Overview of fever of unknown origin in adult and paediatric patients

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ABSTRACT

Fever of unknown origin (FUO) can be caused by a wide group of diseases, and can include both benign and serious conditions. Since the first definition of FUO in the early 1960s, several updates to the definition, diagnostic and therapeutic approaches have been proposed. This review outlines a case report of an elderly Italian male patient with high fever and migrating arthralgia who underwent many procedures and treatments before a final diagnosis of Adult-onset Still's disease was achieved. This case report highlights the difficulties in diagnosing certain causes of FUO that requires a very high index of suspicion. The main causes of FUO in paediatric and adult patients will be reviewed here, underlying the fact that a physician should also consider the possibility that a patient with FUO may have a monogenic autoinflammatory disease (AID). The identification of AIDs requires a careful evaluation of both history and clinical details that may reveal important clues to identify the correct aetiology. We also provide a comprehensive account of specific signs and symptoms that could suggest possible diagnoses and guide the work-up of FUO and non-genetic periodic fevers in children.

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Introduction

Fever of unknown origin (FUO) accounts for around 3% of hospital admissions and has a high impact on health care systems (1, 2). Indeed, more than 200 different causes of FUO have been reported (3).

The first definition of FUO dates back to the early 1960's, when it was defined by Petersdorf and Beeson as a "*Body temperature of more than 38.3°C on several occasions, lasting for more than 3 weeks and no diagnosis after 1 week of hospitalisation"* (4). Refinements to the definition have since been proposed, including removing the requirement for in-hospital evaluation due to an increased sophistication of outpatient evaluation. Expansion of the definition has also been suggested to include sub-categories of FUO. In particular, in 1991 Durak and Street re-defined FUO into four categories: classic FUO; nosocomial FUO; neutropenic FUO; and human immunodeficiency virus (HIV)-associated FUO, and proposed three outpatient visits and related investigations as an alternative to "*1 week of hospitalisation*" (5).

In 1997, Arnow and Flaherty updated the FUO definition and considered the type of diagnostic panel to be more important than the duration of investigations (6). They considered the following list to be the "Minimum diagnostic evaluation to qualify as FUO": comprehensive history; repeated physical examination; complete blood count, including differential and platelet (PLT) count; routine blood chemistry, including lactate dehydrogenase (LDH), bilirubin, and liver enzymes; urinalysis, including microscopic examination; chest radiograph; erythrocyte sedimentation rate (ESR); antinuclear antibodies; rheumatoid factor; angiotensin converting enzyme; routine blood cultures (at least three) while not receiving antibiotics; cytomegalovirus IgM antibodies or virus detection in blood; heterophile antibody test in children and young adults; tuberculin skin test; computerised tomography (CT) of abdomen or radionuclide scan; HIV antibodies or virus detection assay; and, further evaluation of any abnormalities detected by the above tests (6).

Following on from this, a number of diagnostic algorithms have been proposed. Notably, the inclusion of 18 fluorodeoxyglucose-positron emission tomography 18F-FDG PET among the investigations has improved and shortened the diagnostic work-up of FUO (7).

Case report: an adult patient

An Italian male patient aged 69 years old, with a mechanical aortic valve, was admitted to the Internal Medicine ward due to high fever (up to 39°C) and migrating arthralgia, which had started ten days prior. Before being admitted, he had been treated with clarithromycin, which was stopped due to the occurrence of skin rash, and later with amoxicillin-clavulanate, without resolution of the fever. At admission he presented with papular skin rash in the pretibial region, bilaterally. Blood investigations showed white blood cells (WBC) 15,600/mmc, PLT count 405,000/mmc, ESR 114 mm/h, C-reactive protein (CRP) 29 mg/dl, beta-2 microglobulin 7.8 mg/L, procalcitonin (PCT) 2.2 mg/dl, LDH 894 U/L; Interferon-gamma Release Assay (IGRA) test was indeterminate. Widal test, serology for Brucella and HIV, human herpesvirus (HHV)-8, cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus (HCV), enterovirus, parvovirus B19, Dengue, Chikungunya, *Treponema, Francisella, Bartonella, Borrelia, Rickettsia, Coxiella, Leishmania, Toxoplasma, Chlamydia,* and *Mycoplasma* did not show any active infections. Polymerase chain reaction (PCR) for HCV, HBV, CMV, EBV, and HHV-6 were negative. More than 10 blood cultures for bacteria and mycobacteria were negative. Chest x-ray, chest and abdominal CT scan, transthoracic and transoesophageal echocardiography, and colonoscopy were all negative. 18F-FDG PET showed multiple mediastinal and abdominal lymph nodes uptake (SUV max 15), diffuse splenic (SUV max 6.5), and diffuse bone uptake. Laterocervical lymph node biopsy and bone marrow biopsy and aspirate showed non-specific reactive hyperplasia, and immunohistochemistry showed the predominance of CD8 positive lymphocytes; PCR for *Leishmania* and *Mycobacterium tuberculosis*, and mycobacterial cultures on these samples were negative.

Soon after admission, the patient was started on daptomycin, piperacillin-tazobactam and rifampin due to suspected prosthetic endocarditis, followed by normalisation of acute phase reactants. However, due to a relapse of these parameters (PCT 62 mg/ml, CRP 27 mg/dl, lactic acid 24 mg/dl, ferritin 6921 ng/ml, LDH 1512 U/L) the patient was switched to meropenem and linezolid with apyrexia for 7 days. Following this, the patient experienced a relapse of fever. *Candida* spp. was isolated in blood culture, and the patient was treated with caspofungin. Due to a recurrence of skin rash on the arms, legs, and trunk, the patient underwent skin biopsy, which raised the suspicion of psoriasis. He was then treated with topical steroids with fast improvement of the skin rash. At the same time, fever and joint pain disappeared and blood tests were normal. He was then discharged after 35 days in a good clinical condition with a diagnosis of recurrent infections due to the onset of psoriatic arthritis.

Five years later, the patient reported to the Emergency Department due to a recurrence of fever (up to 38°C), night sweats, loss of body weight, and arthralgia over the previous month. Before reporting to hospital, he had been treated with amoxicillin-clavulanate for 6 days without benefit. He complained of a transient rash on the back. WBC were 16,670/mmc (Neutrophils: 93%), CRP 5.93 mg/dl, LDH 600 U/L; chest x-ray was negative. He was admitted for further investigations: blood tests showed WBC 20,000/mmc (Neutrophils: 92%), haemoglobin 10.9 g/dl, beta-2 microglobulin 6.8 mg/L, PCT 1.9 mg/dl, ferritin 7,500 ng/ml, and thyroid function was normal. Two sets of blood cultures were negative. IGRA test was negative. Widal test and serology for Brucella and CMV, *Toxoplasma, Chlamydia, Borrelia*, EBV, HIV, *Treponema, Pallidum, Leptospira, Rickettsia, Bartonella, Aspergillus, Histoplasma, Coxiella,* and *Leishmania* ruled out active infections. CMV DNA PCR and blood smears for Malaria were negative as was Galactomannan and Cryptococcal antigen on serum. Abdominal ultrasound was also negative. 18F-FDG PET showed mild multiple mediastinal, axillary, and inguinal lymph nodes uptake. Transthoracic and transoesophageal echocardiography, and colonoscopy were negative. Chest high-resolution CT showed bilateral peripheral micronodules and multiple mediastinal lymphadenopathies. The patient was initially treated with piperacillin-tazobactam without effect, and then, due to an impairment of acute phase reactants (PCT 65 mg/dl), teicoplanin and fluconazole were added with resolution of fever. The patient was discharged after 30 days and referred to the Fever of Unknown Origin outpatient clinic, Infectious Disease Unit. At that time he was apyretic; he reported asthenia and marked loss of body weight (10 kg over the previous 2 months). WBC were 7,490/mmc (Neutrophils: 63%, Eosinophils 9.2%), ESR 92 mm/h, CRP 3.38 mg/dl, beta-2 microglobulin 8 mg/L, interleukin-6 19.8 ng/ml, serum amyloid A 5.23 mg/dl, fibrinogen 405 mg/dl, LDH 525 U/L, and ferritin 2,370 ng/ml. After 10 days he reported a recurrence of high fever and joint pain. According to his clinical history and laboratory features, a diagnosis of Adult-onset Still's disease (AOSD) was formulated based on four major and three minor Yamaguchi criteria. Antibodies to *Strongyloides stercoralis* were positive and he was treated with oral ivermectin for 2 days before starting steroids. After the start of steroid treatment, the patient achieved complete recovery after a period of one month. He did not show any febrile episodes nor other symptoms while on steroid treatment.

The diagnostic and therapeutic approaches carried out in this patient were particularly aggressive as a blood stream infection was suspected in consideration of his aortic mechanic valve and high values of PCT. The spontaneous remission of fever (related to AOSD) was considered twice to be the effect of antibiotic treatment. However, the correct interpretation of signs, symptoms and lab tests (*e.g.* hyperferritinemia) would have spared useless high cost diagnostic tests, less invasive procedures and treatments, and would probably have achieved the final diagnosis much earlier, with significant advantage to the individual and a reduced cost in health resources. Whilst PCT is considered a strong predictive marker

Table I. Causes of fever of unknown origin in adults [modified from Cunha *et al*. 2015 (54)].

Main causes of classic FUO in adults			
Infections	NIID	Malignancy	Miscellaneous
Bacterial 1. Subacute endocarditis 2. Abdominal, pelvic and renal abscess 3. Spondylodiscitis 4. Chronic prostatitis 5. Periapical dental abscess 6. Vascular graft infection 7. Extrapulmonary and miliary tuberculosis 8. Typhoid fever 9. Bartonellosis 10. Borreliosis 11. Brucellosis 12. Non-tuberculous mycobacteria 13. Q fever 14. Whipple disease 15. Actinomycosis 16. Syphilis 17. Listeriosis *Viral* 1. CMV 2. EBV 3. Multicentric Castleman's disease *Fungal* 1. Histoplasmosis (disseminated) *Parasitic* 1. Visceral leishmaniosis 2. Malaria 3. Toxoplasmosis 4. Amoebic abscess	1. AOSD 2. Polymyalgia rheumatica/giant vessels arteritis 3. Sarcoidosis 4. Polyarteritis nodosa 5. Systemic lupus erythematous 6. Rheumatoid arthritis 7. Small vessels vasculitis 8. Takayasu's arteritis 9. Kikuchis' disease 10. Polyarticular gout 11. Behçet's disease 12. Late-onset rheumatoid arthritis	1. Lymphoma (HL, NHL) 2. Solid tumours (renal cell carcinoma, hepatocellular carcinoma, tumour metastatic to the liver) 3. Myelodysplastic syndrome 4. Leukaemia 5. Atrial myxoma 6. CNS tumours	1. De Quervain thyroiditis 2. Drug fever 3. Factitious fever 4. Inflammatory bowel diseases 5. Sweet syndrome 6. Deep vein thrombosis/pulmonary embolism 7. Hypersensitivity pneumonia 8. Schnitzler syndrome 9. Hemophagocytic syndrome *Hereditary AutoInflammatory Diseases (AIDs)* 1. Familial Mediterranean fever (FMF) 2. Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) 3. Cryopyrin-associated periodic syndromes (CAPS) 4. Mevalonate kinase deficiency (MKD)

AOSD: Adult onset Still's disease; CMV: cytomegalovirus; EBV: Epstein-Barr virus; FUO: fever of unknown origin; HL: Hodgkin's lymphoma; NHL: non-Hodgkin's lymphoma; NIID: non-infectious inflammatory diseases.

of bacterial infections, especially sepsis, some FUO-causing diseases may also increase this protein. Among these, AOSD and DRESS (Drug reaction with Systemic Symptoms) can dramatically increase PCT values (8-11).

FUO in adults

Among the causes of FUO in adults, the so-called "big three" categories are: "infections", "non-infectious inflammatory diseases (NIID)", and "malignancies"; a fourth category, known as "miscellaneous", assembles diseases not fitting the previous categories (see Table I) (12). The rate of undiagnosed FUOs has dropped from over 75% in the 1930's to less than 10% in the 1950s. However, the rate of FUOs classified as "undiagnosed" has increased steadily over the last decade (12).

According to the trend over time of fever and acute phase reactants increment, FUO may be defined as "continuous" or "recurrent". Recurrent FUO was defined as classic FUO with fever-free intervals associated with normalisation of acute phase reactants lasting at least 2 weeks (13, 14).

Recurrent or episodic FUO is probably the most intriguing subtype of FUO and the most challenging to diagnose. A recurrent fever pattern is an independent predictive factor of missed final diagnosis, which is reached in 24-52% of recurrent FUOs *versus* 69-82% in continuous FUOs (15-20).

Recurrent FUO was responsible for around 18-42% of cases in a large series of patients with FUO (17). A large number of patients have a prolonged disease duration, which may last up to several years (17). The symptom-free period may vary from weeks to years.

The so-called "big three" categories account only for 20-30% of recurrent FUOs causes (17). Among "infections", osteomyelitis, endocarditis, infected vascular prosthesis, deep seated abscesses, prostatitis, cholangitis, mastoiditis, as well as infections by *Yersinia, Borrelia, Coxiella, Mycobacteria* (tuberculosis and non-tuberculous mycobacteria), and malaria due to *Plasmodium ovale* or *P. vivax* may present with a recurrent pattern of FUO (17). Among "malignancies", the "Pel-Ebstein fever" pattern of Hodgkin's lymphoma and Non-Hodgkin's lymphoma (21) is notorious, however colon carcinoma may also be characterised by recurrent fever (17). As far as "NIIDs" are concerned, AOSD typically shows a recurrent FUO

pattern (22, 23); Behçet's disease and inflammatory bowel disease (IBD) may also present with recurrent fever (17).
Among the fourth category "miscellaneous", recurrent FUO may be related to hypersensitivity pneumonia and lung embolism (17), and autoinflammatory disorders such as hemophagocytic lymphohistiocytosis and Schnitzler's syndrome (24-26). Finally, the hereditary periodic fever syndrome known as familial Mediterranean fever (FMF) shows a regular "periodic" succession of fever together with spikes of acute phase reactants. The diagnostic work-up of these diseases needs to include genetic tests, taking into consideration that, at least for FMF and especially in adulthood, the negativity of the available genetic tests cannot rule out the genetic disease (27-30).
In addition, the so-called "three minor categories" of FUO (factitious fever, drug-related fever, and habitual hyperthermia), are frequently forgotten by less experienced clinicians and should be considered as well as possible causes of recurrent FUOs. Since these conditions are easy to rule out, they should always be investigated before starting a classical FUO work-up (31).

Table II. Causes of fever of unknown origin (FUO) in children [modified from Antoon *et al*. 2015 (33) and Chusid 2017 (37)].

Causes of FUO in children	
Infectious Causes	Non-infectious Causes
Bacterial 1. Abscess 2. Bartonellosis 3. Brucellosis 4. Leptospirosis 5. Mastoiditis 6. Mycoplasma pneumoniae 7. Osteomyelitis 8. Pyelonephritis 9. Rat bite fever 10. Salmonellosis 11. Sinusitis 12. Tuberculosis 13. Non-tuberculous mycobacteria 14. Tularemia 15. Kingella kingae	*Oncological* 1. Leukaemia 2. Lymphoma 3. Langerhans cell histiocytosis 4. Neuroblastoma 5. Hemophagocytic lymphohistiocytosis
Viral 1. Cytomegalovirus 2. Epstein-Barr virus 3. Human immunodeficiency virus	*Inflammatory* 1. Behçet's disease 2. Inflammatory bowel disease 3. Hyperthyroidism 4. Granulomatosis (with polyangiitis) 5. Juvenile idiopathic arthritis 6. Kawasaki disease 7. Polyarteritis nodosa 8. Sarcoidosis 9. Systemic lupus erythematous (SLE) 10. Antiphospholipid antibody syndrome 11. Subacute thyroiditis
Fungal 1. Blastomycosis (non-pulmonary) 2. Histoplasmosis (disseminated) 3. Cryptosporidium	*Periodic fever* 1. Periodic fevers, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) 2. Cyclic neutropenia *Autoinflammatory diseases (AIDs)* 1. Familial Mediterranean fever (FMF) 2. Tumour necrosis factor Receptor-Associated Periodic Syndrome (TRAPS) 3. Cryopyrin-associated Periodic Syndromes (CAPS) 4. Mevalonate Kinase Deficiency (MKD) 5. Others (Deficiency of the IL-1-receptor antagonist [DIRA]; Majeed syndrome [MS]; Autoinflammation with infantile enterocolitis [AIEC]; Blau syndrome/early-onset sarcoidosis; NLRP12-associated autoinflammatory disorder; STING-associated vasculopathy with onset in infancy [SAVI])
Other 1. Leishmaniasis 2. Lymphogranuloma venereum 3. Malaria 4. Psittacosis 5. Q fever 6. Rocky Mountain spotted fever 7. Toxoplasmosis 8. Visceral larva migrans	*Other* 1. Diabetes insipidus 2. Factitious fever 3. Munchausen's syndrome by proxy 4. Familial dysautonomia 5. Pancreatitis 6. Serum sickness 7. Kikuchi-Fujimoto disease 8. Drug fever 9. Sweet syndrome

FUO in children

Paediatricians deal everyday with febrile children. Indeed, fever, defined as a rectal temperature >38.0°C (100.4°F), is one of the most common reasons for seeking medical evaluation for children and infants, and the most common cause for which children are brought to emergency departments (32). In the majority of cases the cause of fever is easily identifiable with no or few exams and appropriate treatment is straightforward (33). Nonetheless, fever in children requires special consideration and in a minority of cases the clinical picture may be complicated by its persistence in the absence of obvious causes (FUO), or by the recurrence of fever episodes (recurrent fevers). This review will focus on the latter two conditions.
An initial consideration for the discussion of fever in children is that measuring the temperature in children can be difficult, especially when they are uncooperative or restless. In addition, parents use different methods to measure temperature (34). Rectal measurement is preferred in most children, since it is more accurate than the use of peripheral thermometers (tympanic membrane, temporal artery, axillary

Table III. Approach to fever of unknown origin (FUO) in children according to history [modified from Antoon *et al*. 2015 (33), Chusid 2017 (37), and Torreggiani *et al*. 2016 (55)].

Duration and pattern of fever		
Continuous fever	Temperature remains elevated throughout the day but does not fluctuate more than 1°C in 24 hours.	Pneumonia; meningitis; urinary tract infection
Remittent fever	Temperature remains elevated throughout the day and fluctuates more than 1°C in 24 hours.	Endocarditis; Brucellosis; Typhoid infection (Wunderlich's curve)
Intermittent fever	Temperature is elevated for some hours in a day, later cycling back to normal for the remaining hours.	Tuberculosis; Malaria (Quotidian fever with a 24-hour periodicity for Plasmodium falciparum or P. knowlesi; Tertian fever with a 48-hour periodicity for P. vivax or P. ovale; Quartan fever with a 72-hour periodicity for P. malariae malaria); Systemic Juvenile Idiopathic Arthritis (sJIA).
Septic fever	Temperature remains elevated and often fluctuates up to 5°C in 24 hours.	Septicaemia
Pel-Ebstein fever	Regular alternation of high-grade fever that keeps rising and falling approximately every 7–10 days.	Hodgkin's lymphoma; infectious diseases
Relapsing fever	Recurring episodes of high fever usually lasting 3 to 7 days, followed by a few days with a normal temperature.	Louse-borne relapsing fever (Borrelia recurrentis, seen mostly in Africa and associated with poverty and crowding) and tick-borne relapsing fever (other Borrelia species such as B. hermsii, distributed worldwide).
Recurrent fever	Recurring febrile episodes usually associated with the same predictable symptoms, with seeming remission of the disease and fever-free intervals.	PFAPA syndrome; cyclic neutropenia; AIDs
Age		
Newborns	Check for relevant perinatal risk factors for Severe Bacterial Infection (SBI): maternal premature rupture of membranes >18 h for term newborns and >12 h for preterm newborns; maternal intrapartum fever >38°C; foul-smelling amniotic fluid; maternal swabs; neonatal asphyxia; prematurity (56).	
Infants 1–3 months	Remember that late-onset sepsis could occur up to 90 days of life and are acquired from the caregiving environment. Investigate about these following risk factors: prematurity; Central venous catheterisation (duration >10 days); nasal cannula or continuous positive airway pressure (CPAP) use; H 2-receptor blocker or proton pump inhibitor (PPI) use, and GI tract pathology (57).	
Children and adolescents	Investigate GI symptoms, growth failure, malnutrition, pubertal delay, and bone demineralisation: approximately 20–30% of all patients with Crohn's disease present when they are younger than 20 years of age. Also, other autoimmune diseases often start in adolescence.	
History of exposure to wild or domestic animals		
Birds	Psittacosis	
Cats	Bartonellosis, Toxoplasmosis	
Dogs	Salmonella infections	
Lizards, snakes, fish, and turtles	Salmonella infections (even without direct contact with infants and toddlers because of contamination of the child's environment with fecal material)	
Rabbits	Salmonella infections, tularemia	
Rat exposure	Rat bite fever	
Squirrels	Toxoplasmosis, Rickettsia	
Ingestion of contaminated food or water		
Unpasteurised milk and soft cheeses	Brucellosis; intestinal tuberculosis; listeriosis; Campylobacter, enteropathogenic Escherichia coli or Salmonella infections	
History of pica (ingestion of dirt)	Toxocara (visceral larva migrans) infection	
Travels: endemic countries for some pathogens		
Lyme disease	Northern hemisphere temperate regions: Europe (particularly in Slovenia, Austria, United Kingdom), North America	
Malaria	Sub-Saharan Africa, South East Asia, Central and South America	
Relapsing fever	Africa, Western United States, Mexico, Central and South America, Mediterranean region, Central Asia	
Rickettsia	Almost everywhere	
Tularemia (Francisellatularensis)	North America (USA, Canada, Mexico), Europe (Finland and Sweden) and Asia (Russian Federation, Kazakhstan, Turkmenistan)	
Visceral leishmaniasis	Indian subcontinent, East Africa, Brazil, Southern Europe	
Adopted children may have been infected before adoption in their country of origin with a variety of infectious agents including tuberculosis, human immunodeficiency virus, hepatitis B or C, or even malaria or typhoid in their country of origin (58).		

Table III. *continued*

Medication history	
Drugs	- Drug fever: common causes could be antimicrobial agents, anticonvulsants, antidepressants, antineoplastic agents, cardiovascular drugs, histamine-2 blockers, immunosuppressants, NSAIDs (33). - Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: is a rare, potentially life-threatening adverse drug reaction with cutaneous manifestations and internal organ involvement that occurs in both adults and children, 2 to 6 weeks after drug administration (see RegiSCAR criteria) (59). - Sweet syndrome (SS), an infrequent skin disease characterised by sudden onset of fever, leukocytosis, neutrophilia, and tender erythematous plaques infiltrated by neutrophils). SS presents three clinical settings: classic (or idiopathic), malignancy associated, and drug induced. In drug-induced SS, there is a temporal relation between the drug administration and the symptom development (60).
Previous abdominal or pelvic surgery, trauma or history of diverticulosis or peritonitis	Occult intra-abdominal abscess (most commonly in the subphrenic space, liver, right lower quadrant, and retroperitoneal space).
Contact with infected person	
Tuberculosis	A contact investigation should be considered if the index patient has a confirmed or suspected pulmonary, laryngeal, or pleural tuberculosis.
Suggestive case history findings	
Attack provoked by cold exposure	Familial cold autoinflammatory syndrome (FCAS)
Attack in the first year of life, typically after a childhood vaccination	Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)
Immunosuppression	
Primary immunodeficiency	When episodes became more severe in frequency and characteristics, different sets of warning signs can be used if a primary immunodeficiency (PID) is suspected. Among these, the 10 warning signs developed by the Jeffrey Modell Foundation (2009) are the most known (61).
Human Immunodeficiency virus (HIV)	Mycobacteria and cytomegalovirus are opportunistic infections in patients with HIV infection that often cause aspecific symptoms, including fever.
Leukaemia and lymphoma	Consider constitutional symptoms (as unexplained weight loss, paleness, asthenia, night sweats, itching) and intermittent fever: acute leukaemia and lymphoma are another important neoplastic group that can cause FUO.
Factitious disorders	
Factitious fever (FF)	FF is responsible for around 2.2–9.3% of FUO cases in some series: therefore, it should be suspected in school-age children and adolescents with a history of persistent fever, normal clinical and laboratory findings, prolonged absence from school, and a normal temperature when admitted to hospital (62).
Munchausen's syndrome by proxy	Of infants brought to a clinic in Australia because of serious illness, 1.5% were cases of Munchausen syndrome by proxy. Pay attention to how parents describe episodes and how many exams they have already ruled out (63).

AID: autoinflammatory disease; GI: gastrointestinal; NSAIDs: nonsteroidal anti-inflammatory drugs; PFAPA: periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis; USA: United States of America.

or oral) (34, 35), although it may be contraindicated in some conditions (*i.e.* neutropenic, oncologic or immunocompromised children) (36). It is also important to remember that, in the normal child, body temperature has a circadian rhythm, with temperature as low as 36°C in the early morning and as high as 37.5°C in the late afternoon (37). Mean basal temperature also varies according to age, gender, body habitus, time of day, activity level, menstrual cycle, and other factors (33).

Causes of FUO in children

As already introduced, FUO can be caused by a wide group of diseases, including both benign and serious conditions (see Table II). Infections are the main causes of FUO in children, accounting for 51% of cases according to data from a meta-analysis of 18 studies from industrial countries and emerging economies (38). Conversely, malignancy accounts for a higher percentage (11%) of FUOs in adults than it does in children (6%). Rheumatologic conditions (16%) are also a more important cause of fever in adults than in children (9%). It is also important to note that between 25–30% of children with FUO remain without a final diagnosis, even after a thorough work-up and after resolution of the fever (38, 39). When comparing data between developed and developing nations, infection is consistently the most common cause of FUO, but the type of infection varies; bacterial infections, and *Bartonella* infections were more commonly diagnosed in developed countries, whereas brucellosis, typhoid fever, tuberculosis, rickettsial infections, and abscesses were more common in developing nations. Viral aetiologies for FUO were more commonly identified in the developed countries, particularly *Epstein-Barr Virus* infection (38). Among the chronic inflammatory and autoimmune disorders that can present as FUO, the more common in children

Table IV. Approach to fever of unknown origin (FUO) in children according to physical examination [modified from Antoon *et al*. 2015 (33), Chusid 2017 (37), and Torreggiani *et al*. 2016 (55)].

General appearance	
Fatigue	Endocarditis; systemic JIA; oncologic diseases
Weight loss	Tuberculosis; tumours; IBD; HIV infection
Short stature	IBD; pituitary gland involvement
Skin	
Absence of sweating during fever	Dehydration due to vomiting, diarrhoea or central or nephrogenic diabetes insipidus; anhidrotic ectodermal dysplasia
Decreased body hair and hypohidrosis	Anhidrotic ectodermal dysplasia
Erythema migrans	Lyme disease
Erythema nodosum	IBD; JIA; SLE; BD; Parvovirus B19; and various infectious diseases
Eschar	Tularemia (Francisella tularensis infection)
Evanescent macular salmon-coloured rash	Systemic JIA (usually present during periods of fever elevation, lasting a few hours)
Malar erythema	SLE (malar erythema is one of the SLICC criteria for diagnosis)
Palpable purpuric lesions	Polyarteritis nodosa
Petechiae	Endocarditis; meningococcal meningitis (less commonly in children with chronic meningococcemia); viral infection; rickettsia
Rashes or fever blisters	Pneumococcal; streptococcal; malarial and rickettsial infections
Seborrheic rash	Histiocytosis
Urticarial macular rash	Serum sickness; FCAS; Muckle-Wells syndrome; neonatal-onset multisystem inflammatory disease (NOMID)
Eyes	
Conjunctivitis	Viruses (EBV, Newcastle disease, measles); Kawasaki disease; Leptospirosis; Tuberculosis; SLE
Conjunctivitis associated with fever attacks	FCAS
Ischaemic retinopathy	Polyarteritis nodosa
Periorbital oedema and conjunctivitis during flares	TRAPS
Petechial conjunctival haemorrhage	Infective endocarditis
Proptosis	Orbital tumour, thyrotoxicosis or metastasis
Retinitis	CMV infection; toxoplasmosis; syphilis
Uveitis	JIA; sarcoidosis; SLE; IBD; BD; vasculitis
Nose and oropharynx	
Abnormal pupillomotor function	Hypothalamic or autonomic dysfunction
Anomalous dentition (pointed or cone shaped teeth)	Anhidrotic Ectodermal Dysplasia
Dry eyes	Familial dysautonomia; SLE; Polyarteritis nodosa; Sjögren's syndrome
Gingival hypertrophy and oral ulcers	Langerhans cell histiocytosis (64)
Gingival hypertrophy or inflammation and loss of teeth	Leukaemia
Hyperemia of the pharynx	Infectious mononucleosis; CMV infection; toxoplasmosis; Kawasaki disease; leptospirosis
Oral ulcers	Crohn's disease; BD; Cyclic neutropenia; PFAPA; HIDS; HSV; drug fever
Pain on percussion of the sinus	Sinusitis
Purulent or persistent nasal discharge	Sinusitis
Recurrent oral candidiasis	Immunodeficiencies
Red, dry, cracked lips	Kawasaki disease
Smooth tongue devoid of fungiform papillae and taste buds	Familial dysautonomia (or Riley-Day syndrome) (65)
Ears	
Hearing impairment	CINCA
Lymph nodes and neck	
Lymphadenopathy	Tuberculosis; Non-tuberculous mycobacteria; lymphoma; leukaemia; Kawasaki disease; Kikuchi – Fujimoto disease; Bartonellosis; Tuberculosis; Lymphogranuloma venereum; HIV infection; cyclic neutropenia; PFAPA; systemic JIA; HIDS; EBV infection; FCAS
Meningeal irritation	Meningitis
Chest	
Bradycardia (due to a conduction defect)	Acute rheumatic fever; endocarditis
Dyspnea/tachypnea, abnormal breathing sounds	Pneumonia; Lung involvement of AIDs; SLE
Heart murmur	Endocarditis; Acute rheumatic fever; Pericarditis
Relative bradycardia	Brucellosis; drug fever
Abdomen and pelvis	
Abdominal pain	IBD; FMF; HIDS; TRAPS; Parvovirus B19 infection; relapsing fever
Abdominal tenderness or rigidity	Abscess; hepatitis; peritonitis
Genital ulcers	BD
Hepatomegaly	Lymphoma; metastatic carcinoma; relapsing fever; granulomatous hepatitis; hemophagocytic lymphohistiocytosis; Q fever; typhoid fever; viral infections; salmonellosis; brucellosis; bartonellosis; endocarditis; malaria; leukaemia
Liver edge tenderness	Bartonellosis; liver abscess
Splenomegaly	Systemic JIA; HIDS; FMF; TRAPS; EBV infection; relapsing fever; chronic meningococcemia; brucellosis; malaria; visceral leishmaniasis
Perirectal lymphadenopathy or tenderness at rectal examination	Deep pelvic abscess; iliac adenitis; pelvic osteomyelitis
Back and joints	
Back pain	Discitis; Osteomyelitis
Joint swelling, limited range of motion	JIA; osteomyelitis; leukaemia; systemic JIA; FMF; HIDS; TRAPS; CAPS; BD; Parvovirus B19 infection; relapsing fever; Trench fever (Bartonella Quintana infection); chronic meningococcemia; rat bite fever; brucellosis

AID: autoinflammatory disease; BD: Behçet's disease; CAPS: cryopyrin-associated periodic syndrome; CINCA: chronic infantile neurological, cutaneous, and articular syndrome; CMV: cytomegalovirus; EBV: Epstein-Barr virus; FCAS: familial cold autoinflammatory syndrome; FMF: familial Mediterranean fever; HIDS: hyperimmunoglobulinemia D with periodic fever syndrome; HIV: human immunodeficiency virus; HSV: Herpes simplex virus; IBD: inflammatory bowel disease; JIA: juvenile idiopathic arthritis; PFAPA: periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis; SLE: systemic lupus erythematosus; TRAPS: TNF receptor-associated periodic syndrome.

are IBD, and Crohn's Disease in particular. Among neoplasia, the more common causing FUO are lymphoma and leukaemia. Rheumatic conditions, such as the systemic form of juvenile idiopathic arthritis are also a possibility. There are a lot of miscellaneous and rare causes of FUO, including drug fever, dysautonomia, diabetes insipidus, ectodermal dysplasia, pulmonary embolus, and haematoma (40).

It is reassuring to observe that, in a retrospective study published in 2016, the majority of children referred to a Paediatric Infectious Disease outpatient service for unexplained fevers did not have a serious illness (41). In fact, 95% of 221 included patients had no fever, self-limited illnesses, conditions for which no specific diagnosis was made (but fevers resolved), or mild-to-moderate illnesses (which may or may not have warranted treatment). Similarly, only 1 patient in this study was diagnosed with a malignancy, in contrast to a number and variety of malignancies seen in earlier studies. This discrepancy could be secondary to the fact that most of the studies on FUO, from which epidemiological data are retrieved, are based exclusively on inpatient populations. In other words, it is very important to consider that in everyday clinical practice the presence of a child with FUO could be much less worrisome than what is known from the literature (41). One crucial point is to carefully consider the general appearance of the child presenting for FUO: the presence or absence of signs of systemic involvement and the presence or absence of "red flags" (as will be discussed later) for serious conditions should dictate the pace of further work-up (42).

Table V. Work-up of fever of unknown origin in paediatric patients.

First level work-up	
Complete blood count with differential count; peripheral blood swear	
C-reactive protein; ESR; ferritin; procalcitonin	
Renal and hepatic function tests; LDH	
Urine: routine and microscopy examination with culture	
Throat swab culture	
Mantoux intradermal or IGRA test	
Cardiologic evaluation with echocardiography	
Abdominal ultrasound	
Chest X-ray (to rule out infiltrates, effusions, or enlarged hilar lymph nodes)	
Second level/Categorical work-up	
Infectious diseases	• Specific antibody or molecular test for EBV, CMV, *Toxoplasma*, *Parvovirus*, HIV, *Salmonella, Brucella, Bartonella, Yersinia, Borrelia, Leishmania*; • Blood culture (including quantitative cultures drawn from central catheters and peripheral veins); • Stool culture; • Cerebrospinal fluid culture if indicated; • Thick and thin blood smears for malaria; • Whole-body Tc-99m MDP bone scan for suspected bone infection; • Head MRI for suspected central nervous system infections.
Oncologic diseases	• Bone marrow biopsy and aspiration when malignancy is suspected; • 24-hour urine collection for total catecholamines, vanillylmandelic acid, and metanephrines, and blood pressure/heart rate monitoring for suspected pheochromocytoma; • Uric acid for suspected leukaemia and lymphoma (consider tumour lysis syndrome); • Chest-abdomen-pelvic CT scan for suspected masses (or pyogenic collections) and related enlarged lymph nodes; • Positron emission tomography/computerised tomography (PET/CT) in order to detect neoplasms, infections and inflammation.
Autoimmune/Rheumatological disorders	• Antinuclear antibodies, extractable nuclear antigens antibodies, anti-native DNA antibodies wherever an arthritis is suspected; • C3, C4, CH50; • Thyroid function tests.
Immunodeficiency	• Immunoglobulins and lymphocyte surface marker analysis for humoral and cellular immunodeficiencies; • Consider antibody titres to known vaccinations; • Assessment of neutrophil function (e.g. Dihydrorhodamine 123).
Gastrointestinal	• Upper GI series and barium enema to detect changes or abnormalities in oesophagus, stomach, duodenum, and colon; • Bowel ultrasound for the assessment of Crohn's disease • EGD test (esophagogastroduodenoscopy) and colonoscopy with biopsies in order to detect inflammatory GI disorders; • ASCA, ANCA, LKM, ASMA antibodies for suspected inflammatory GI disorders.

ANCA: anti-neutrophil cytoplasmic antibodies; ASCA: anti-Saccharomyces cerevisiae antibodies; ASMA: anti-smooth muscle antibody; CT: computed tomography; EBV: Epstein-Barr virus; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; HIV: human immunodeficiency virus; LDH: lactate dehydrogenase; LKM: liver kidney microsome; MDP: methylene diphosphonate; MRI: Magnetic resonance imaging.

Approach to the child with FUO

As already pointed out, the first useful step in approaching a child with FUO is to try to differentiate between the "big three" categories of causes. A thorough medical history could be very useful, revealing important clues to identify the correct aetiology (see Table III). Medical history should look not only for the obvious, such as history of travel, animal contacts etc., but also to information that are often overlooked, such as how the temperature was taken, how many fever spikes the child has during the day, whether the fever spike is accompanied by signs or symptoms, etc. Frequently, an accurate history review by an experienced clinician can result in rapid diagnosis of a previously perplexing case (37). For example, a child who appears to have had an extended febrile illness may simply be experiencing a consecutive series of self-limited minor infections ("Pseudo-FUO") (42, 43). This is especially likely if the child is attending school for the first time or has older siblings who bring home infectious agents. Daycare attendance is a com-

Table VI. Non-genetic periodic fevers in children.

	Pathogenesis	Fever pattern and associated symptoms
Bacteria		
Focal occult infections	Endocarditis could be low-grade pathogen difficulty detected (such as a HACEK organism or a viridians streptococcus) (66).	Fever is often the only symptom: avoid inappropriate administration of antibiotics that can suppress bacterial growth in blood cultures.
Brucellosis	Brucellosis is caused by ingestion of unpasteurised milk or undercooked meat from infected animals, or close contact with their secretions. Only four species can cause human brucellosis: *Brucella abortus, B. melitensis, B. suis, and B. canis* (67).	*Brucella melitensis:* - Incubation period: up to many weeks; - Symptoms may be delayed for months; - High fever spikes usually occur every afternoon (68).
Relapsing fever (Borreliae)	Ticks bites may go unnoticed. *Borrelia recurrentis* is transmitted by the human body louse, *Pediculus humanus* (69).	*Borrelia recurrentis*: - Incubation period: 3–10 days; - Febrile episodes with abrupt onset and a duration of 3–5 days.
Bartonellae	Cat scratch disease is caused by *Bartonella henselae*, associated with a history of cat scratch or bite (70). Trench fever is caused by *B. quintana,* transmitted by the human body louse, *Pediculus humanus* (71).	Cat scratch disease: -Incubation period: 1–3 weeks; -Prolonged febrile episodes without other obvious symptoms in 5–10% of cases. Trench fever: - Incubation period: 2–3 weeks; - Febrile episodes with a duration of 1–3 days, associated with headache, shin pain, and dizziness that recur every 4–6 days.
Tuberculosis	Extrapulmonary diseases without clear localising features are the most frequent presentations as FUO. Bacteriological confirmation is difficult.	A disseminate form called TB sepsis (Landouzy's disease) can be fulminant or subacute: patients, frequently older children, developed several weeks of continuous fever (72).
Chronic meningococcemia	A persistent meningococcal bacteremia (mostly by serogroup B) could occur also in immunocompetent patients; it may sometimes be associated with a complement deficiency (73).	- Intermittent febrile episodes with a duration of at least 1 week, associated with migratory arthralgia and cutaneous vasculitis (erythematous macules and papules, nodules, petechiae or purpura); - During afebrile periods, the patient seems healthy. - In the initial days of the illness, bacterial cultures are frequently negative, so if clinical suspicion is high, antibiotic treatment should be initiated early.
Rat-bite fever	*Streptobacillus moniliformis* or *Spirillum minus* could be transmitted by rodents (not only bites but also by close contact, such a kiss) (74).	-Febrile episodes with headache, chills, and vomiting; on resolution of these symptoms (2-4 days), characteristic maculopapular rash and migrating polyarthralgia occur (75).
Virus		
Epstein Barr Virus (EBV)	EBV infection usually occurs within the first few years of life and does not cause clinically important illness. However, if primary infection is delayed until adolescence or beyond, it is associated with the clinical syndrome of infectious mononucleosis (76). Very rarely, patients, particularly children, suffer from severe and recurrent or persistent symptoms. These can be associated with a persistently high EBV load and a failure in the normal maturation of the antibody response. Different systemic type EBV infection-associated lymphoproliferative diseases have been reported (77).	Infectious Mononucleosis: - Incubation period: 4-7 weeks; - Febrile episodes are associated with pharyngitis, typically symmetric lymphadenopathy, and fatigue. Urticarial and maculopapular rashes are rare except among those patients given beta-lactam antibiotics erroneously, 90% of whom will develop a rash (78).
Cytomegalovirus (CMV)	The infection is usually asymptomatic in immunocompetent individuals but it can cause severe diseases in immunocompromised patients and pregnant women, inducing congenital infection (79).	In immunocompetent hosts, the most common clinical presentation is mononucleosis-like syndrome (CMV mononucleosis).
Parvovirus B19	Parvovirus B19V is transmitted mainly by the respiratory route. As infection causes acute anaemia (transient aplastic crisis) when the patient's bone marrow is susceptible because of underlying erythroid stress, anaemia is chronic (pure red blood cell aplasia) when the immune system fails to mount a neutralising antibody response (80).	Febrile episodes are associated with malaise, headache, and myalgia rather than respiratory symptoms.

Table VI. *continued*

	Pathogenesis	Fever pattern and associated symptoms
Fungi		
Histoplasmosis	Among clinical forms of *Histoplasma capsulatum* infection, a Chronic disseminated histoplasmosis has been described. Patients often experience symptoms for months before being diagnosed (81).	Fever-associated symptoms include, night sweats, weight loss, and fatigue. Hepatosplenomegaly is found in 89% of infants. Chest radiographs are characterised by lobar or diffuse infiltrates, cavitation and/or hilar adenopathy. However, a normal chest X-ray has been reported in 40% to 50% of immunocompromised patients.
Coccidioidomycosis	Coccidioidomycosis, also known as Valley fever, is an infection caused by inhalation of *Coccidioides spp*. spores (82).	The primary infection may present with fever, weight loss, sweating, cough, and chest pain. Other symptoms may include arthralgia and cutaneous manifestations, such as erythema nodosum and erythema multiforme.
Blastomycosis	Clinical characteristics of granulomatous *Blastomyces spp*. infection can include asymptomatic infection, pulmonary infection, or extrapulmonary disease (bone, genitourinary, cutaneous, and central nervous system infections) (83).	Fever and poor oral intake were more likely in patients with pulmonary infection than in those with extrapulmonary infection, respectively.
Parasites		
Malaria (*Plasmodium spp*.)	Malaria is transmitted among humans by female mosquitoes of the genus *Anopheles*: in sub-Saharan Africa, *Plasmodium falciparum* is the predominant Plasmodium species; *P. vivax* is the most prevalent outside Africa. The clinical manifestations of malaria, the severity and course of a clinical attack depends on the species and strain of the infecting plasmodium parasite and on characteristics of the child. The malaria paroxysm results from the lysis of parasitised red blood cells and release of merozoites into the circulation at the completion of asexual reproduction. Fever and chills are accompanied by constitutional symptoms, alternating with periods of fatigue but otherwise relative wellness (84).	- Quotidian fever with a 24-hour periodicity for *Plasmodium falciparum* or *P. knowlesi* malaria - Tertian fever with a 48-hour periodicity for *P. vivax* or *P. ovale* malaria - Quartan fever with a 72-hour periodicity for *P. malariae* malaria In children, symptoms are varied and often mimic other common childhood illness particularly gastroenteritis, meningitis/encephalitis, or pneumonia. Fever is the key symptom, but the characteristic regular tertian and quartan patterns are seen in <25% of children; however, children are more likely to have high fever (>40°C), which may also lead to febrile convulsions.
Visceral Leishmaniasis (VL)	*Leishmania* and *infantum donovani* infection (Kala-Azar or Black fever) is transmitted to humans by sandflies of *Phlebotomus spp*. VL manifestations are a consequence of the host immunologic response against the parasite. Splenomegaly (eventually accompanied by hepatomegaly and lymphadenopathy) is secondary to hyperplasia of the infected reticuloendothelial system. Pancytopenia can be explained by hypersplenism, hemophagocytosis, chronic inflammation, and dietary factors.	Some authors described how clinical and laboratory features of VL may clearly mimic SLE, mostly for chronic infection (85).
Oncologic diseases		
Hodgkin's lymphoma	A classic pattern of Pel-Ebstein fever is characteristic of (although not pathognomonic for) Hodgkin's lymphoma. Infectious agents need to be considered too (86).	Patient experience fevers which cyclically increase then decrease over an average period of one or two weeks (87).
Wilms' tumor (WT)	Wilms' tumor (nephroblastoma), an embryonal malignancy of the kidney, is the most common renal tumour of childhood, often diagnosed in first years of life (88).	Up to 23% of children present with fever. Most children with Wilms' tumor present with an asymptomatic palpable mass found by a parent or physician. Abdominal pain, gross haematuria, and hypertension could be frequent findings at diagnosis.
Neuroblastoma	Neuroblastoma is the third most common paediatric tumour in childhood, and 90% of cases are diagnosed by 5 years of age (89).	The clinical features of neuroblastoma are non-specific and include abdominal pain, irritability, and arthralgia. Recurrent fever with no signs of infection is another classic presentation of neuroblastoma. Affected children may present paraneoplastic syndromes as opsomyoclonus at the time of diagnosis.
Pheochromocytoma	A pheochromocytoma is a rare, catecholamine-secreting tumour that may precipitate life-threatening hypertension. The tumour is malignant in 10% of cases but may be cured completely by surgical removal (90).	Intermittent fever, chills and weight loss have been reported before the diagnosis of a pheochromocytoma by some authors (91).

Table VI. *continued*

	Pathogenesis	Fever pattern and associated symptoms
Castleman's disease	Paediatric Castleman's disease (CD) most commonly occurs in the unicentric form, which typically is asymptomatic and cured by lymph node excision, although systemic manifestations are possible. Multicentric CD (rare in paediatric populations) can progress to severe pancytopenia, multiorgan failure, or malignancy.	Diagnosis of multicentric CD should be considered in children with fever, elevated CRP, and lymphadenopathy who exhibit progression and a negative evaluation for bacterial infection, malignancy, and rheumatologic conditions (92).
Inflammatory diseases		
Inflammatory bowel diseases	Among the common causes of recurrent fever, it is important to mention Crohn's disease, especially in adolescents (93). Microcytic hypochromic anaemia and growth retardation are useful diagnostic clues (94).	In Crohn's disease, fever may precede the other typical manifestations of inflammatory bowel disease, such as abdominal discomfort or loose stools, by weeks or months.
Behçet's disease (BD)	BD is a systemic inflammatory disease with a variable vasculitis. Paediatric onset is very rare and carries a strong genetic component. An international expert consensus has recently proposed new classification criteria for children with BD: three of six items are required to classify a patient as having paediatric BD (95).	Recurrent fevers were not significantly associated with the diagnosis of BD in the cited PEDBD cohort, but they were present in 44% (68/156) of patients of the largest prospective cohort to date (95).
Systemic lupus erythematosus (SLE)	The presentation of lupus in childhood and adolescence can be quite variable, similar to that in adults with SLE. Fever is not included in latest SLICC (Systemic Lupus International Collaborating Clinics) diagnostic criteria for SLE (2012) (96). Fever could be a clinical presenting feature of childhood-onset SLE, as reported by different authors, ranging from 39% to 71% (97, 98).	Constitutional symptoms such as fatigue, fever, and weight loss are very common (99).
Systemic juvenile idiopathic arthritis (s-JIA)	Systemic juvenile idiopathic arthritis is clinically distinct from other types of JIA. Quotidian fevers are a classic feature of s-JIA, but only 64% of patients actually present with this fever pattern (100).	International League of Associations for Rheumatology (ILAR) criteria have been developed to establish the diagnosis of s-JIA: arthritis in one or more joints with or preceded by fever of at least 2-weeks duration that is documented to be daily ("quotidian") for at least 3 days and is accompanied by one or more of the following: evanescent (non-fixed) erythematous rash, generalised lymph node enlargement, hepatomegaly and/or splenomegaly, and serositis.
Kawasaki disease (KD)	Kawasaki disease must be considered in the differential diagnosis of any child with prolonged fever and compatible laboratory features, even in the absence of the classic clinical signs. Prompt therapy (a single 2 g/kg dose of intravenous gamma globulin) is required, because delayed or unrecognised KD can lead to lifelong heart disease or death in previously healthy children.	Classic clinical criteria to establish the diagnosis of KD comprehend intermittent high fever (5 days) and at least four of the following five features: (1) Bulbar conjunctival injection, generally without exudate and often with limbal sparing; (2) Oral changes: redness of the throat, strawberry tongue, redness of the lips, sometimes with bleeding or peeling of the lips; (3) Rash: erythematous maculopapular, scarlatiniform, or erythema multiforme, sometimes with marked groin erythema and desquamation; (4) Extremity changes: redness and swelling of the hands and feet during the first week; typical periungual desquamation occurs in the second or third week; (5) Cervical lymphadenopathy 1.5 cm or more in diameter (101).
Kikuchi-Fujimoto disease (KFD)	Kikuchi-Fujimoto disease or histiocytic necrotising lymphadenitis is a rare and benign cause of lymphadenopathy (102).	KFD has an acute or subacute onset, with low-grade fever, upper respiratory symptoms and a unilateral cervical lymphadenopathy of posterior cervical lymph nodes (with firm, tender or painful enlarged lymph nodes), over a period of 2–3 weeks (103).

FUO: fever of unknown origin; TB: tuberculosis; SLE: systemic lupus erythematosus.

mon cause of frequent viral infections as well as bacterial infections caused by pneumococci or *Kingella* (44).

After obtaining a complete medical history, a thorough medical examination will be done. As already pointed out, evaluation of the general appearance of the child and the presence or absence of "red flags" are crucial in deciding the intensity of further investigations. Moreover, specific signs and symptoms could suggest possible diagnoses and guide the work-up (see Table IV). The most important "red flags" for serious conditions are a miserable-looking child who refuses to play, the presence of weight lost, anorexia or asthenia, the presence of pale skin and mucous membranes, the presence of petechiae, generalised lymphadenopathy or hepatosplenomegaly, signs of dehydration, and severe bone pain. If the history and medical evaluation is reassuring, the physician could de-

cide to keep the child under observation and wait for the fever to resolve or other signs to appear. In this case, strict follow-up is warranted and asking the parents to keep a "fever diary" could be a useful tip (42). In the majority of cases, some blood-work are asked for, even in conditions that do not appear to be serious. We believe reasonable first-step laboratory investigations should include complete blood count, blood smear, ESR, CRP, kidney and liver function tests, muscle enzymes, LDH, urinalysis, and, in younger children, urine culture. Other first-level work-up should be guided by clinical suspicion and could include chest x-ray, echocardiography, abdominal ultrasound, pharyngeal swab, and urine culture (see Table V). In cases where the medical history is not reassuring or the child presents with signs or symptoms of serious condition, further work-up will be decided upon hospital admission, and guided by the main hypothesis (see Table VI).

Approach to the child with recurrent fever: when to suspect an autoinflammatory disease

Sometimes the fever becomes a clinical dilemma not because it is without an apparent cause, but for its recurrence. The sentence "my child has always fever" is one of the commonest paediatricians could hear in their routine practice. In the majority of cases, a skilled paediatrician could easily discuss this statement with the parents and demonstrate that what the child is experiencing is just the normal recurrence of infections, as expected in the paediatric age. For this purpose, it is crucial to underline again the importance of a "fever diary" and to take some time to clearly observe the evolution of the clinical picture over time, if there are no "red flags" for dangerous situations. From a practical point of view, when approaching a child with recurrent fever, it may be useful to differentiate between "periodic" and "recurrent" fevers. The term "periodic" refers to a situation where fever episodes recur very regularly and, to our knowledge, there are only two clinical entities that are true periodic fevers: cyclic neutropenia and periodic fever with aphthous stomatitis and adenitis syndrome (PFAPA) (42, 45).

In cyclic neutropenia, blood neutrophil counts reach a nadir every 21 days, resulting in fever, malaise, mouth ulcers, and bacterial infections, most commonly of the airways (otitis, pneumonia). The disease is caused by mutations in the neutrophil elastase gene (ELANE), which is inherited through an autosomal dominant pattern and leads to a reduced production and accelerated apoptosis of myeloid progenitor cells in the bone marrow. In cases of clinical suspicion, it is necessary to obtain weekly haemograms of the patient consecutively for 6 weeks, in order to document a drop in neutrophil levels. Definitive diagnosis is made by gene testing. Patients usually respond well to treatment with granulocyte colony-stimulating factor (46).

PFAPA syndrome, first described in 1987, is the most common periodic fever in children. Distinctive features of PFAPA syndrome are: the recurrence of stereotyped episodes of fever plus the typical signs of pharyngitis (almost 90% of patients), lymphadenopathy (75% of patients), and oral aphtosis (30% of patients). Other possible signs and symptoms are abdominal pain and arthralgia. The episodes are typically self-limiting and affected children show normal growth and development. The fever episodes are typically aborted by the prompt administration of steroids, the disease usually resolves spontaneously after a few years, and tonsillectomy is effective in more than 90% of children with PFAPA, while it is probably less effective in adult patients. Indeed, once believed to be an exclusively paediatric disease, it is now known that PFAPA may also affect adults (47-49). Although PFAPA was considered the only "non-monogenic periodic fever", Cheung *et al*. recently performed whole exome sequencing in 82 unrelated PFAPA patients and identified a frameshift variant in the *CARD* gene (CARD8-FS); the mutant CARD8-FS protein was unable to bind the NOD domain of the NLRP3 inflammasome (50).

After ruling out periodic fevers it is necessary to address the different causes of recurrent fevers. As for FUO, the three main categories of recurrent fevers are infections, neoplasia, and autoimmune/inflammatory. It is beyond the scope of this review to describe all these forms, which are summarised in Table VI. Once the "big three" are excluded, the physician should consider the possibility the patient has a monogenic autoinflammatory disease (AID). The characteristics of these syndromes are reviewed elsewhere in this volume. From a general point of view, the physician should be aware that AIDs with the differential of recurrent fevers have, as their most striking feature, the recurrence of stereotyped episodes of fever with variable signs of systemic and multi-organ inflammation. Once again, the identification of AIDs requires a careful evaluation of both history and clinical details and, if a monogenic AID is suspected, the next step would be to identify the most probable one. For this purpose it is important to consider:

– The family history: the possible presence of more than one affected individual within a family may be very useful in identifying the inheritance pattern. Moreover, some AIDs are more common within specific ethnicities.
– The age at onset: this is an important piece of information to rule out mevalonate kinase deficiency (MKD), since this syndrome has not been described to have an adult onset.
– The duration of the attacks: each one of the four main monogenic AIDs has a characteristic duration of fever episodes, and this information will be of much help in differentiating them.
– The free interval between the episodes: the extreme regularity of the attack is more typical for PFAPA syndrome than monogenic AIDs.
– The sign(s)/symptom(s) that recur regularly at every fever episode and possibly dominate the clinical picture: even though monogenic AIDs show a large overlap of clinical manifestations, each one of them has more specific clinical signs or symptoms (for example, monocytic fascii-

tis for TRAPS [TNF receptor-associated periodic syndrome], erysipelas-like erythema for FMF, urticaria-like rash for CAPS [cryopyrin-associated periodic syndrome], and vomiting for MKD). If at least one of these symptoms is present in the clinical picture then the clinical diagnosis may be quite straightforward.

Final confirmation will be obtained with genetic analysis. This approach is relatively easy with some clinical experience and in the case of a very typical clinical history. Unfortunately, it is not infrequent that, especially in adult patients, the disease manifests itself in oligosymptomatic forms. In such cases, the final diagnosis relies on a very high index of suspicion and may require evaluation by a physician with expertise in these diseases. One helpful measure in identifying patients with AIDs and in deciding which genetic test to run may come from two sets of published criteria, developed for children and adults, and also from the diagnostic criteria published by experts in the field (51-53).

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