Macrophage Activation Syndrome (MAS)

Labs	• Very high ferritin levels • High LDH • Normal CRP • Elevated TGs and high AST/ALT
Natural History	High mortality rate (~25%) if not treated quickly
Treatment	• High dose steroids • IVIG • Cyclosporine • Anakinra

Autoinflammatory Diseases & Periodic Fever Syndromes

Presentation	• ≥3 recurrent episodes of unexplained fever in a 6 month period, w/ each episode occurring at least 7 days apart (some autoimmune disorders do not present w/ fever; see below) • Recurrent episodes of inflammation (rash, serositis, arthritis, meningitis, uveitis) • LAD + splenomegaly • Elevated ESR/CRP • NO high-titer autoantibodies
Pathology	• Aberrant antigen dependent activation of the innate immune system (vs. adaptive immune dysfunction in autoimmune dz) • Equally common in M and F

Most Commonly Described Periodic Fevers	• Familial Mediterranean Fever (FMF)
	• TNF Receptor-associated Periodic Syndrome (Hibernian Fever)
	• Hyper IgD Syndrome (HIDS)
	• Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis (PFAPA)
	• Cryopyrin-Associated Periodic Syndromes (CAPS) include:
	  ▪ Familial Cold Autoinflammatory Syndrome (FCAS)
	  ▪ Muckle-Wells Syndrome (MWS)
	  ▪ Chronic Infantile Neurologic Cutaneous & Articular syndrome or Neonatal Onset Multisystem Inflammatory Disorder (CINA/NOMID)

Periodic Fever Syndromes

	FMF	TRAPS	HIDS	MWS	CINCA/NOMID	PFAPA
Inheritance	AR	AD	AR	AD	AD/sporadic	Sporadic
Protein Defect	Pyrin	TNF receptor	Mevalonate kinase	Cryopyrin	Cryopyrin	Unknown
Ethnicity	Jewish, Turkish, Italian, Arab	Any	Dutch, French	Northern European	Any	Any
Duration	1-3 days	>7-14 days	3-7 days	2-3 days	Continuous w/ flairs	3-4 days
Interval Between Events	Variable	Variable (days- wks)	Fixed (4-8 wks)	Variable URI trigger	N/A	Fixed (2-8 wks)
Age of Onset	School age	School age	Infancy	School age	School age	Early adulthood

Autoinflammatory Diseases & Periodic Fever Syndromes

Periodic Fever Syndromes

	FMF	TRAPS	HIDS	MWS	CINCA/ NOMID	PFAPA
Clinical	Serositis-, Peritonitis -, Erysipelas-like lesions	Conjunctivitis Painful skin lesions Migratory myalgias	Cerebellar atrophy Painful cervical LAD	Sensorineural hearing loss Conjunctivitis	Saddle nose Rec. aseptic meningitis Mental retardation	Multiple fever spikes per a day
Notes	Most common inherited PFS	Increased risk of vasculitis (HSP)	May last through adulthood	Occasionally assoc. W/ Amyloidosis	Improved w/ IL-1 antagonist	Possibly cured w/ tonsillectomy
Treatment	Colchicine	Steroids Etanercept	Colchicine Steroids	IL-1 Antag	IL-1 Antag	Tonsillectomy

Autoinflammatory Disorders W/O Fever	• Deficiency of the interleukin-1 receptor antagonist (DIRA) • Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) • Juvenile systemic granulomatosis (Blau Syndrome) • Chronic atypical neutrophilic dermatitis w/ lipodystrophy and elevated temperature (CANDLE) • Chronic recurrent multifocal osteomyelitis (CRMO) • Stimulator of interferon genes (STING)-associated vasculopathy w/ onset in infancy (SAVI) • Congenital sideroblastic anemia w/ immunodeficiency, fevers, and developmental delay (SFID)
Differential	Must also consider recurrent infections, malignancies, cyclic neutropenia and systemic onset JRA when evaluating a patient w/ recurrent fevers
Diagnosis	Careful H&P (r/o malignancy, infection, cyclic neutropenia, systemic onset JRA) → may confirm w/targeted genetic testing