, et alActa Clinica Belgica 2014, Vol 69; no 6; pages 412-417
3. Cunha BA, et al. Infect Dis Clin North Am, 2007; 21(4):867-915
4. Brown M. Postgrad Med J 2015; 91:665-669

Secondary investigations

- Imaging studies

- CT chest-abdomen-pelvic sensitivity 82-92% and specificity 60-70%[1]

- Echocardiogram requested in suspicious cases[1,3]

- MRI give benefit on vasculitis on aortic arch and great vessel of neck[1]

- F-FDG-PET could find 40% diagnostic yield, and up to 54% with combined with CT[2]

1. Elizabeth C, et al, American Family Physician, 2014, Vol 90;91-96
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Secondary investigations

- Invasive tests

  - LN biopsy is the most, 10-35% provided positive results[2], avoid in anterior cervical, axillary, or inguinal area due to minute chance[1]

  - BM biopsy revealed 25% causes of fever, but culture and aspiration showed only 0-2% results[2]

  - Liver biopsy found out 14-17% final outcome[2]

- Molecular techniques in immunocompetent pt has high false positive result in whom the yield is low[3]

1. Cunha, et al, The american Journal of medicine(2015) 128, 1138 2. .Elizabeth C, et al, American Family Physician, 2014, Vol 90;91-96
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Treatments

- Antipyretic and antimicrobial therapy should be abstinence[1] and reduced the diagnostic rate[2]
- Empirical therapy is considered in[3]
  - Antituberculous drug for suspected military tuberculosis in elderly
  - Culture negative endocarditis
  - Naproxen for probable malignancy fever
  - Steroid for giant cell arteritis
- “ Doxycycline deficiency disease ”[4]
  - Few patient might be ricketsial, coxiella, and leptospirosis
- Drug resistance bugs should be taken to account in some situations[4]

1.Knockaert D.C, et al. J Intern Med 2003; 253: 263-275
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Prognosis

FUO related deaths: comparison with historical series

Series first author (reference)	Study period	Country	Length of follow-up	Number of cases	FUO-related mortality rate	Percentage of malignant cases in total group	Percentage of malignant cases in non-survivors	Malignancy-associated mortality rate
Petersdorf[5]	1952–1957	United States	Not stated	100	32%	19%	59%	89%
Deal[6]	1960s	United States	Not stated	34	21%	21%	86%	86%
Larson[7]	1970–1980	United States	⩾12 months	105	33%	31%	83%	88%
Barbado[8]	1968–1981	Spain	Not stated	133	23%	18%	43%	54%
Kazanjian[9]	1984–1990	United States	Average: 22 months	86	16%	24%	79%	52%
Knockaert[10,11]	1980–1990	Belgium	5 years in group without diagnosis	199	6.5%	7.0%	Not stated	Not stated
De Kleijn[12]	1992–1994	The Netherlands	>2 years in group without diagnosis	167	11.3	13%	Not stated	Not stated
Vanderschueren[1]	1990–1999	Belgium	Median: 810 days	223	12%	11%	62%	67%
Goto[13]*	1994–2002	Japan	In-hospital	226	8.4%	7.1%	84%	Not stated
Bleeker-Rovers[14]	2003–2005	The Netherlands	Median: 12 months	73	6.8%	7.0%	40%	40%
Present series (–)	2000–2010	Belgium	⩾6 months	436	6.9%	11%	60%	38%

Note: *Not all patients suffered from FUO; body temperature ⩾37.0°C in a hospitalized patient sufficed for inclusion.

Non-Hodkin lymphoma had high disproportionally mortality rate
Factors related mortality; age, continuous fever, anemia, leucopenia, LDH level, hepatomegaly

Vanderschueren S, et al, Acta Clinica Belgica 2014, Vol69; no 1 pages12-16

Current research questions

- Role of PET in the diagnostic algorithm of FUO
- Impact of using IL-1 receptor antagonists, rituximab, sterioid in high ferritin states
- Cost-effective approach to diagnosis in different environment, eg IPD vs OPD, ID vs other, bedside vs remote
- Future cytokine assays determined in FUO

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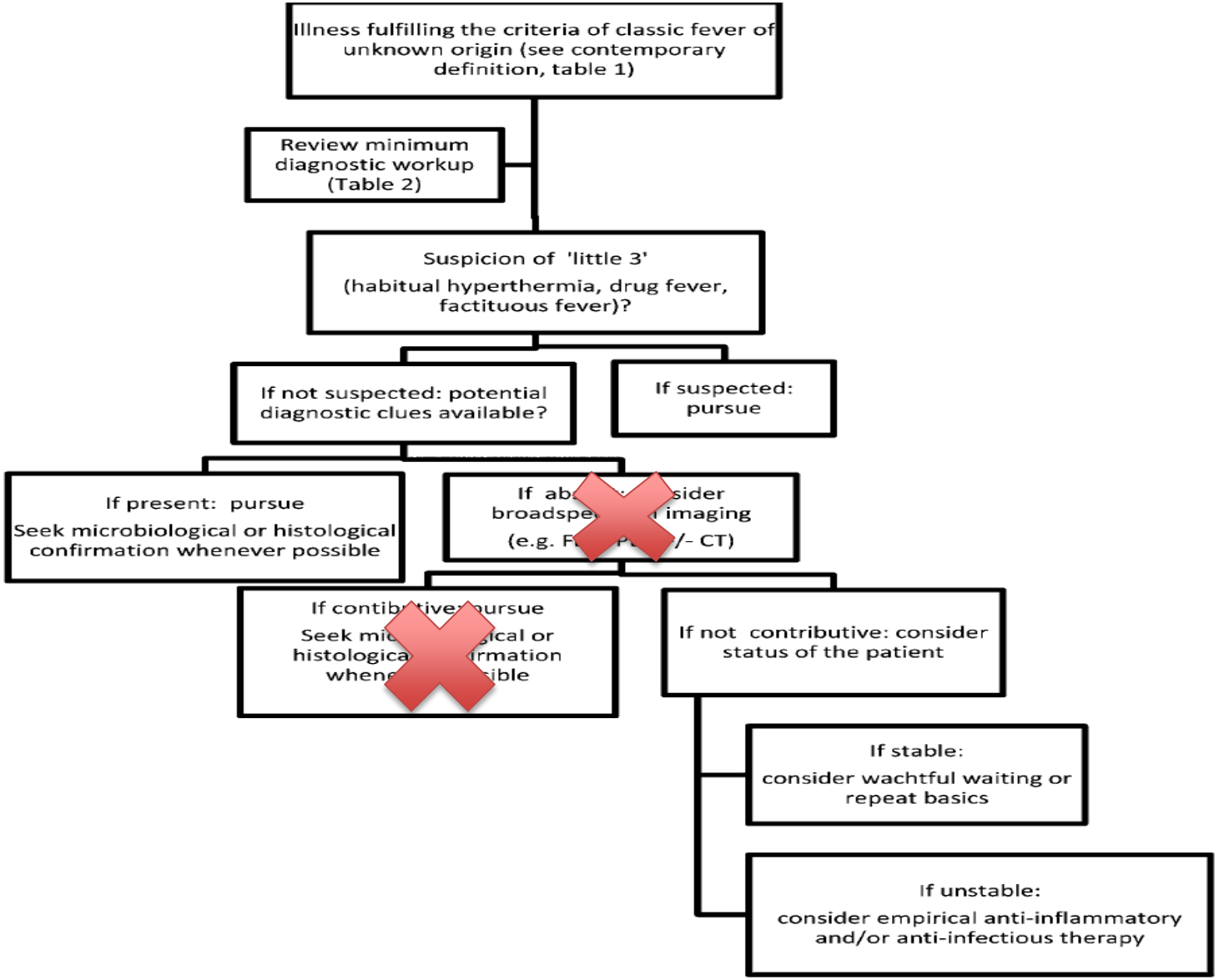
Algorithm



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Thank you