Clinical Approach to Periodic Inflammation of Unknown Origin in Adults, with a Focus on the Diagnosis of Systemic Autoinflammatory Diseases

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"In most of these unknown cases, it's not that I'm completely lost. I know in a general sense that there is an inflammatory disease present. I know that there doesn't appear to be cancer in the background, or infection. I have a lengthy list of conditions that the patient does not have. But one of my most difficult tasks when I sit down with a patient at a follow-visit is to take a deep breath, adjust my glasses and admit that I don't know what's wrong." Charles Radis. The rheumatologist as detective. *The Rheumatologist*, 1 Feb 2015. Patients with periodic inflammation who remain undiagnosed after initial rational and targeted investigation pose a clinical conundrum. This editorial presents an approach to these cases and focuses on the recognition and diagnosis of systemic autoinflammatory diseases (SAIDs). This approach utilises genetic testing for SAIDs, recognising the presentations of non-genetic SAIDs, and empiric trials of therapy in suspected inflammatory disease. Ultimately, not achieving a final diagnosis is very common and the clinician's role is to help manage the uncertainty around this through support, follow-up and reassurance.

Keywords

Adult-onset Still's disease, cryopyrin-associated periodic syndrome, familial Mediterranean fever, fever of unknown origin (FUO), genetics, inflammation, inflammation of unknown origin, periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA), recurrent pericarditis, systemic autoinflammatory disease, TNF receptor-associated periodic syndrome (TRAPS)

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This editorial outlines a clinical approach to patients with periodic inflammation of unknown origin despite initial rational and targeted investigation. The focus of the editorial is on the recognition and diagnosis of systemic autoinflammatory diseases (SAIDs). Although rare, SAIDs are valuable diagnoses given they carry a risk of disease-associated damage and are often treatable. The authors are from a subspecialty clinic in London, UK, which is the national referral centre for adult SAIDs. The basis of this approach is both a review of the literature and our experience from our fever clinic to which patients are referred for the consideration of a SAID diagnosis in the setting of periodic fever and inflammation.

Periodic inflammation

Fever of unknown origin (FUO) was first defined by Petersdorf and Beeson in 1961 as a temperature greater than 38.3°C on three or more occasions which remained unexplained after one week of inpatient investigation.[1] This definition has been updated several times in the intervening years with advances in diagnostics.[2] In our clinical practice we utilize a definition that is tailored towards a higher probability of systemic autoinflammation and occult rheumatic disease. It requires a duration of six months or more in which no diagnosis has been found by rational targeted investigation. It excludes the immunocompromised patient subgroup but includes patients presenting with inflammation of unknown origin (IUO), defined as elevated serum inflammatory markers without markedly elevated temperature (Figure 1).

The main categories of diseases found to be responsible for FUO presentations in the financially privileged countries of the northern hemisphere are: infection (20%), non-infectious inflammatory diseases (NIIDs; 25%), malignancy (10%), miscellaneous (5–10%) and unknown (35–40%).[3] The major 'miscellaneous' cause is drug-associated fever, but others include obesity and liver cirrhosis.[3] The causes underlying FUO presentations have varied over time and location. Previously, infection accounted for up to 50% of FUO in financially privileged countries and still does in the developing world (primarily caused by tuberculosis). As infection has reduced as a cause in financially privileged countries, NIIDs have correspondingly become more common.[3,4] Diagnosis of an NIID is more likely with longer duration of fever/inflammation and the presence of IUO.[5]

The clinical significance of patients presenting with recurrent low-grade temperatures (≤38.2°C) without evidence of inflammation is unclear and how they should be approached is an issue for clinicians. One suggestion is to avoid extensive investigation in this group - in the absence of any potential diagnostic clues, symptoms or signs suggestive of significant systemic illness, only a complete blood count, inflammatory markers, and urinalysis are suggested, although our practice is to exclude connective tissue disease too.[2] If these are normal, the clinician must validate the reality of the patient's symptoms while reassuring them about the results of testing. Management

Figure 1: A definition of periodic inflammation of unknown origin for use in a clinic designed to diagnose systemic autoinflammatory diseases and other rheumatic conditions

Significant clinical disease with:

↑Acute Phase Response (CRP > 30 mg/L) ± Temperature ≥ 38.3°C

≥ 3 times

Duration ≥ 6 months

Non immunocompromised patient (no: neutropenia; HIV-infection; hypogammaglobulinemia or 10mg prednisone or equivalent for ≥2 weeks in prior 3 months).

Cause uncertain despite thorough history-taking, physical examination and rational directed investigation.

CRP = C reactive protein; HIV = human immunodeficiency virus.

can consist of symptom control, sympathetic holistic care and close follow up.[2]

Diagnostic process

The initial diagnostic process for periodic IUO is well described and set out in *Table 1*.[6,7] Some caveats to this process must be noted - in adults, an accurate history of fever can be hard to elicit; a focus on rigors and night sweats can improve specificity. Conversely, in very long-standing IUO, individuals may have 'hardened' to their symptoms and minimize the impact, resulting in low sensitivity on screening questioning. In the authors' experience, an example of this is the diagnosis of parents with autosomal dominant SAIDs only after their children have presented. Any concerns in an infection history should prompt referral for specialist input. It is also worth noting that the descriptions of classical rashes are based upon their appearance in Caucasians and may present differently or be absent in persons of colour.

A trial of cessation of any potential culprit medications for drug-induced fever is advisable. Drug-induced fevers have a median onset of 7–10 days post medication commencement, but there can be very marked variation in timing. Some of the common culprit medications are antibiotics (beta-lactams and sulphonamides), allopurinol, anticonvulsants (phenytoin and carbamazepine), antiarrhythmics (procainamide and quinidine), and antineoplastic agents.[8]

FDG-PET/CT is now established as the advanced imaging modality of choice for FUO, and is often utilised by our clinic.[9] In a meta-analysis, FDG-PET/CT had high sensitivity (83%) and moderate specificity (64%) for identifying the underlying diagnoses causing FUO.[3] The diagnostic yield of 54% indicates that over half of the patients undiagnosed following initial investigation were guided to a final diagnosis by FDG-P ET/CT.[3] Biopsy is indicated only when targeted by potential diagnostic clues. Protocol bone marrow biopsies have a low diagnostic pick up rate and are not recommended unless specifically looking for a haematological malignancy or myelodysplasia, or investigating an infectious disease which resides in bone marrow.[10]

Our practice is to collect serial fortnightly inflammatory markers, C reactive protein and serum amyloid A, over at least 3 months in all patients with IUO. These specific markers are preferred due to their short half-lives and rapid response to the presence or removal of inflammation.[11] It is our experience that in patients with isolated fever, persistently normal inflammatory m arkers c an provide u seful r eassurance, and in patients with episodic inflammation, serial bloods are more informative than isolated clinic blood draws. Certain patterns of inflammation, as described in *Figure 2*, can aid diagnosis.

SAID remains a rare cause of IOU, but SAIDs are extremely high-value diagnoses because they carry risks of disease-associated damage if untreated and are often amenable to effective long-term therapy. There are published criteria to guide the decision to order genetic testing for SAIDs.[12–15] Using classification criteria prior to genetic testing allows the selection of the simplest genetic test available to answer the specific clinical question and can support interpretation of equivocal results. Our practice is to use a next-generation sequencing (NGS) panel of 24 selected SAID genes in all patients with IUO except in those where there is a clinical suspicion for a distinct single SAID, such as familial Mediterranean fever (FMF), where single-gene Sanger sequencing is used.[16] Our real-world experience has been that the NGS panel returns a variant of uncertain significant in 60% of patients.

When diagnostic work-up fails, there is a role for research-led investigation of individuals or families in whom there is a high suspicion of SAID. This can involve techniques such as whole exome sequencing, whole genome sequencing and cytokine panels.[15] The description of VEXAS (vacuoles, E1 enzyme, x-linked, autoinflammatory, somatic) syndrome is an example of this process - a research-based theory regarding the likely pathogenic outcome of somatic mutations in the *UBA1* gene was applied to the genetic data of many patients with unspecified inflammatory disease. Through this genotype-driven approach, a clinical phenotype was identified.[17]

High-value non-SAID diagnoses

In our experience, the malignancies which most closely mimic SAIDs and can evade early detection are Castleman's Disease, Hodgkins and non-Hodgkins lymphomas, and renal cell carcinoma. These have all been associated with elevated levels of interleukin (IL)-6, and this may be the driver of their febrile presentation.[18] Clinicians are understandably concerned about possible aggressive malignancies, such as acute leukaemia or high-grade lymphomas; however, these usually present with a rapid trajectory and with several diagnostic clues which lead to accurate diagnosis.[19]

The most common NIID diagnoses for IUO are: adult-onset Still' disease (AOSD) (20%), large vessel vasculitis (10%), systemic lupus erythematosus (10%), anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (7%), and polymyalgia rheumatica (7%).[5] An index of suspicion must be maintained for atypical infections and for uncommon presentations of

Table 1: Initial 'classical' diagnostic process for periodic inflammation[6,7]

History			
Features/symptoms	**Risk factors**	**Family history**	**Targeted history for occult cases**
Duration	Drug history	Suggestive features of hereditary disease	Atypical and occult infections
Age at onset	Travel history	Ethnicity	Occult NIIDs: LVV, PMR, SLE
Precipitating event	Sexual history	Consanguinity	Serositic diseases
Constitutional symptoms: fever, rigors, weightloss, night sweats	Occupation		IBD
Lymphoreticular symptoms: adenopathy, tonsillitis	Hobbies		Sacroiliitis
Mucocutaneous symptoms: rash, ulcers, lesions	Vaccination history		Features of endometriosis
Musculoskeletal symptoms: arthritis, arthralgia, myalgia	Antimicrobial history		
Serosal symptoms: pericarditis, pleuritis, abdominal	Immunosuppresive history		
Luminal GI symptoms: inflammatory diarrhoea			
CNS symptoms: sensorineural hearing loss			

Physical Examination	
Purpose	**Specific systems and signs often missed**
Looking for pathognomonic signs	Full skin examination for rash
To direct further targeted investigations	Examination of mucus membranes, mouth and tonsils
	Palpation of lymph nodes
	Palpation for organomegaly
	Eye examination with fundoscopy

Investigations		
Obligatory tests	**Additional tests worth considering**	**Cardiovascular risk factors**
ESR	Procalcitonin	BP
CRP	Serum ACE	Lipid profile
FBC and differential	TFTs, FSH, LH	Folate
Creatinine, electrolytes, total protein	Cryoglobulins	
ALP, AST, ALT, LDH, CK	Fuller auto antibody screen	
ANA, RF	C3 and C4	
Protein electrophoresis	ASOT	
Ferritin		
Three blood cultures, urine culture		
TB testing		
Microscopic urinalysis		
CXR, abdominal ultrasonography		

ACE = angiotensin conversion enzyme; ALP = alkaline phosphatase; ALT = alanine transaminase; ANA = anti nuclear antibody; ASOT = anti-streptolysin O titre; AST = aspartate transaminase; BP = blood pressure; C3 = complement 3; C4 = complement 4; CK = creatine kinase; CNS = central nervous system; CRP = C reactive protein; CXR = chest X-ray; ESR = erythrocyte sedimentation rate; FBC = full blood count; FSH = follicle-stimulating hormone; GI = gastrointestinal; IBD = inflammatory bowel disease; LDH = lactate dehydrogenase; LH = luteinising hormone; LVV = large vessel vasculitis; MSK = musculoskeletal; NIIDs = non-infectious inflammatory diseases; PMR = polymyalgia rheumatica; RF = rheumatoid factor; SLE = systemic lupus erythematosus; TB = tuberculosis; TFTs = thyroid function tests.

the more common NIIDs, such as occult inflammatory bowel diseases and sacroiliitis.

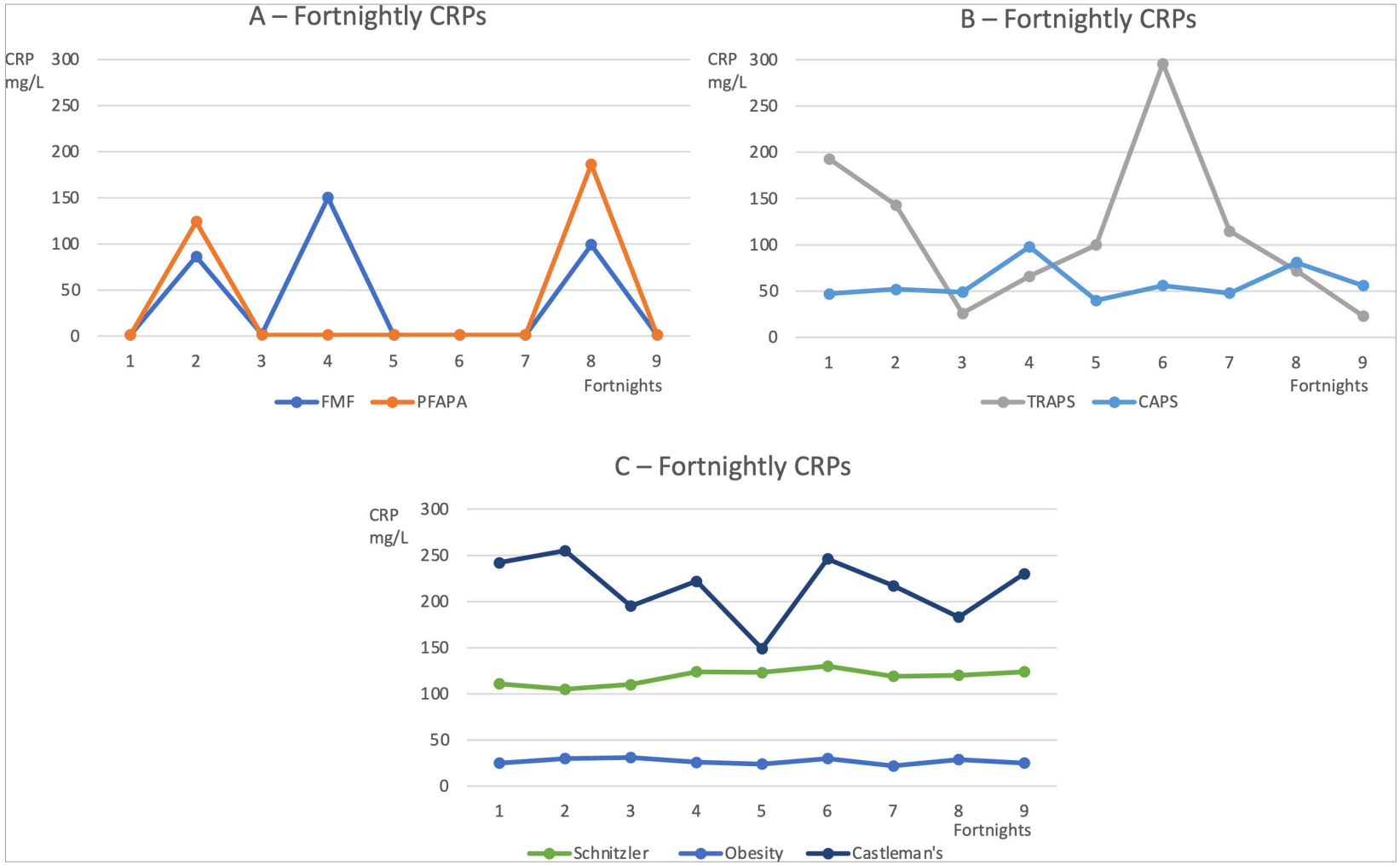
Systemic autoinflammatory diseases

In 2017, of 273 new referrals at our national referral clinic for adult SAID, 25% received a diagnosis of a monogenic SAID, primarily FMF, cryopryrin-associated periodic syndrome (CAPS) and tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS). Most of these patients had life-long disease and missed diagnoses in childhood. A minority had adult-onset disease due to milder late-onset symptoms or somatic mosaicism. The recent discovery of VEXAS syndrome has now broadened the scope of adult-onset monogenic SAID.[17]

Of our patients, 12% received a diagnosis of a specific non-monogenic SAID: either AOSD, Schnitzler syndrome, PFAPA (periodic fever, aphthous ulcers, pharyngitis and adenopathy), or idiopathic recurrent pericarditis (IRP). These are high-value diagnoses as they have effective therapies available, as outlined in *Table 2*.[20–22] A further 13% had a suspected SAID, but no specific diagnosis and were classed as undifferentiated SAID (USAID). There is a recognition that these non-genetic diagnoses are useful groupings for guiding management, but may in turn prove to be incorrect as we gain more knowledge.

The authors' opinion is that a trial of therapy is warranted for suspected SAID, but this relies upon a robust predefinition agreed upon by the

Figure 2: Characteristic patterns of inflammation from fortnightly CRP measurement



Example animations of common patterns of inflammation. (a) – periodic inflammation with complete normalization in between attacks. Seen in milder FMF and in PFAPA. (b) – Persistent inflammation with flares. Seen in TRAPS, and, to a lower extent, in CAPS. (c) – Fixed inflammation. High-grade fixed inflammation in Castleman's disease and to a less severe extent in Schnitzler syndrome. Low-grade fixed inflammation in obesity.
CAPS = cryopryrin associated periodic syndrome; CRP = C-reactive protein; FMF = familial Mediterranean fever; PFAPA = periodic fever, aphthous ulcers, pharyngitis and adenopathy; TNF = tumour necrosis factor; TRAPS = TNF-receptor associated periodic fever syndrome.

Table 2: High-value non-genetic systemic autoinflammatory disease diagnoses with effective therapy available

Disease	Onset	Diagnostic clues	Treatment
AOSD	Adult (sJIA in children)	Yamaguchi criteria[20]:*	Anti IL-1
		Major criteria:	Corticosteroids
		Fever ≥39°C (≥1 week)	NSAIDs
		Arthralgia (≥2 weeks)	
		Typical rash	
		Leukocytosis (≥10,000 /mm^3) with ≥80 % granulocytes	
		Minor criteria:	
		Sore throat	
		Lymphadenopathy and/or splenomegaly	
		Liver dysfunction	
		Negative RF and ANA	
		Exclusion criteria: infections, malignancy, rheumatic diseases	
		Diagnosis:≥5 criteria, including ≥2 major criteria	
PFAPA	Most commonly children ages 1-4 years, some adult onset	Periodic fever: usually lasts 3-5 days and predictably repeats every 3-4 weeks	Colchicine
		Aphthous ulcers: small, shallow and usually resolve quickly	Stat. prednisolone
		Pharyngitis: with or without exudate	Tonsillectomy
		Adenopathy: usually cervical and short lived	
		Arthralgia very frequent	
		Not all features present in one attack, but all occur over disease course	
Schnitzler Syndrome	Adult	Strasbourg criteria[21]:	Anti IL-1
		Urticarial rash, monoclonal IgM component, and ≥2 of the following:	
		Fever	
		Arthralgia/arthritis	
		Bone pain	
		Palpable lymph nodes and/or liver or spleen enlargement	
		Elevated erythrocyte sedimentation rate	
		Leukocytosis	
		Abnormal findings on bone morphologic investigations	
IRP	Any age	European Society of Cardiology criteria[22]:	Colchicine
		≥2 episodes of pericarditis with at least a 4-6 week symptom-free interval	Anti IL-1
		Episode must be confirmed by presence of ≥2 of the following:	NSAIDs
		Chest pain, pericardial rub, consistent ECG changes, new or worsening pericardial effusion.	
		Supportive features: elevated inflammatory markers, CT/MRI support	
		Exclusion criteria: infection, malignancy, rheumatic disease, cardiac trauma	

**Note there are other diagnostic criteria available for AOSD, however these are the most commonly used/recognised criteria.*
ANA = anti nuclear antibody; AOSD = adult-onset Still disease; ECG = electrocardiogram; IgM = immunoglobulin M; IL-1 = interleukin 1; IRP = idiopathic recurrent pericarditis; NSAIDs = non-steroidal anti-inflammatory drugs; PFAPA = periodic fever, aphthous ulcers, pharyngitis and adenopathy; RF = rheumatoid factor; sJIA = systemic juvenile idiopathic arthritis; Stat = statim.

clinician and the patient as to what constitutes clinical success and when ineffective treatments should be stopped. Caution should be taken with corticosteroids as the risk of iatrogenic harm is high. Our first-line choice is a trial of therapeutic dose colchicine as outlined in Figure 3. Anti IL-1 biological treatments can also be very effective, if they are able to be accessed.

A baseline review of cardiovascular disease (CVD) risk factors should be sought and actively managed in all individuals with prolonged inflammation.[23] CVD is a leading cause of mortality and morbidity in many inflammatory conditions.

No diagnosis

In up to 50% of patients with periodic inflammation, no diagnosis is made.[7] In these cases, invasive tests and radiation-based imaging should not be repeated unless new diagnostic clues emerge, or the patient deteriorates. Stable patients have a good prognosis and should be reassured and NSAIDs can be used for symptom control. Mortality rates are extremely low and up to 95% will experience spontaneous resolution of fevers over extended follow-up.[24,25]

Conclusions

Patients with periodic inflammation who have not been diagnosed by an initial rational and targeted investigation process pose a clinical conundrum. In this article, we have set out our approach to these patients, with a focus upon how to diagnose SAIDs. This approach involves seeking high-value diagnoses via genetic testing and recognition of specific non-genetic SAIDs. Empiric trials of therapy are warranted when SAIDs are suspected but not confirmed. Not achieving a final diagnosis is very common, and the clinician's role is to help manage the uncertainty around this. ❑

Figure 3: Authors' recommendations for trials of therapeutic dose colchicine

Starting doses
children under 6 years 250mcg od, over 6 years 500mcg od

Weaning up
Adults: increase by 500mcg/week up to 1.5 to 2 mg od
Children: if no response by 3 weeks, wean up by 250mcg/month - max 1.5mg

Simple regime
Always once daily, always same dose, always used as prophylaxis

Potential interactions
PGP inhibitors: clarithromycin, erythromycin, cyclosporine, verapamil
CYP3A4 inhibitors: statins– best options fluvastatin or pravastin

Blood monitoring
FBC, EUC, LFT at 3 months, 6 months, and then annually

Side effects
Upper GI upset and diarrhoea at initiation –if high-risk put on lactose free diet
Transaminases may reach 2 X ULN – non-progressive, non-harmful
If hair thinning – suggest a general multi vitamin

Stress child-proof packing and avoiding overdose

A trial of therapy requires 6 weeks at a full therapeutic dose

Colchicine intolerance/resistance
Up to 5%

OD = once daily; PGP = P glycoprotein; CYP = cytochrome P450; FBC = full blood count; EUC = electrolytes, urea and creatinine; LFT = liver function tests; GI = gastrointestinal; ULN = upper limit of normal.

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: Report on 100 cases. *Medicine (Baltimore)*. 1961;40:1–30. DOI: 10.1097/00005792-196102000-00001.
2. Ginier-Gillet M, Esparcieux A. Habitual hyperthermia: An interpretive paradigm of the 20th century? Not really. *Int J Gen Med*. 2021;14:2063–8. DOI: 10.2147/IJGM.S306423.
3. Minamimoto R. Optimal use of the FDG-PET/CT in the diagnostic process of fever of unknown origin (FUO): A comprehensive review. *Jpn J Radiol*. 2022;40:1121–37. DOI: 10.1007/s11604-022-01306-w.
4. Fusco FM, Pisapia R, Nardiello S, et al. Fever of unknown origin (FUO): Which are the factors influencing the final diagnosis? A 2005–2015 systematic review. *BMC Infect Dis*. 2019;19:653. DOI: 10.1186/s12879-019-4285-8.
5. Betrains A, Moreel L, De Langhe E, et al. Rheumatic disorders among patients with fever of unknown origin: A systematic review and meta-analysis. *Semin Arthritis Rheum*. 2022;56:152066. DOI: 10.1016/j.semarthrit.2022.152066.
6. Cunha BA, Lortholary O, Cunha CB. Fever of unknown origin: A clinical approach. *Am J Med*. 2015;128:1138e1–15. DOI: 10.1016/j.amjmed.2015.06.001.
7. Bleeker-Rovers CP, Vos FJ, de Kleijn EMHA, et al. A prospective multicenter study on fever of unknown origin: The yield of a structured diagnostic protocol. *Medicine (Baltimore)*. 2007;86:26–38. DOI: 10.1097/MD.0b013e31802fe858.
8. Patel RA, Gallagher JC. Drug fever. *Pharmacotherapy*. 2010;30:57–69. DOI: 10.1592/phco.30.1.57.
9. Kouijzer IJE, Bleeker-Rovers CP, Oyen WJG. FDG-PET in fever of unknown origin. *Semin Nucl Med*. 2013;43:333–9. DOI: 10.1053/j.semnuclmed.2013.04.005.
10. Sharvit G, Schwartz D, Heering G, et al. Evaluation of the clinical impact of bone marrow cultures in current medical practice. *Sci Rep*. 2022;12:9664. DOI: 10.1038/s41598-022-14059-3.
11. Epstein FH, Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med*. 1999;340:448–54. DOI: 10.1056/NEJM199902113400607.
12. Gattorno M, Hofer M, Federici S, et al. Classification criteria for autoinflammatory recurrent fevers. *Ann Rheum Dis*. 2019;78:1025–32. DOI: 10.1136/annrheumdis-2019-215048.
13. Romano M, Arici ZS, Piskin D, et al. The 2021 EULAR/American College of Rheumatology points to consider for diagnosis, management and monitoring of the interleukin-1 mediated autoinflammatory diseases: Cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist. *Ann Rheum Dis*. 2022;81:907–21. DOI: 10.1136/annrheumdis-2021-221801.
14. Hansmann S, Lainka E, Horneff G, et al. Consensus protocols for the diagnosis and management of the hereditary autoinflammatory syndromes CAPS, TRAPS and MKD/HIDS: A German PRO-KIND initiative. *Pediatr Rheumatol Online*. 2020;18:17. DOI: 10.1186/s12969-020-0409-3.
15. Shinar Y, Ceccherini I, Rowczenio D, et al. ISSAID/EMQN best practice guidelines for the genetic diagnosis of monogenic autoinflammatory diseases in the next-generation sequencing era. *Clin Chem*. 2020;66:525–36. DOI: 10.1093/clinchem/hvaa024.
16. Puzriakova A, Freimane L. Genomics England Panelapp. Autoinflammatory Disorders (Version 1.11). 2022. Available at: https://panelapp.genomicsengland.co.uk/panels/1075/ (Date last accessed: 2 October 2023).
17. Beck DB, Ferrada MA, Sikora KA, et al. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. *N Engl J Med*. 2020;383:2628–38. DOI: 10.1056/NEJMoa2026834.
18. Foggo V, Cavenagh J. Malignant causes of fever of unknown origin. *Clin Med (Lond)*. 2015;15:292–4. DOI: 10.7861/clinmedicine.15-3-292.
19. Sehn LH, Salles G. Diffuse large B-cell lymphoma. *N Engl J Med*. 2021;384:842–58. DOI: 10.1056/NEJMra2027612.
20. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. *J Rheumatol*. 1992;19:424–30.
21. Lipsker D, Veran Y, Grunenberger F, et al. The Schnitzler syndrome. Four new cases and review of the literature. *Medicine (Baltimore)*. 2001;80:37–44. DOI: 10.1097/00005792-200101000-00004.
22. Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *Eur Hear J*. 2015;36:2921–64.
23. Nurmohamed MT, Heslinga M, Kitas GD. Cardiovascular comorbidity in rheumatic diseases. *Nat Rev Rheumatol*. 2015;11:693–704. DOI: 10.1038/nrrheum.2015.112.
24. Harada Y, Masuda M, Hirosawa T, et al. Safety and efficacy of outpatient follow-up for referred patients with undiagnosed fever. *Medicine (Baltimore)*. 2020;99:e18532. DOI: 10.1097/MD.0000000000018532.
25. Vanderschueren S, Eyckmans T, De Munter P, Knockaert D. Mortality in patients presenting with fever of unknown origin. *Acta Clin Belg*. 2014;69:12–6. DOI: 10.1179/0001551213Z.0000000005.