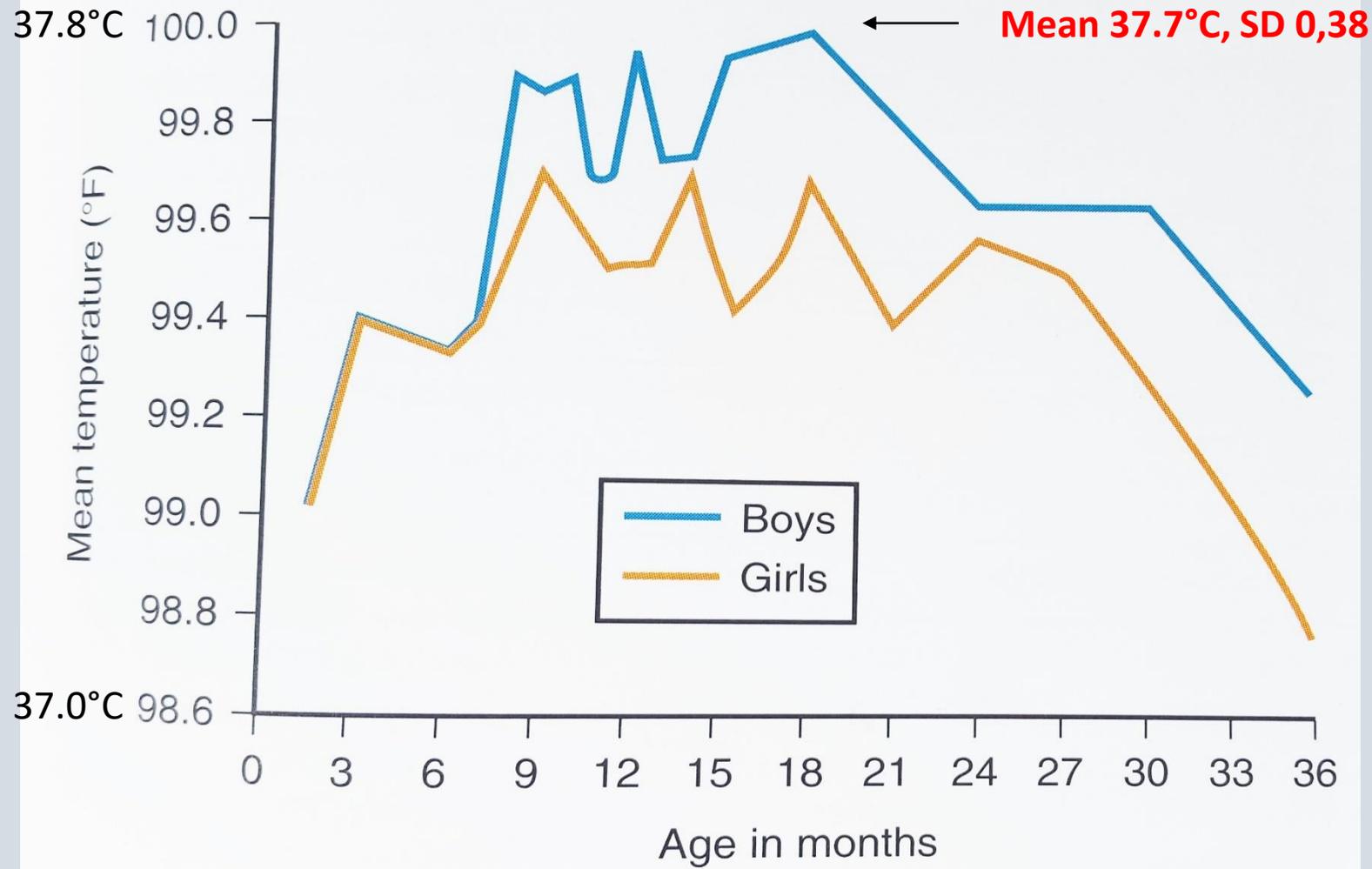


# Prolonged and recurrent fevers in children

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Marie-Louise von Linstow, MD, PhD  
Dept. of Paediatrics and Adolescent Medicine  
Rigshospitalet  
Copenhagen

# Normal mean rectal temperature



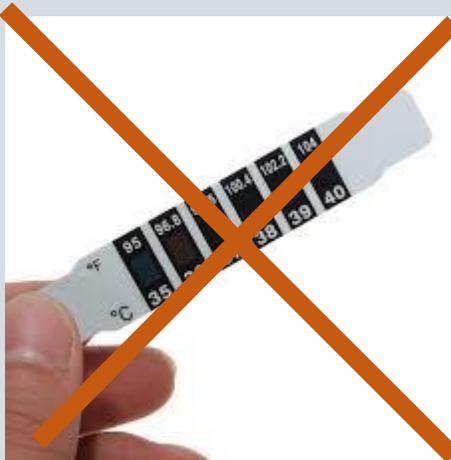
# Measuring temperature

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# Measuring temperature

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# Brighton collaboration definition of fever

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Fever is defined as an endogenous elevation of **at least one measured body temperature of  $\geq 38^{\circ}\text{C}$**

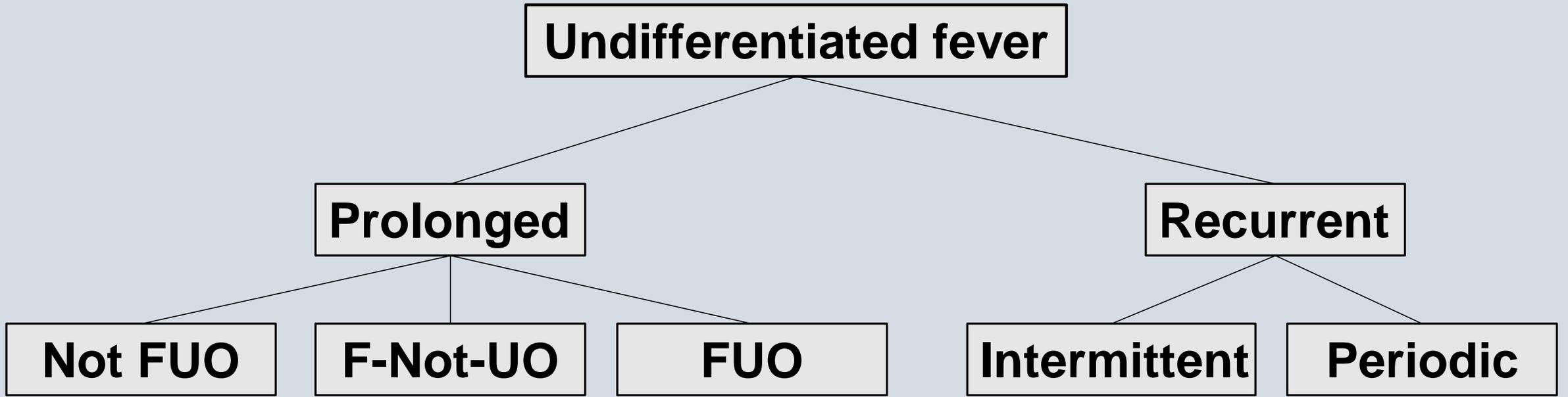
... irrespective of device, anatomic site, age, or environmental conditions



# Undifferentiated fever

---

- Fever is the main complaint
  - Not associated with a defined clinical illness
  - Not "fever without a source"
  - Previously healthy
-



# Undifferentiated fever

Prolonged

Recurrent

Not FUO

F-Not-UO

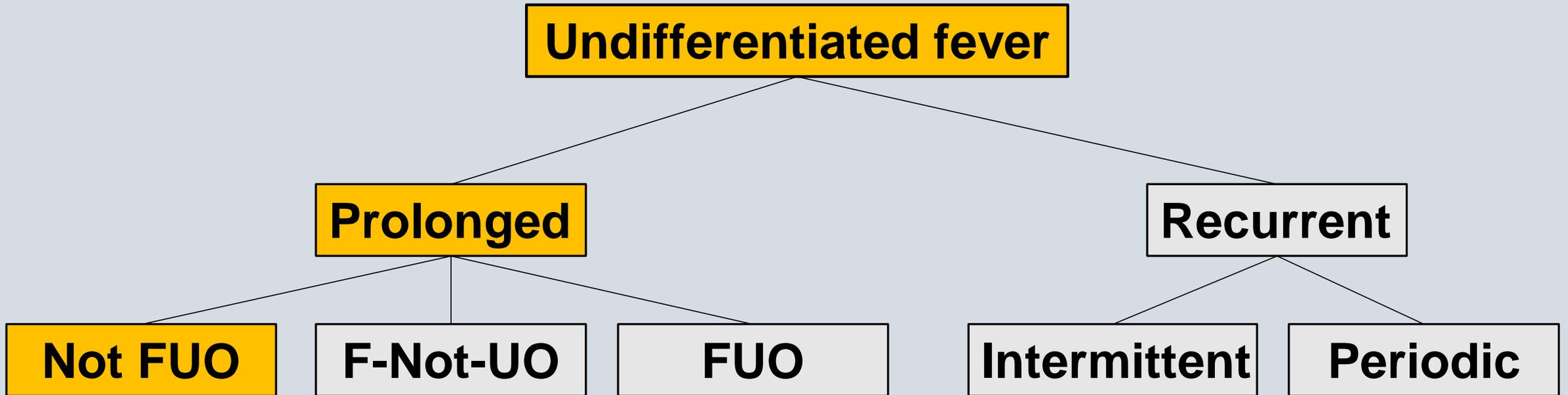
FUO

Intermittent

Periodic



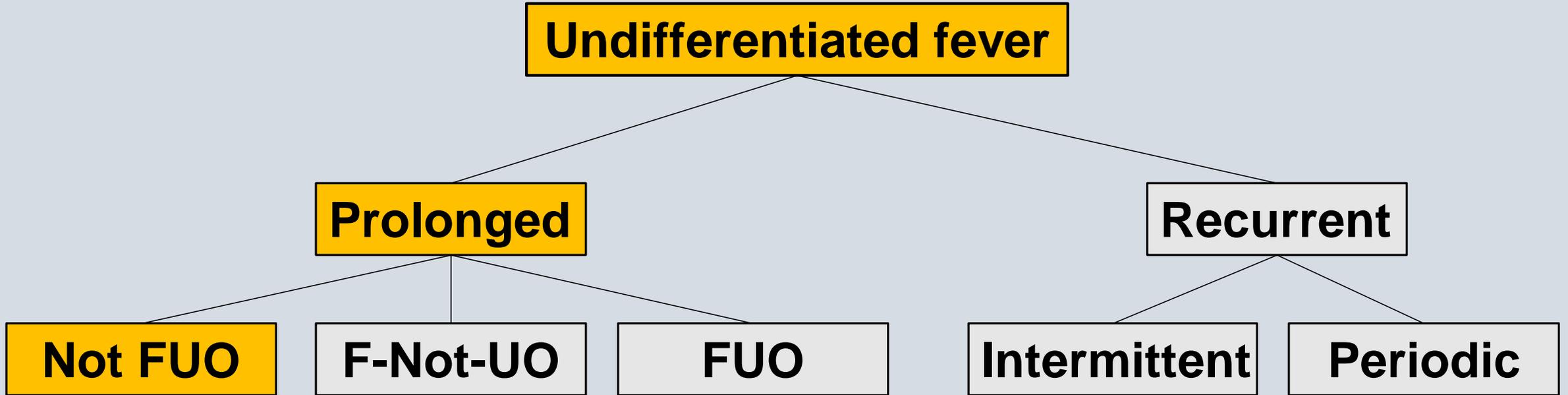
Patient is NOT having abnormal temperatures



### Causes

- Temperatures usually runs low
- Diurnal temperature variation
- Meals

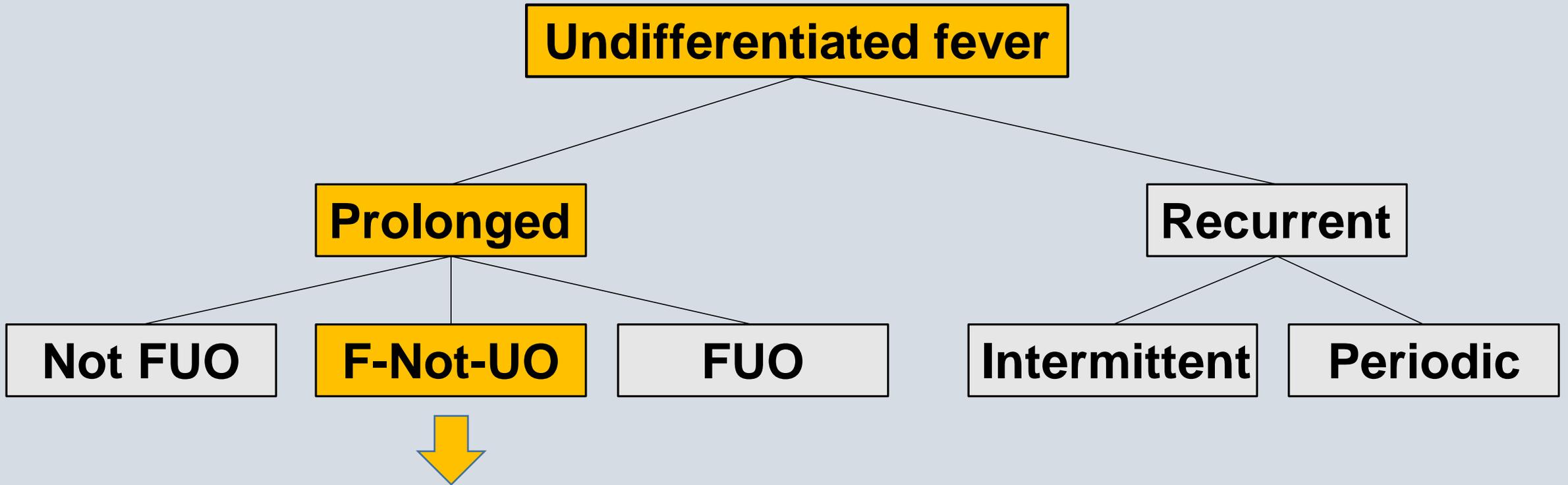
- Ovulation
- Tobacco and chewing gum
- Exercise
- Environmental conditions



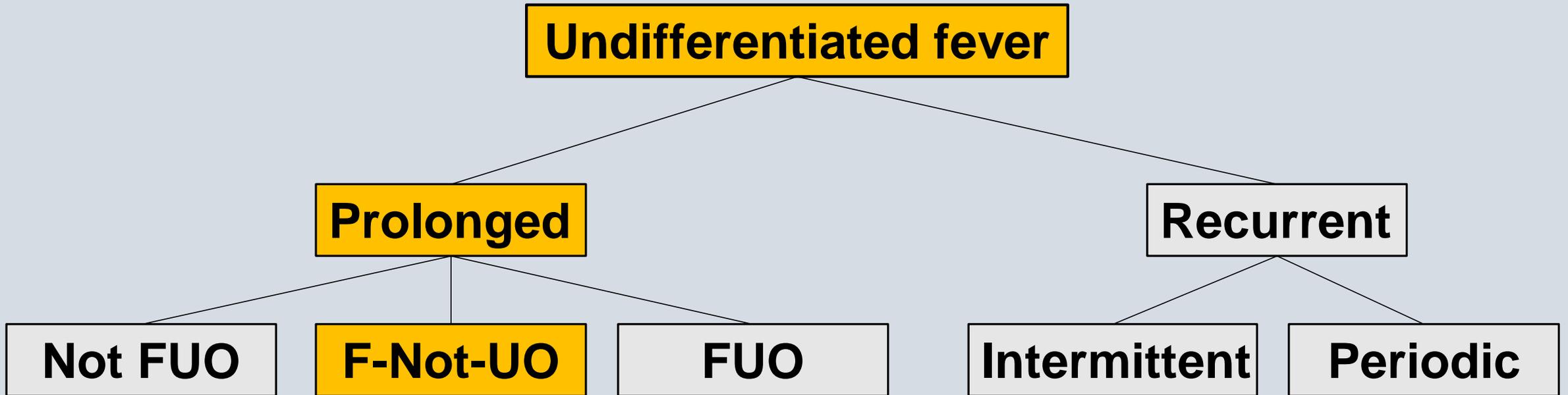
### Clues

- Healthy appearance
- Normal growth/development
- Stable weight
- School absences for subjective complaints

- Behavioral problems
- Fear of malignancy
- Family stress
- Normal physical exam



Diagnosis achievable in the primary care setting  
Clues on history, physical exam or simple laboratory tests  
Uncommon presentation of a common disease  
Seperate illnesses that blend together



**Diagnoses**

- URTI (otitis media, sinusitis)
- LRTI (pneumonia)
- CNS infection
- TB
- Leukemia
- Kawasaki disease
- JIA
- IBD

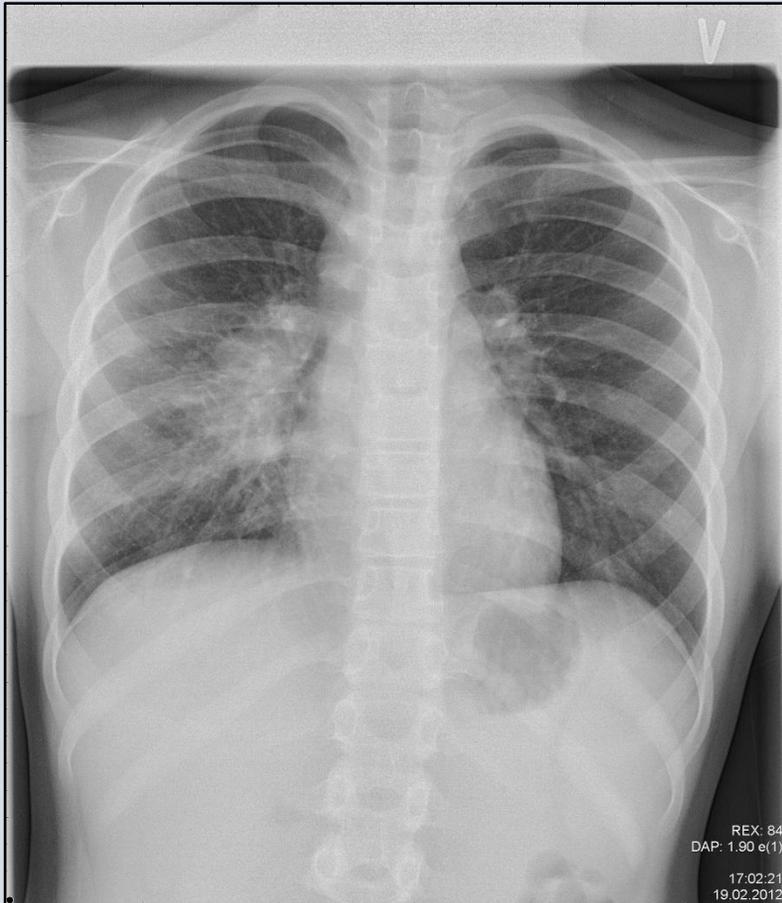
# Fever for 3 weeks

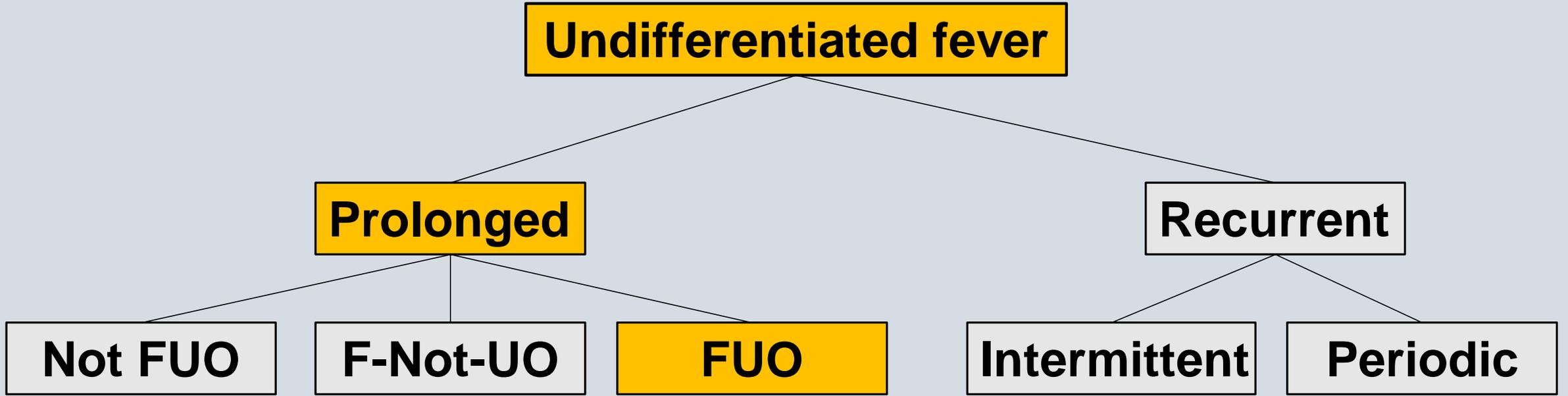
---

- 8 year old girl
- Turns up at the Paediatric Department
- Headache, back pain, leg pain, stomach pain
- Tired, 3 kg weightloss
- Normal examination except dry cough and temp. 38.0°C
  
- Previously: asthmatic bronchitis
- Pakistan for 4 months 1 year ago

# Fever for 3 weeks

---





# Defining prolonged fever of unknown origin

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FEVER OF UNEXPLAINED ORIGIN: REPORT ON 100 CASES

ROBERT G. PETERSDORF\* AND PAUL B. BEESON'

*From the Department of Internal Medicine, Yale University School of Medicine,  
New Haven, Connecticut*

- Illness > 3 weeks
- Fever > 38.3°C on several occasions
- Diagnosis uncertain after 1 week in hospital

# Defining prolonged fever of unknown origin

---

Reference	Temperature ( $\geq$ )		Frequency	Duration
	$^{\circ}\text{C}$	$^{\circ}\text{F}$		
McClung, 1972	38.9	102.1	Multiple occasions	Outpatient: 3 wk Inpatient: 1 wk
Pizzo, 1975	38.6	101.4	$\geq 5$ occasions	2 wk
Lohr, 1977	38.4	101.1	Multiple occasions	Outpatient: 3 wk Inpatient: 1 wk
Steele, 1991	38.1	100.5	$\geq 2$ occasions/wk	3 wk Normal U/A and CXR
Jacobs, 1998	38.1	100.5	Daily	2 wk

---

# UpToDate definition of FUO in children

---

- Core body temperature of  $\geq 38.3^{\circ}\text{C}$
- $\geq 1$  occasion every day
- $\geq 8$  consecutive days
- No diagnosis after initial outpatient or hospital evaluation including careful history, physical examination and initial laboratory assessment

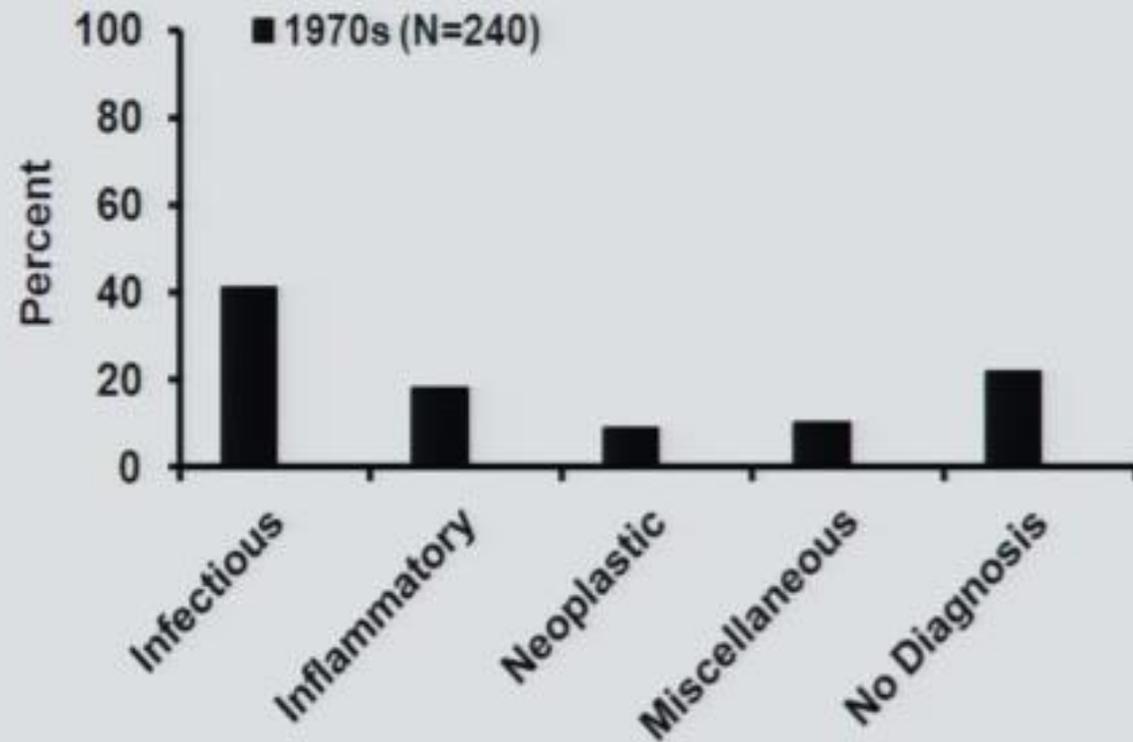
# Factors affecting cause of FUO in case series

---

- Geography
  - Age
  - Host factors
  - New diseases
  - Physician experience
  - Referral patterns
  - Availability of laboratory tests and imaging
  - Managed care
-

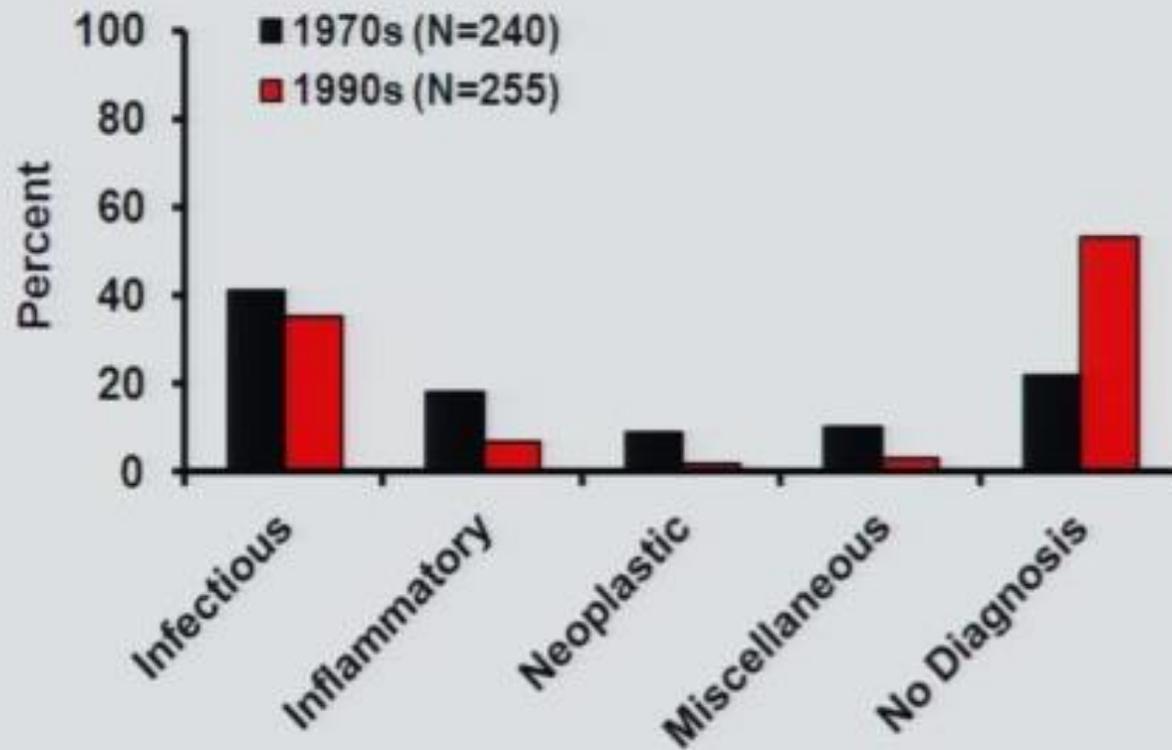
# Causes of FUO in children - USA

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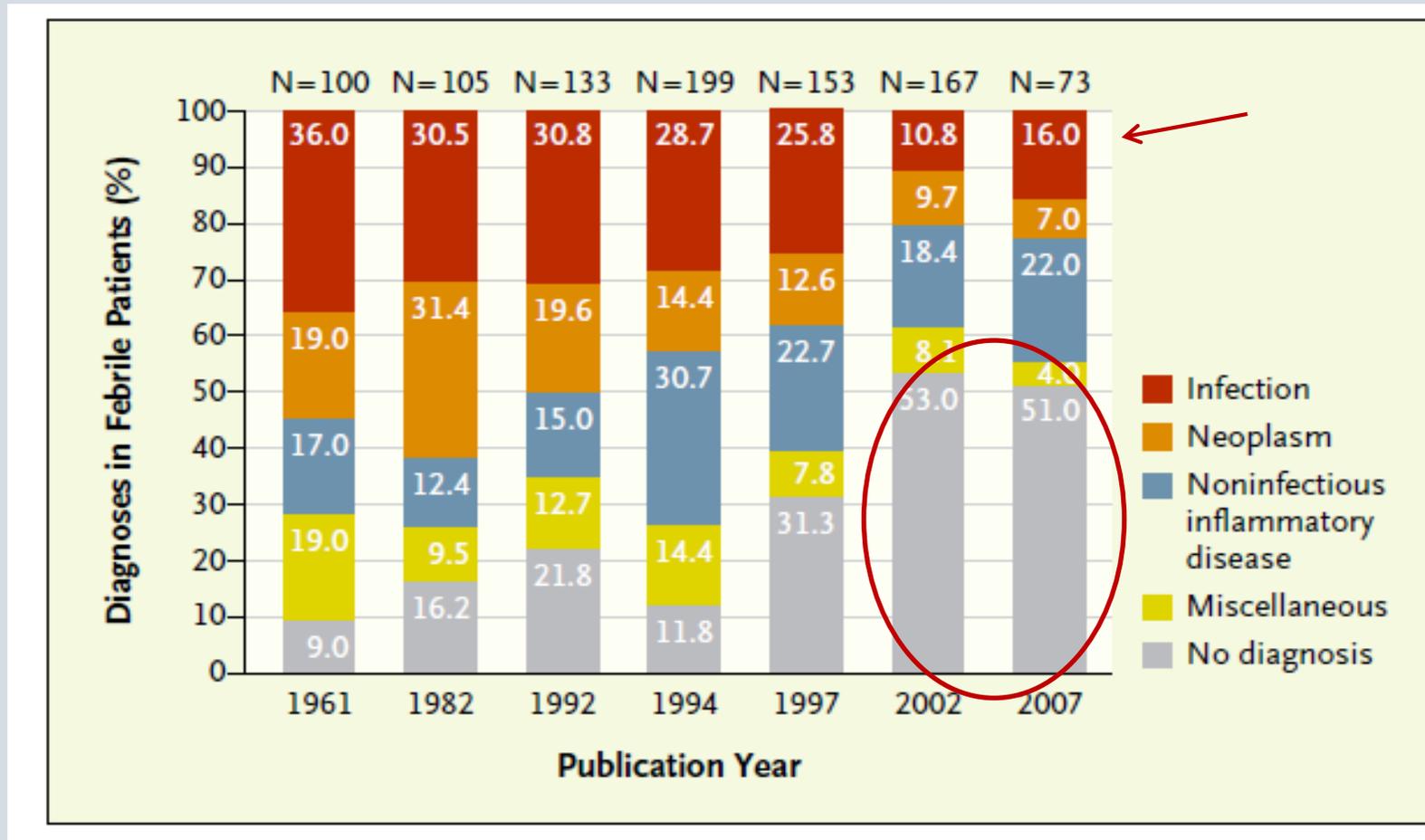


# Causes of FUO in children - USA

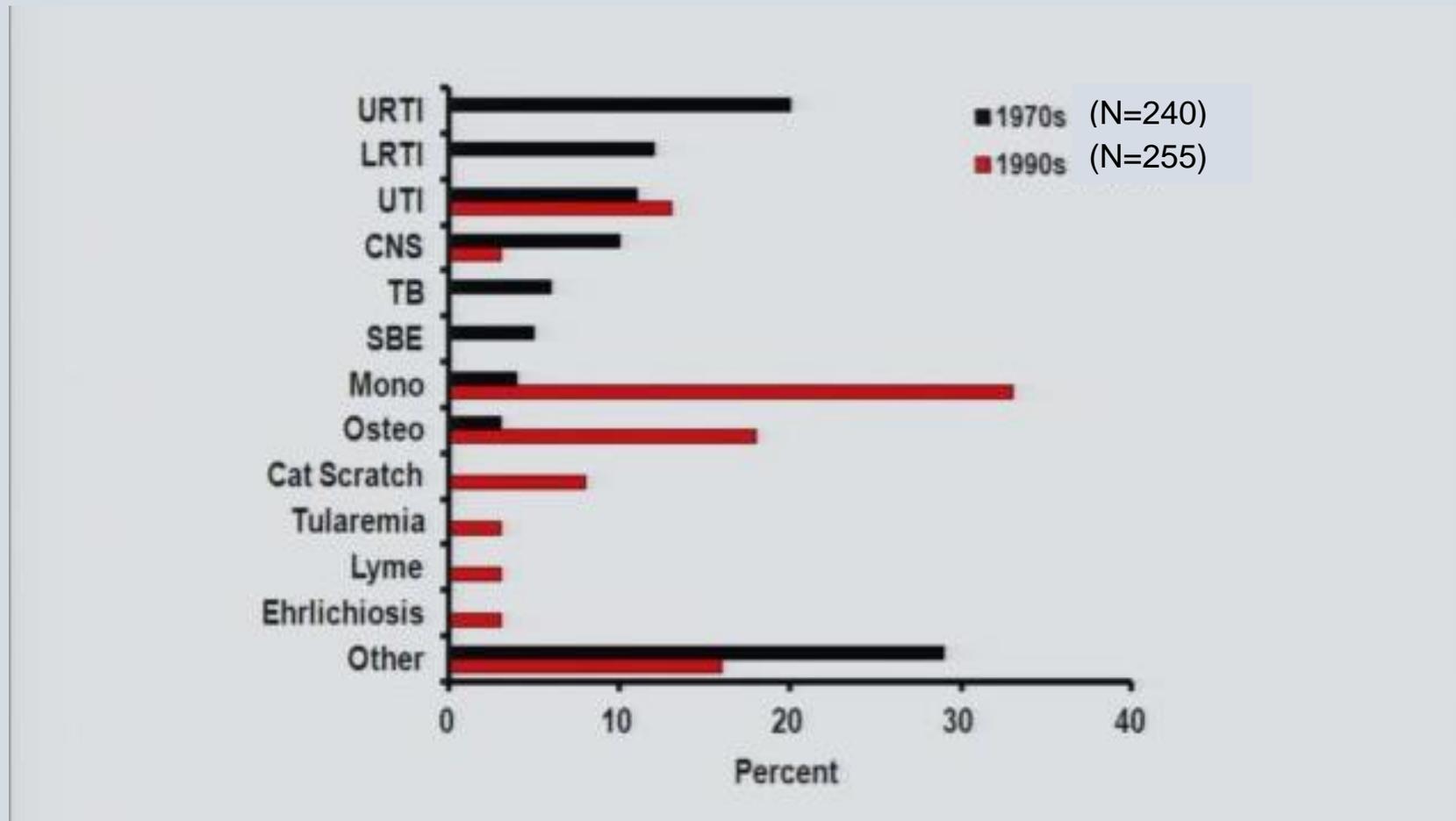
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# FUO in adults

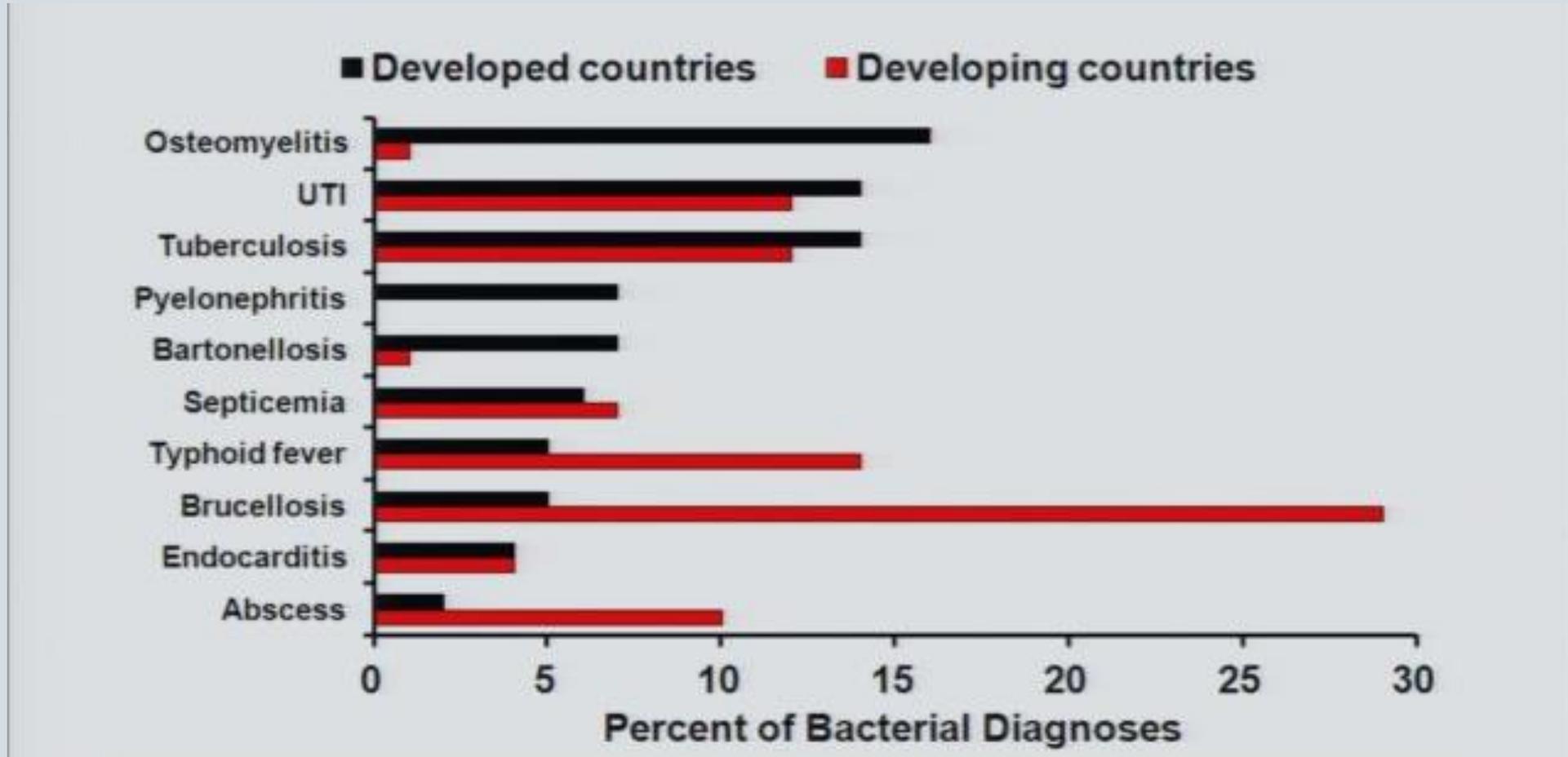


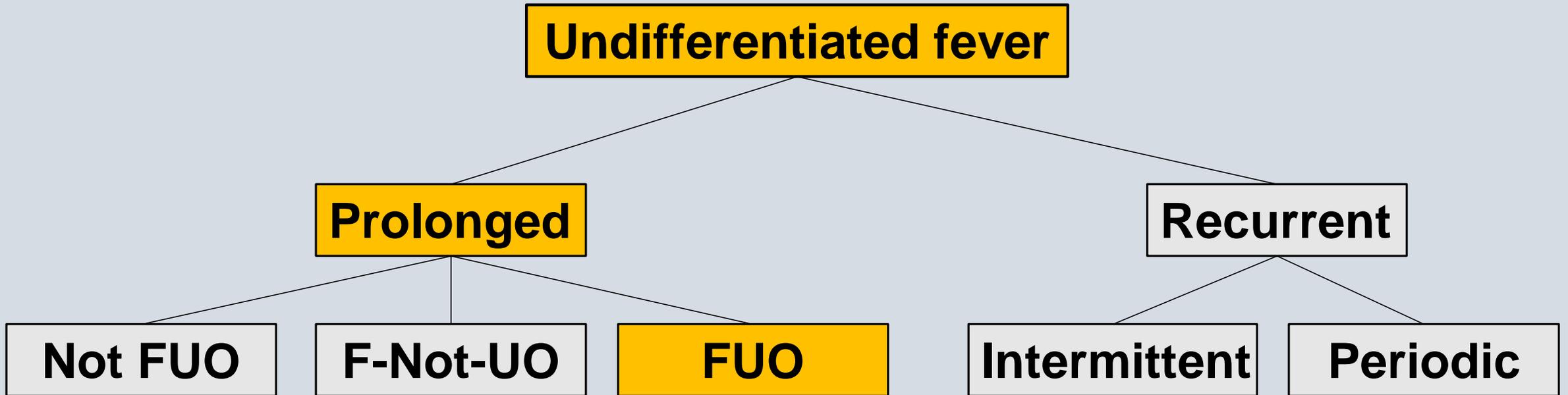
# Infectious causes of FUO in children - USA



# Bacterial infections in children with FUO

---





**If it's infection there is always a source**

- Travel
- Raw foods
- Ill persons
- Insect bites

- Animals
- Transfusions
- Recent procedures
- Unusual activities

# Undifferentiated fever

## Prolonged

Not FUO

F-Not-UO

FUO

## Recurrent

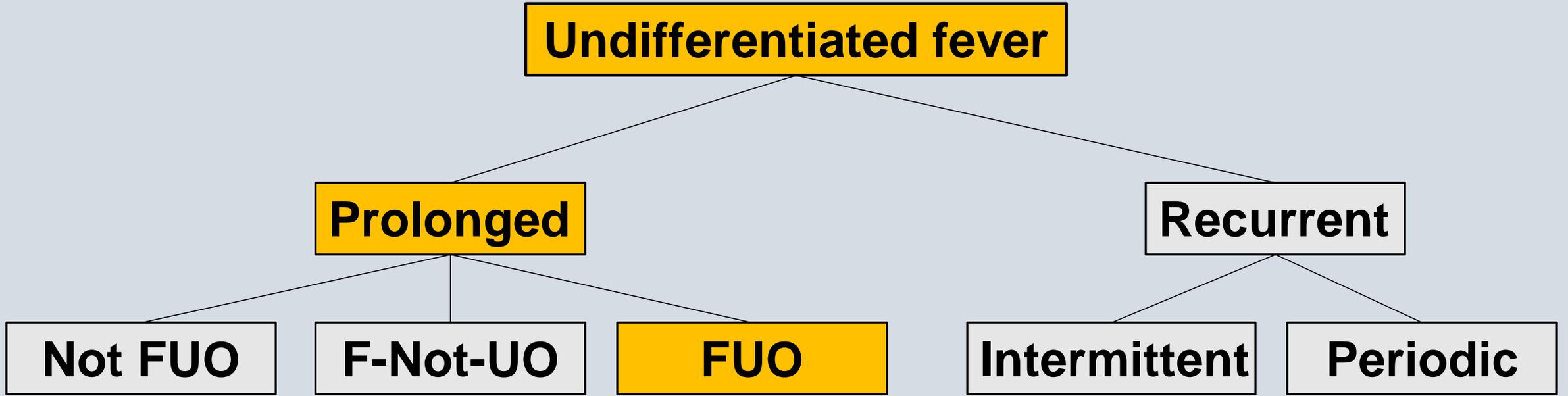
Intermittent

Periodic

### Inflammatory and autoimmune diseases

- Inflammatory bowel disease
- Juvenile idiopathic arthritis
  - Rheumatic fever
- Kawasaki disease (incomplete)

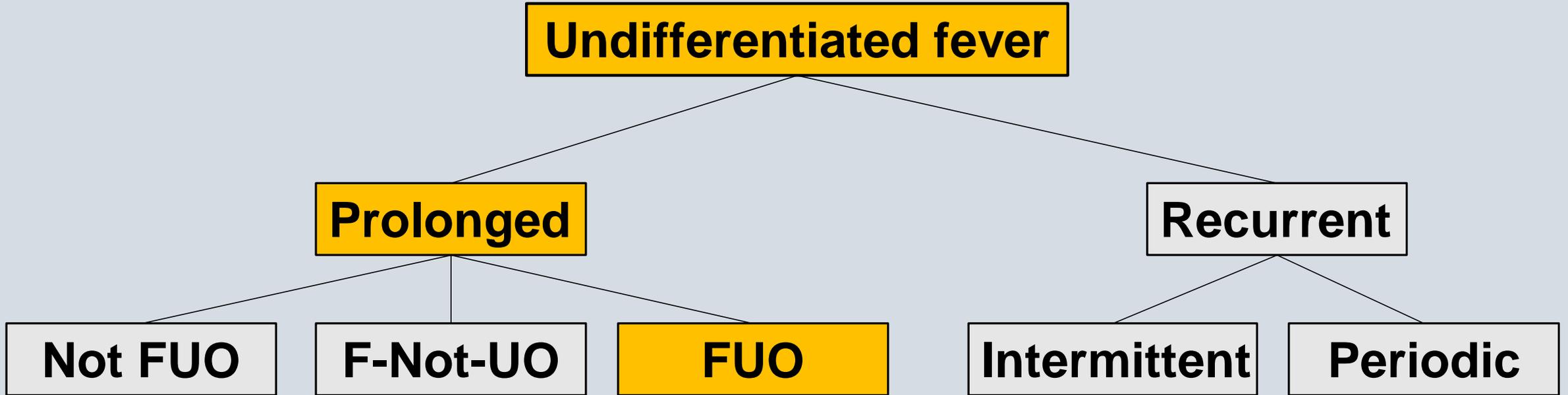
- Wegeners granulomatosis
- Sarcoidosis
- Behcet disease
- Lupus
- HLH



**Malignancies**

- Leukemia
- Lymphoma
- Neuroblastoma

- Hepatoma
- soft tissue sarcoma



**Miscellaneous**

- Munchausen by proxy
- Factitious fever
- Drug fever
- Central fever
- Pulmonary embolus

- Dysautonomia
- Diabetes insipidus
- Ectodermal dysplasia
- Hyperthyroidism
- Hematoma

Original Article

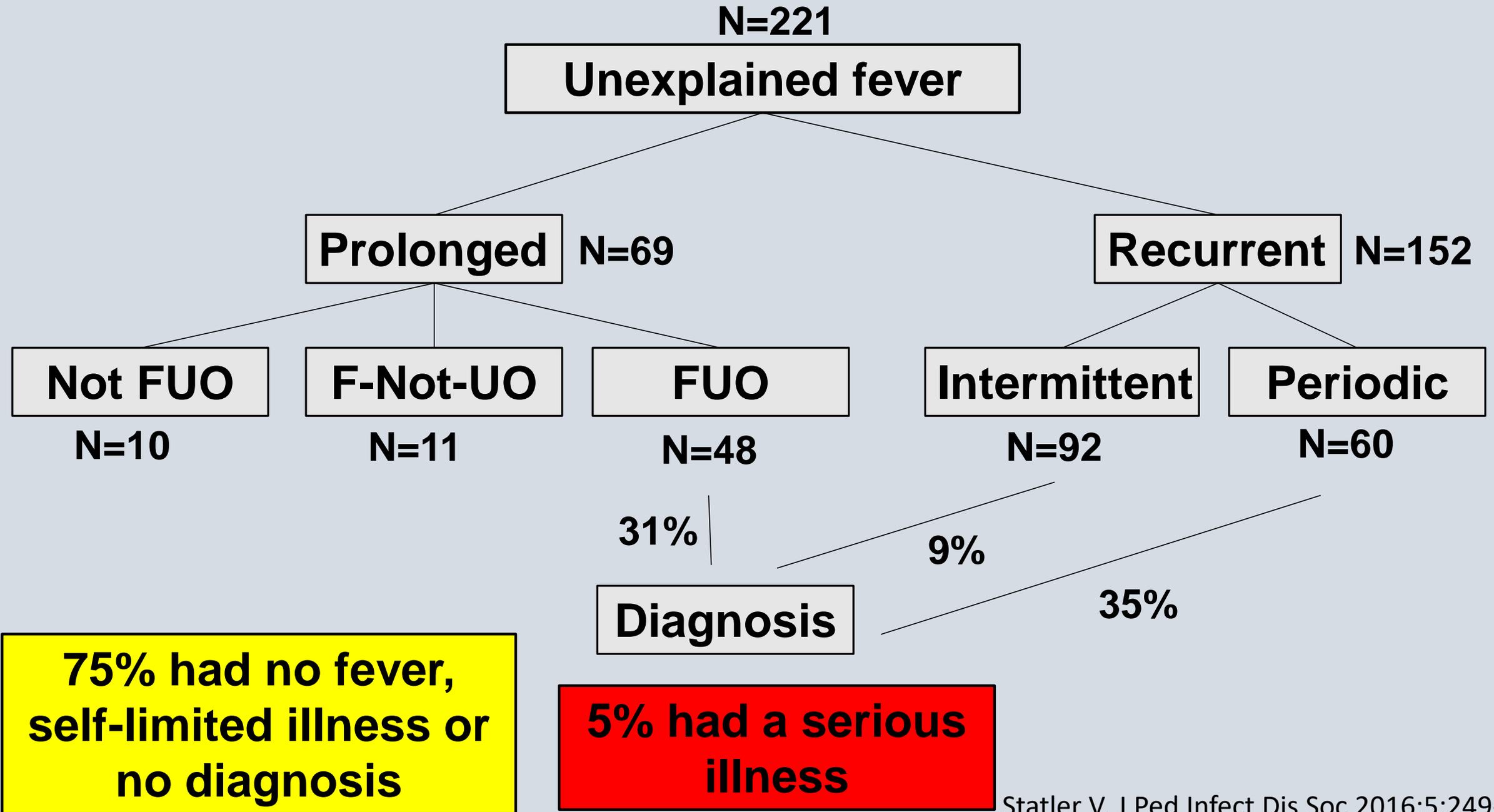
# Characteristics of Patients Referred to a Pediatric Infectious Diseases Clinic With Unexplained Fever

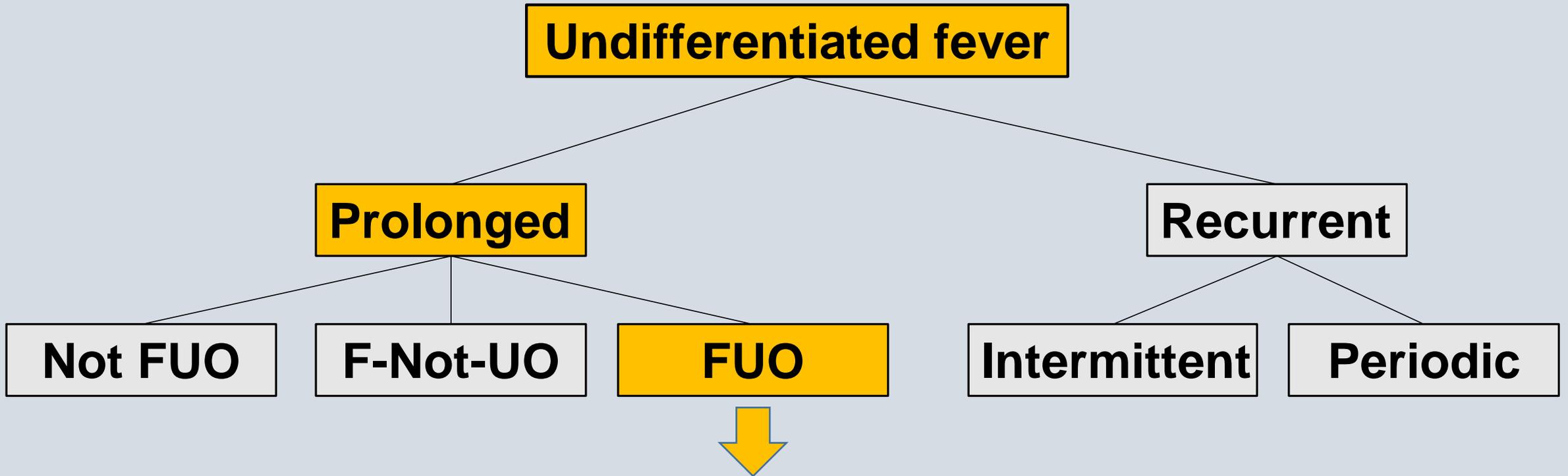
Victoria A. Statler and Gary S. Marshall

Division of Pediatric Infectious Diseases, University of Louisville School of Medicine, Louisville, Kentucky

**Corresponding Author:** Victoria A. Statler, MD, MSc, Department of Pediatrics, University of Louisville School of Medicine, Louisville, KY 40202. E-mail: [victoria.statler@louisville.edu](mailto:victoria.statler@louisville.edu).

Received December 16, 2014; accepted February 3, 2015; electronically published March 8, 2015.



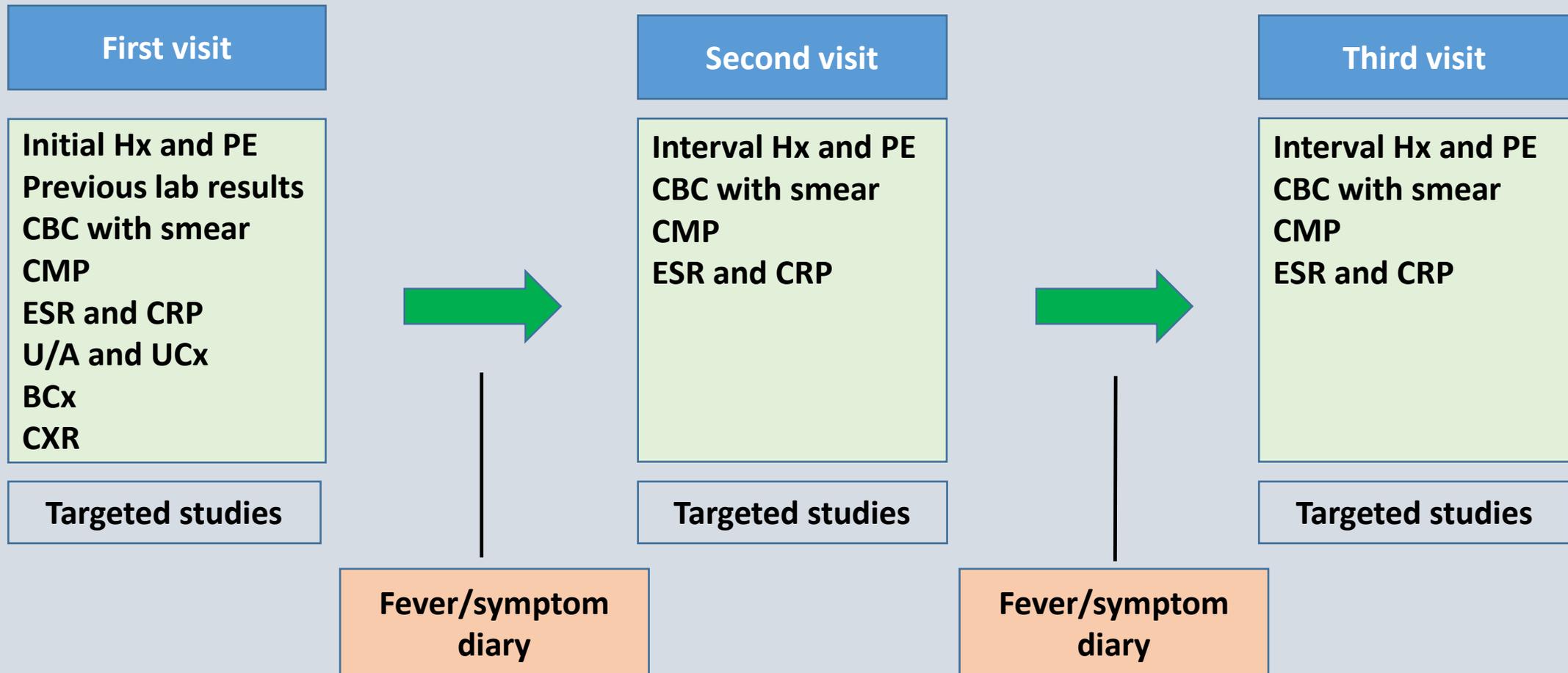


### Approach to diagnosis

- Severity of findings dictates pace of evaluation
- Serial evaluations
- Avoid antimicrobials
- Use time as a diagnostic tool

# Diagnostic approach

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# Targeted studies

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- **Infectious diseases**

- TST, IGRA
- EBV and CMV serology
- HIV Ab/Ag or PCR
- Bartonella serology
- Brucella serology
- Toxoplasma serology
- Tularemia serology
- Histoplasma serology
- Stool culture

- **Autoimmune/autoinflammatory**

- ANA and RF
- ASO and anti-DNAse-B
- C3, C4

- **Malignancy**

- Flowcytometri
- LDH and uric acid
- Bone marrow
- PET-CT

- **Miscellaneous**

- Thyroid function tests
  - Sinus CT
  - Echocardiogram
  - Endoscopy
  - Abdominal US or CT
  - Bone scan
  - PET scan
-

# FDG-PET-CT in children with FUO

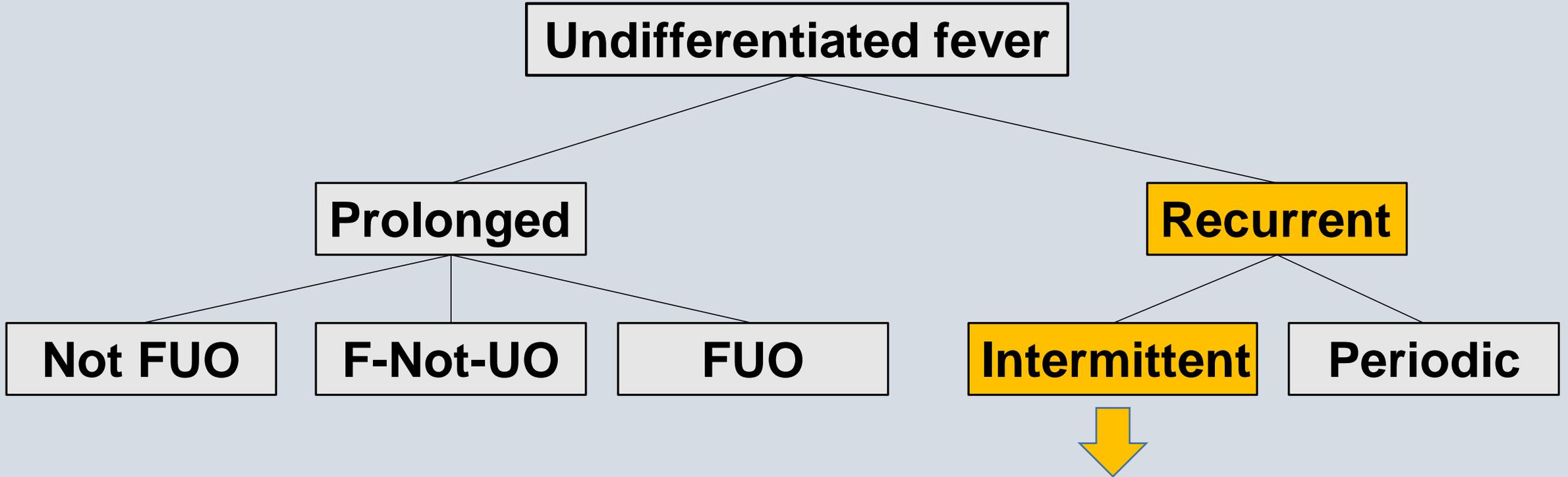
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- Results similar to adults
- Sensitivity 80-90%
- Clinical helpful 45%
- FP
- FN



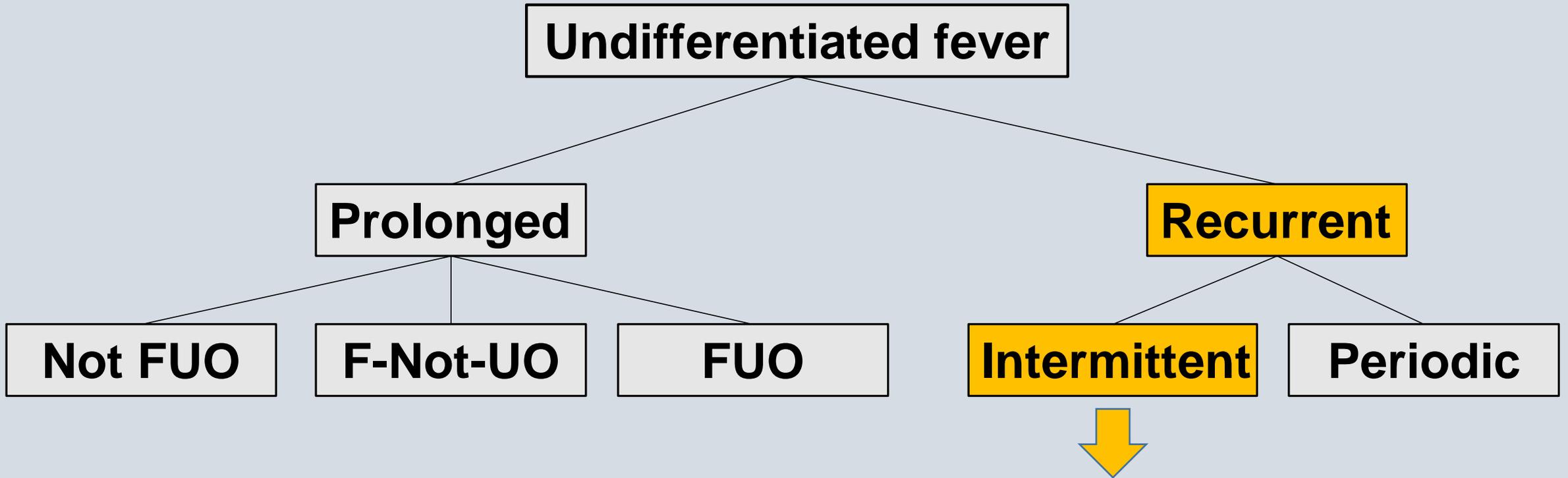
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Jasper N. Eur J Nucl Med Mol Imaging, 2010;37:136-145  
Houseni M. PET Clin 3, 2009: 605-19  
Kouijzer I. Semin Nucl Med, 2013;333-9



**Sequential, common, self-limited illness**

- Epidemiological clues (daycare)
- Diagnosis
  - Careful fever and symptom chart
  - Screening laboratory studies
  - Time



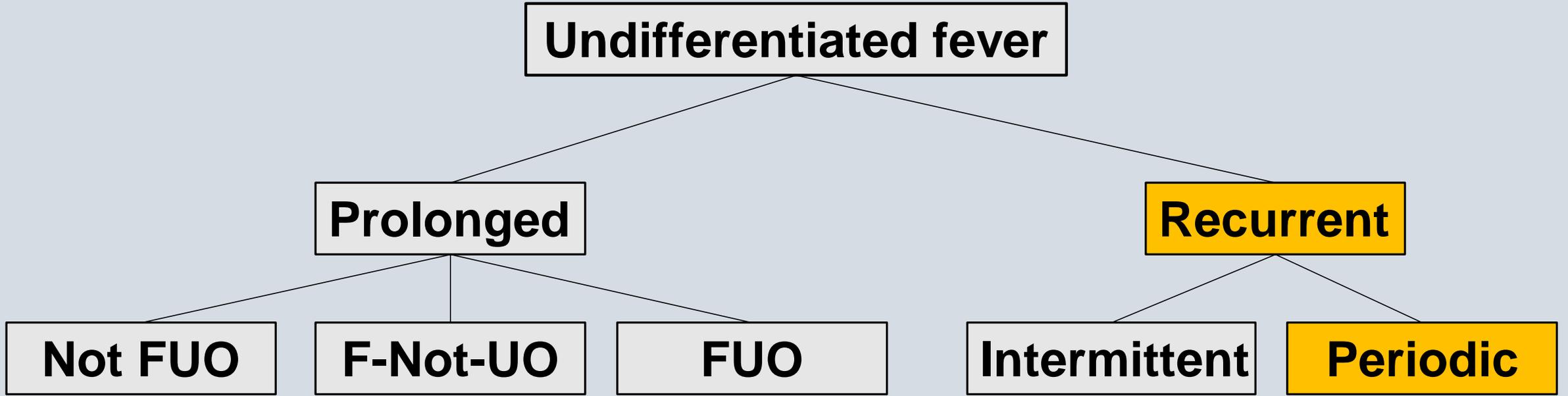
Sequential, common, self-limited illness

### **Autoinflammatory diseases**

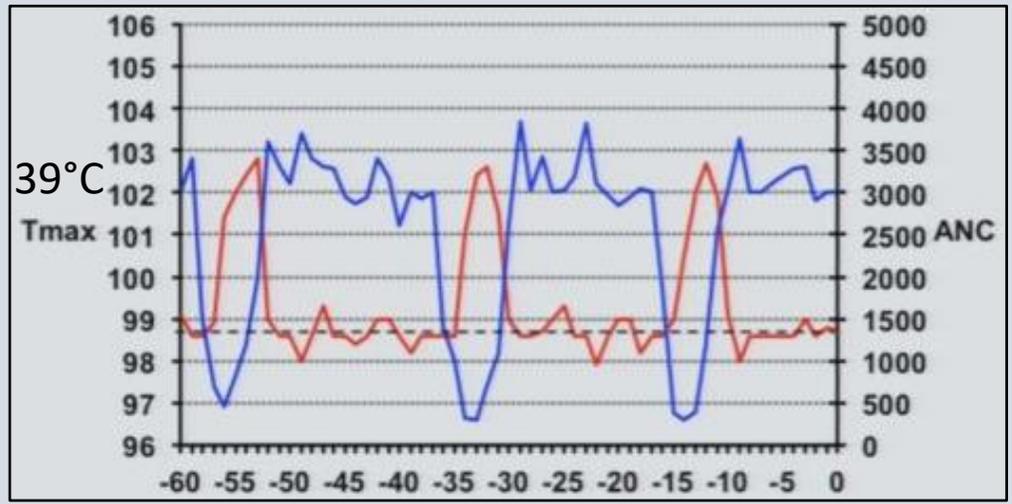
- Abnormally increased inflammation
- Predominantly mediated by molecules and cells of the innate immune system (as opposed to autoantibodies or autoreactive T cells)
- Significant host predisposition

## Autoinflammatory diseases

Feature	Inflammasomopathies					Protein folding disorder
	Intrinsic			Extrinsic		
	FCAS	MWS	NOMID	FMF	HIGDS	TRAPS
<b>Inheritance</b>	AD	AD	Sporadic	AR	AR	AD
<b>Ethnicity</b>	European	European	Any	Mediterranean	European	European
<b>Age at onset</b>	<1 yr	<20 yr	<1 yr	<20 yr	<1 yr	<20 yr
<b>Triggers</b>	Cold	Cold	-	-	Vaccination	-
<b>Frequency</b>	Variable	Variable	Continuous	Variable	2-4 wk	Variable
<b>Duration</b>	1-2 days	2-3 days	Continuous	1-3 days	3-7 days	> 7 days
<b>Distinctive features</b>	Rash Conjunctivitis Nausea Headache	Rash Conjunctivitis Deafness	Rash Meningitis Arthropathy Deafness Adenopathy ↑Liver&spleen	Serositis ↑Spleen Erysipeloid erythema	Abd. pain Vomit,diarrhea Rash Adenopathy Arthralgia Headache	Rash Arthritis Conjunctivitis ↑Spleen
<b>Amyloidosis</b>	No	Yes	No	Yes	No	Yes
<b>Treatment</b>	Anti-IL-1	Anti-IL-1	Anti-IL-1	Colchicine	Anti-IL-1 Anti-TNF	Anti-IL-1 Anti-TNF



**Cyclic neutropenia**



— Temperature  
— Neutrophile count/mL

# Undifferentiated fever

Prolonged

Recurrent

Not FUO

F-Not-UO

FUO

Intermittent

Periodic



PFAPA

Periodic fever,  
aphthous stomatitis,  
pharyngitis and  
adenitis syndrome

# Distinctive Features of PFAPA Syndrome

---

- Clockwork periodicity
- Fever episodes are stereotypical and unprovoked
- Identifiable prodrome is common
- Upper respiratory tract inflammation
- No rash or arthritis
- Elevated acute phase reactants
- No failure-to-thrive
- Episodes are aborted by steroid therapy
- Episodes resolve after tonsillectomy
- Resolves by adolescence
- No long-term sequelae



# Cases

---

**3 year old girl  
with recurrent  
fever**

---



# Neonatal History

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- Uncomplicated pregnancy, para 1
  - Acute caesarean section at GA 38
  - Apgar scores 3/1, 6/5 and 9/10. Birth weight 3,510 g
  - Neonatal sepsis and hepatitis
  - Treatment: n-CPAP, phototherapy, antibiotics, diuretics, and blood transfusions
  - Congenital viral infection?
-

# History & Examination

---

- From 3 mo: recurrent white coatings and blisters on the tongue
  - From 5 mo: episodes of fever 39-40°C every second week, cervical lymphadenitis, rash, and more blisters in the mouth
  - Each illness episode between 6 and 14 days
  - Adenotonsillectomy no effect
  - Normal growth and development
  
  - Normal physical exam, no fever
  - CRP 7 mg/L, tbc  $505 \times 10^9$ /L, leuco  $12.7 \times 10^9$ /L, hgb 5.8 mmol/L, ESR 29 mm/h
  - Negative HIV, CMV and EBV antibodies
-

# 1 month later

---

- Temp 38.5° C
- Rhinitis
- Tender cervical adenitis
- No other physical findings
- Normal chest X-ray
- CRP 142 mg/L , ESR 72 mm/h

Investigation	Result
Haemoglobin	<b>5.2 mmol/L</b>
Leucocytes	10.9x10 <sup>9</sup> /L
Thrombocytes	<b>505x10<sup>9</sup>/L</b>
Urat	0.49 mmol/L (ref. 0.15-0.35)
Lactate dehydrogenase	203 U/L (ref. 155-450)
IgD	100 IU/mL
IgG	<b>12.3 g/L</b> (ref. 3.4-9.1)
IgA	<b>3.08 g/L</b> (ref. 0.12-1.49)
IgM	1.64 g/L (ref. 0.39-2.08),
IgG subclasses	Normal
Blood culture	Negative
Blood smear	Reactive, no lymphoblasts
Complement defect screening	Normal
Vaccination response to HiB, diphtheria, tetanus	Normal
Mannan binding lectine (MBL)	220 g/L
Haemoglobin electrophoresis	Normal
Tracheal aspirate	<b>Moraxella catarrhalis</b>
Chest X-ray	Discrete perihilar infiltrates
Urine culture	Negative



# Following 6 weeks

---

- 3 hospitalizations
- Symptoms: Fever, rhinitis, cervical adenitis, **stomatitis**, macular rash on the legs
- CRP 104-235
- Chest X ray: normal
- Urine dip stick: normal
- Treatment: cefuroxim, gentamycin, amoxi/clav

Investigation	Result
Blood smear	Atypical lymphocytes, no malignancy
Bone marrow aspiration	Hypoplastic marrow, no malignancy
Mutation analysis for FMF	Negative
ANA	Negative
ANCA	Negative
Anti-dsDNA	Negative
PCR parvovirus	Negative
PCR EBV	Negative
Lymphocyte subpopulations	Normal
Lymphocyte stimulation tests	Normal
Tuberculin Skin Test	Negative
Sweat test	Sweat Sodium 68 mmol/L (slightly elevated)
Delta 508 mutation analysis	Negative
X-ray thorax	Normal
Echocardiography	Small mitral insufficiency, not haemodynamic significant
US abdomen	<b>Slight hepatomegaly</b> with hyperechogenic patches

# Diagnosis?

---

- IgD 2012.6 IU/mL
- Urine mevalonic acid: 21.8  $\mu\text{mol}/\text{mmol}$
- Genetic analysis: compound heterozygote for the V377I and the c.417insC mutations in the MVK gene
  
- ~ 100 sick days a year

# Mevalonate Kinase Deficiency (Hyper IgD Syndrome)

---

- IgD 2012.6 IU/mL
- Urine mevalonic acid: 21.8  $\mu\text{mol}/\text{mmol}$
- Genetic analysis: compound heterozygote for the V377I and the c.417insC mutations in the MVK gene
  
- ~ 100 sick days a year

Treatment:  
Steroids  
Eternacept  
Anakinra

## Autoinflammatory diseases

Feature	Inflammasomopathies					Protein folding disorder
	Intrinsic			Extrinsic		
	FCAS	MWS	NOMID	FMF	HIGDS	
<b>Inheritance</b>	AD	AD	Sporadic	AR	AR	AD
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<b>Amyloidosis</b>	No	Yes	No	Yes	No	Yes
<b>Treatment</b>	Anti-IL-1	Anti-IL-1	Anti-IL-1	Colchicine	Anti-IL-1 Anti-TNF	Anti-IL-1 Anti-TNF



**10 year old girl with fever**

# History

---

- Fever, cough and malaise 2 weeks ago
- Now fever for 7 days
- Coughing
- Itchy rash on legs and arms
- Pain all over the body
- Antihistamines no effect
- Cefur+genta no effect
- Transferred for second opinion



# Past history

---

- Family Hx: Mom has asthma, brother asthmatic bronchitis, no rheumatic diseases
- Exposures:
  - Charter trip to Turkey 1 yr ago
  - 1 Cat, 4 kittens and a turtle at home
  - 3 weeks prior to symptoms slept in an animal park. Hugged a donkey
- No allergies
- Asthma for 1 yr
- Appendectomy 1 yr ago
- + all childhood vaccinations
- Medicine: Pulmicort 200 microg x 2, beta2agonist p.n.

# Physical examination day 7 of fever

---

- Pale
- Superficial breathing, tachypnoeae
- Heart murmur
- Mild cervical adenitis
- Red throat, normal tonsils
- Rash on inner legs and arms
- Pain in left shoulder
- A spider in the left ear
- No visible joint involvement
- Temp. 38.3°C in ear
- RF 60
- P 128
- BT: 106/56
- Sat: 98% → 90%
- CCR 2 sek

# Lab results

---

- CRP 279 → 325
- ESR 100
- Leuco 27 (24 neutro)
- HgB 6.4
- Thrombocytes 464
- Ferritin 602
- Albumin 18
- IgG 9.2
- Normal U&E, Liver parametres
- Normal RF and ANA screen

# Chest X-ray day 7

---

Fluid on left side?

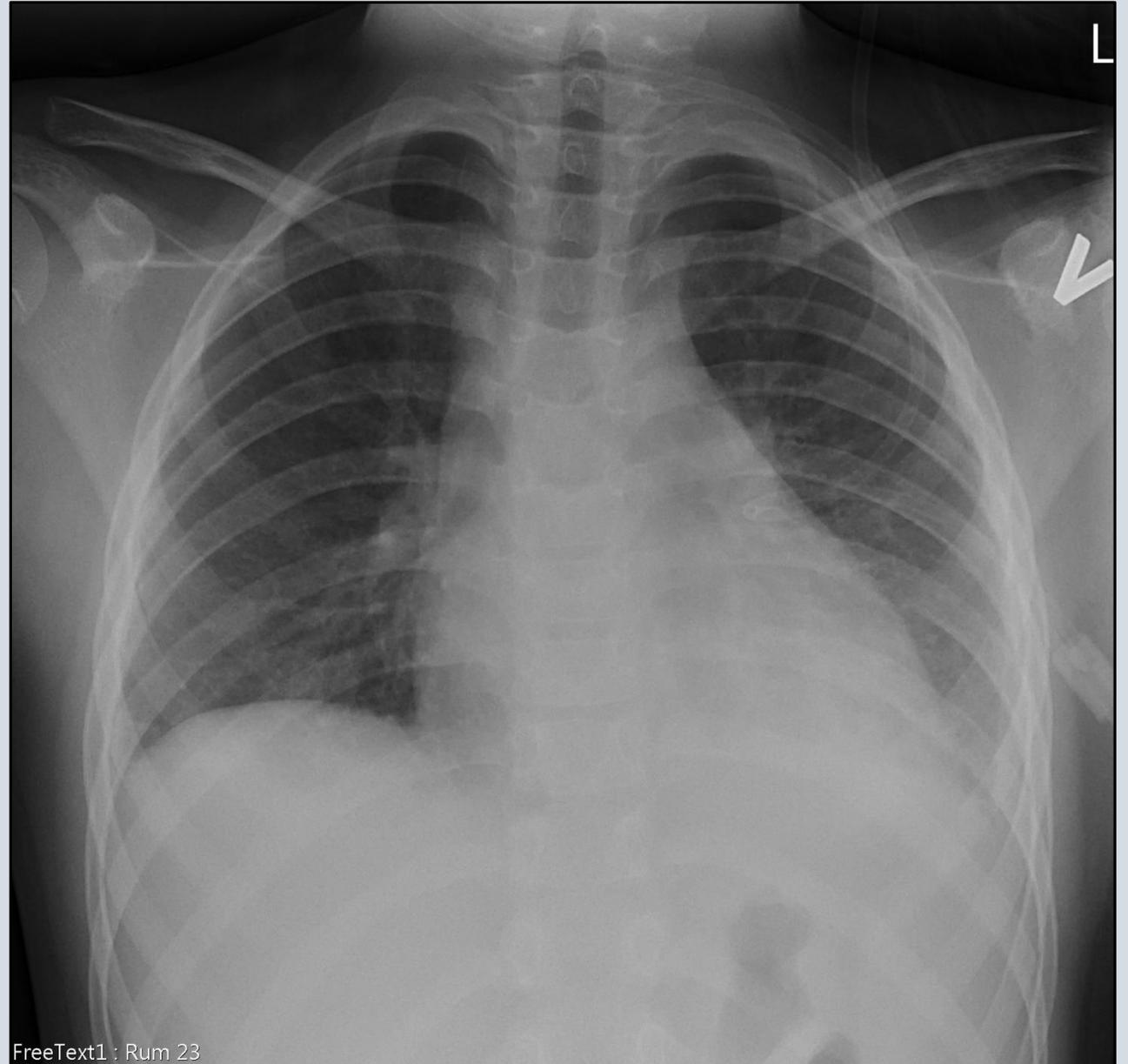
Cardiomegaly?

US: 8 mm fluid

Puncture 12 mL yellow fluid

**ECHO:** small pericardial effusion

→ Meronem + cipro



# PET-CT day 9

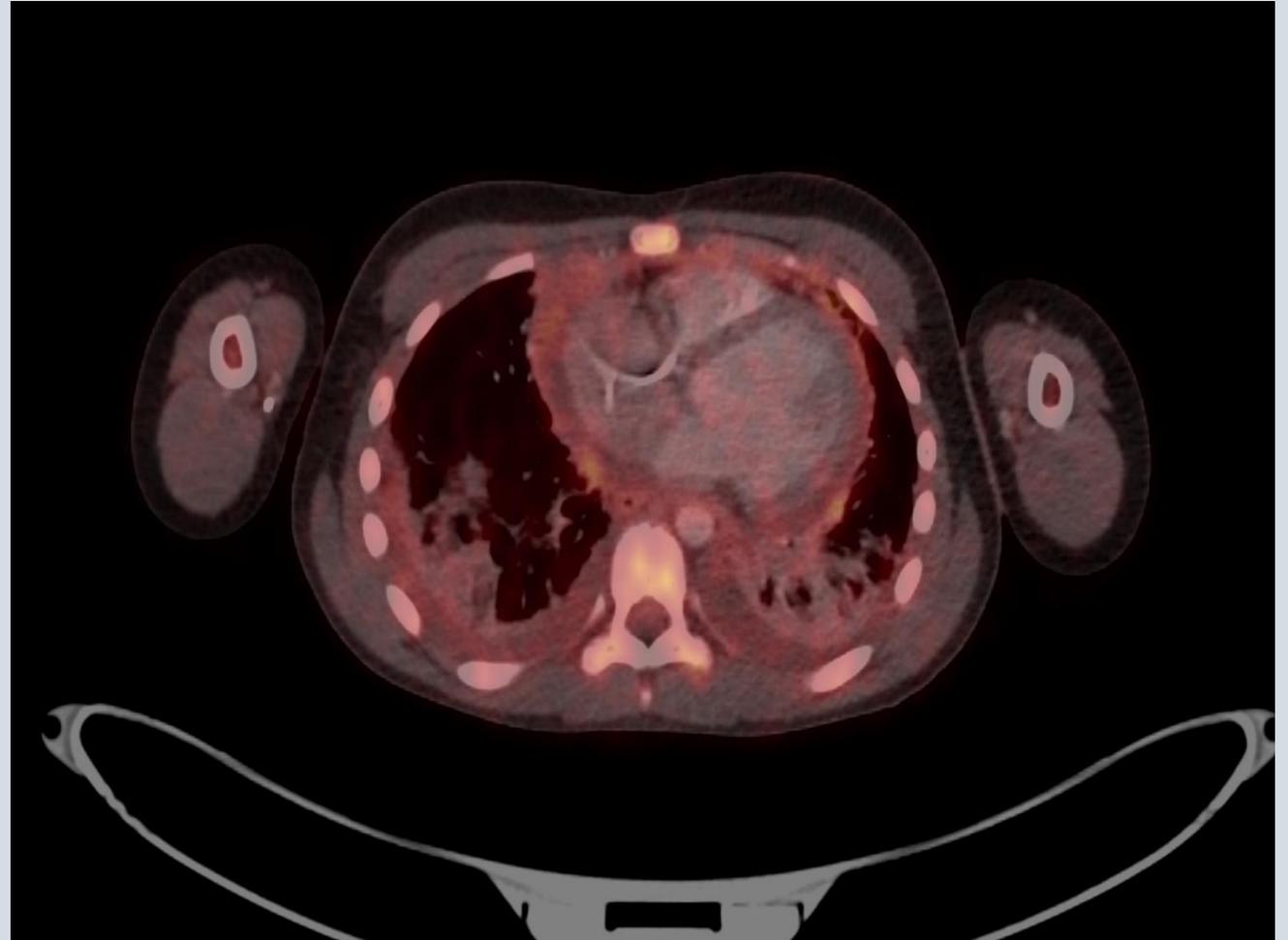
---

Bilat. infiltrates in lungs

Bilat. pleural effusion 1 cm

Pericardial effusion 1.5 cm

No other sites of  
inflammation



# Day 10 of (high) fever

---

- Meropenem & cipro
- Paracetamol, ibuprofen, morphine
- Temp. 40°C
- ECHO: No aneurisms
- IVIG 2 g/kg



# Next few days

---

## Day 11

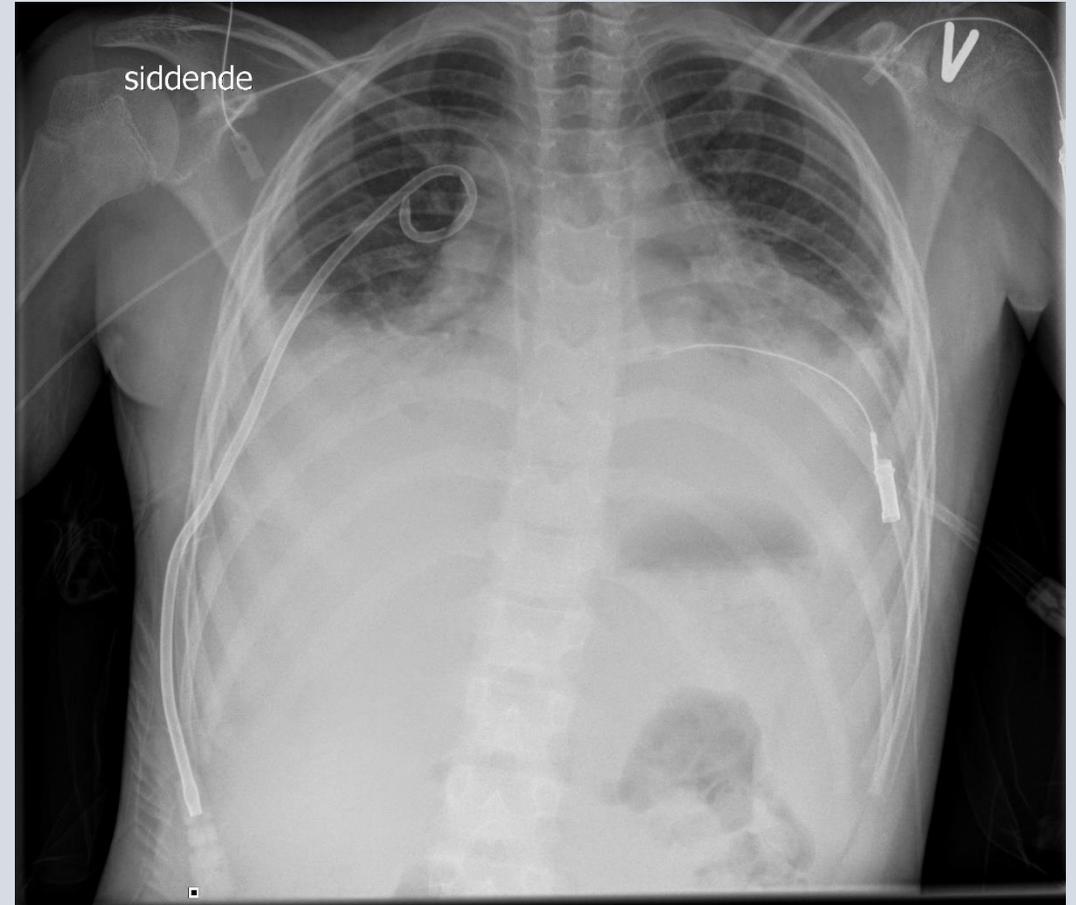
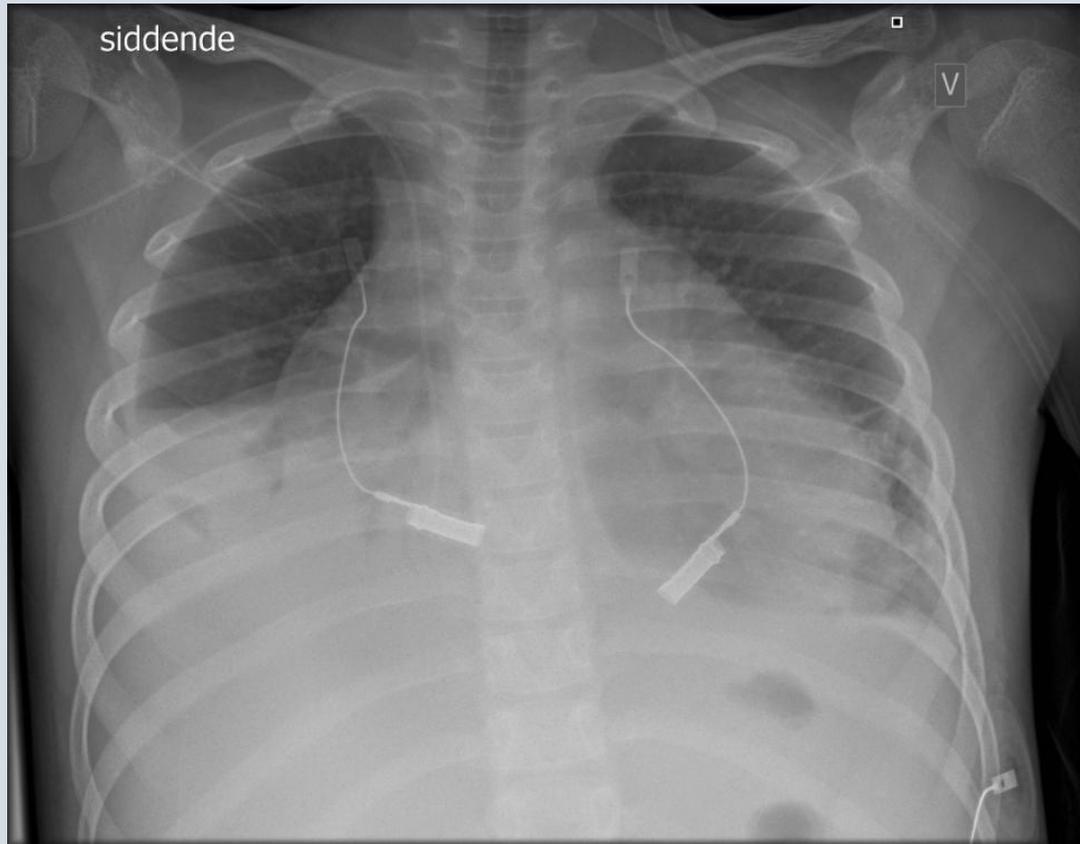
- Afebrile
- Good appetite
- Out of bed
- CRP 144
- Leucocytes 17.3

## Day 12

- Temp. 38.7°C
- IVIG

# Day 13 of fever

---



# Day 14 of fever

---

- CRP 170 mg/L
- Sep cipro
- Rp. Doxycycline
- Rp. azihromycine
- Rp. Methylprednisolone 15 mg/kg 3 days

→ Afebrile day 15

# Microbiology

---

Blood culture	F. tularensis
Urine culture	Bartonella
EBV & CMV & parvovirus serology	Toxoplasmosis
Adenovirus PCR	Borreliosis
Mycoplasma, legionella, c. pneumoniae, c. psittaci	Coxiella
Throat swab	Mercuriosis
Resp. Viruses PCR	IGRA
BAL for pneumocystis & TB	Galactomannan
LUT, PUT	HBsAg, HAV
Pleural exudate culture + 16S	F-calprotectin
Brucellosis	Faeces culture
leptospirosis	

**NEGATIVE**

# Further investigations- and treatment

---

- Ophthalmologic exam
  - Fibroscan
  - LFU: FEV1 31%, FVC 35%
  - HRCT lungs
  - BAL
  - Day 26: US right knee synovitis
  - Day 27: Methylprednisolone 30 mg/kg 3 days
  - Prednisolone
- Afebrile and well
- Continues low-grade fever

# Final diagnosis?

---

**Systemic juvenile idiopathic arthritis**

**Started on roActemra (IL-6 inhibitor) 2 months after first hospitalization**

**Feels better**

**All inflammation parameters normalized**

**Lung function improved**

**Undifferentiated fever**

**Prolonged**

**Recurrent**

**Not FUO**

**F-Not-UO**

**FUO**

**Intermittent**

**Periodic**

