Table 1: Initial 'classical' diagnostic process for periodic in□ammation[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.

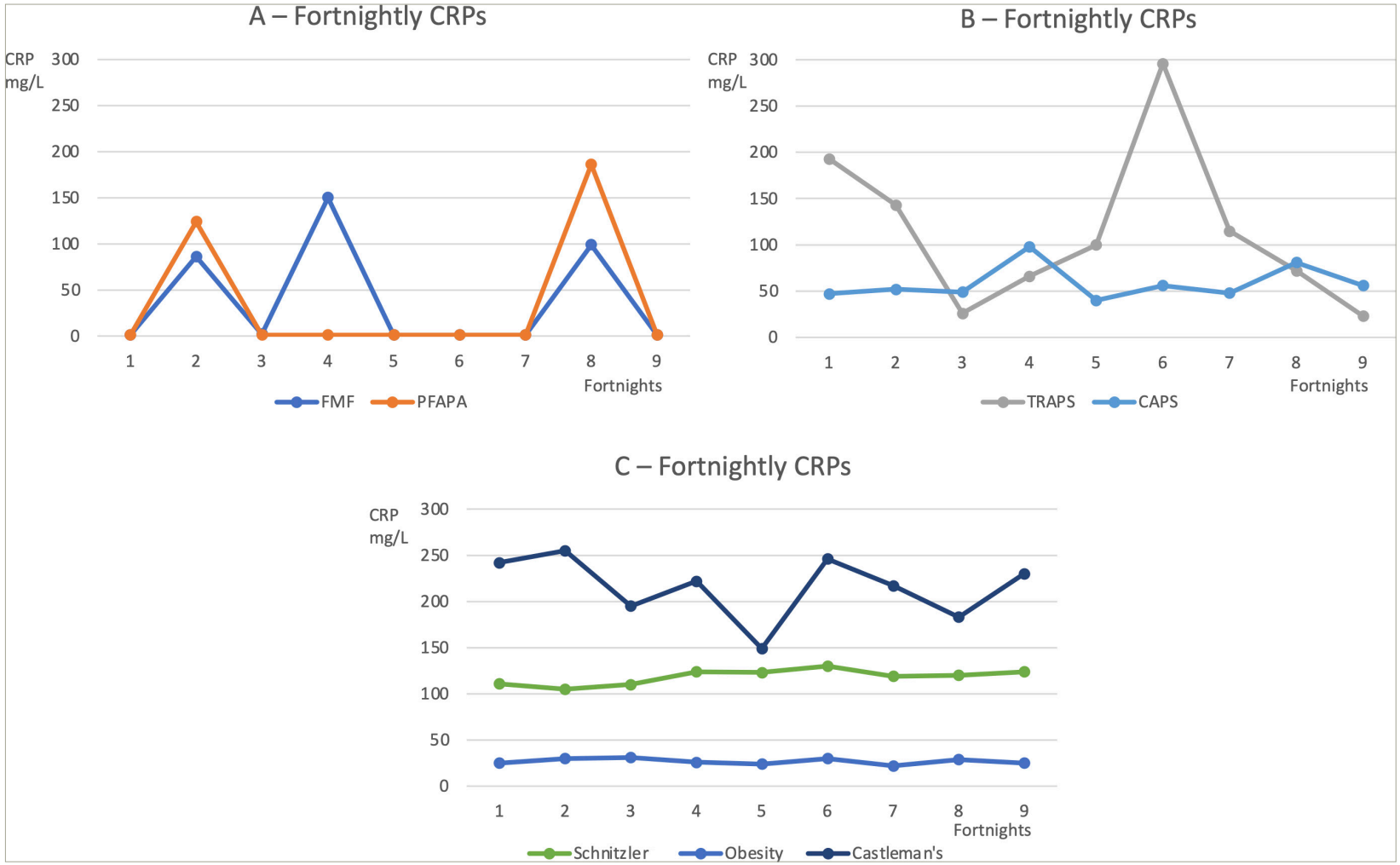
Systemic autoinflammatory diseases

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.

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