Periodic Fever and Recurrent Fever Syndromes

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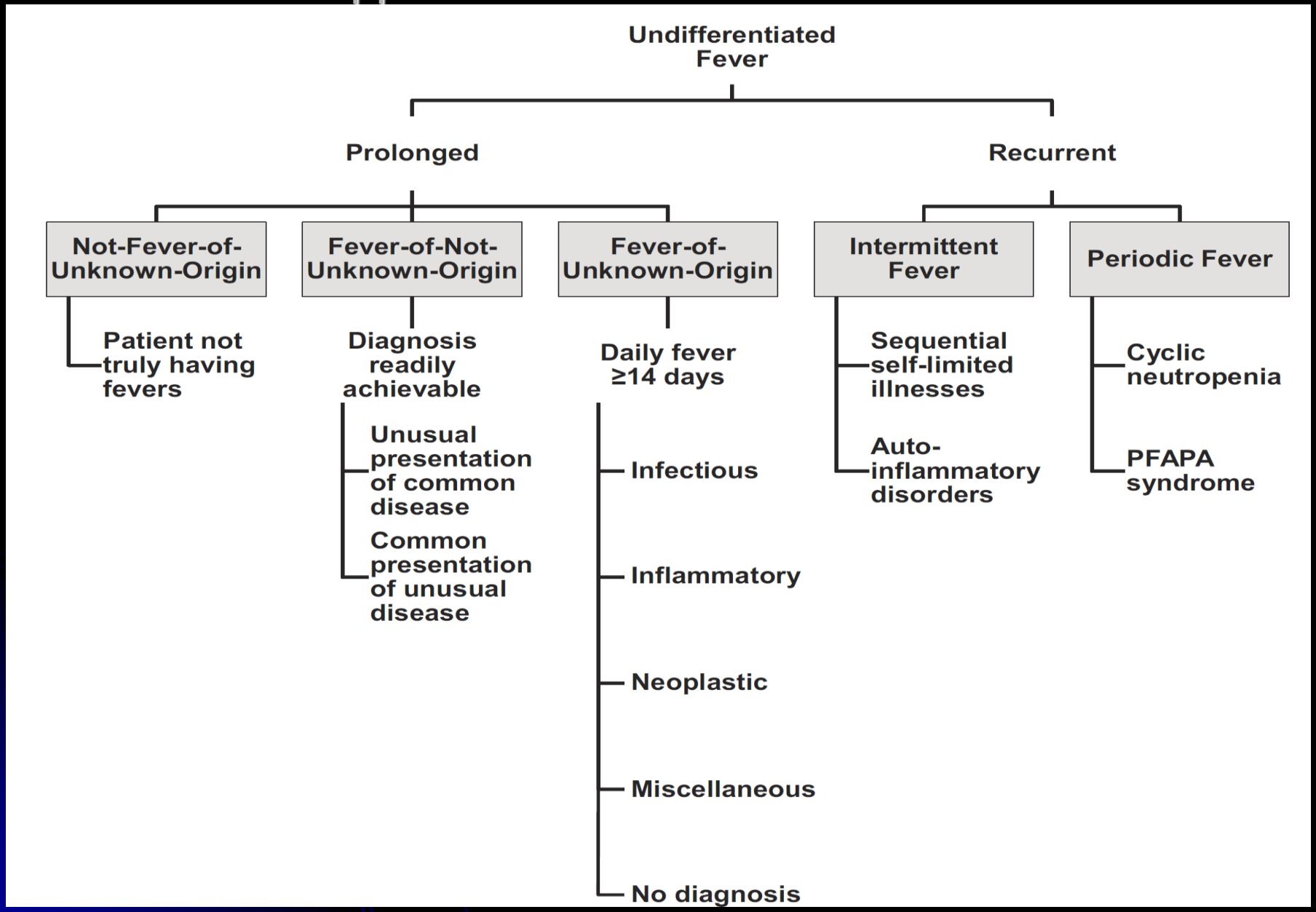
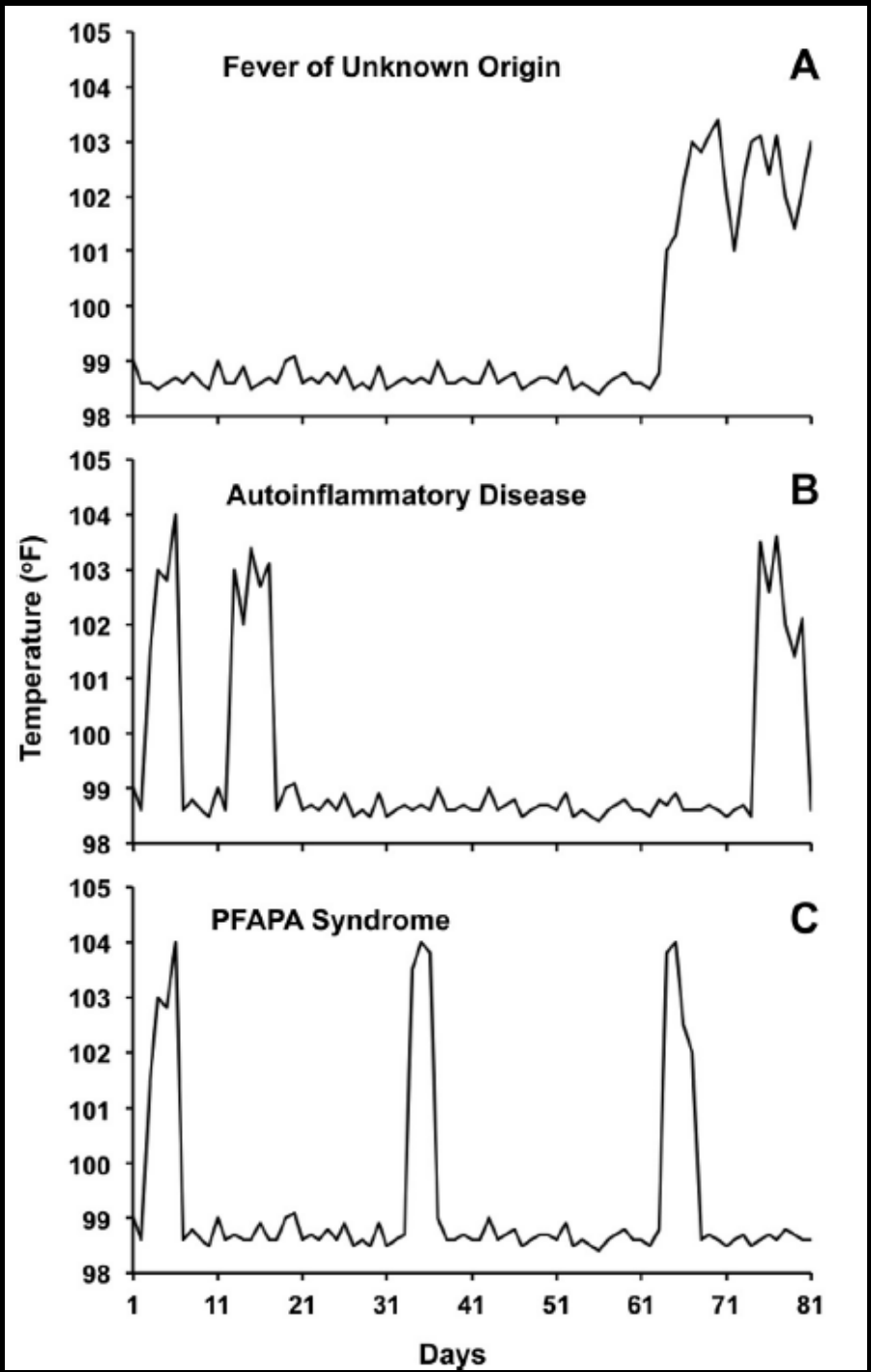
Approach to Undifferentiated Fever



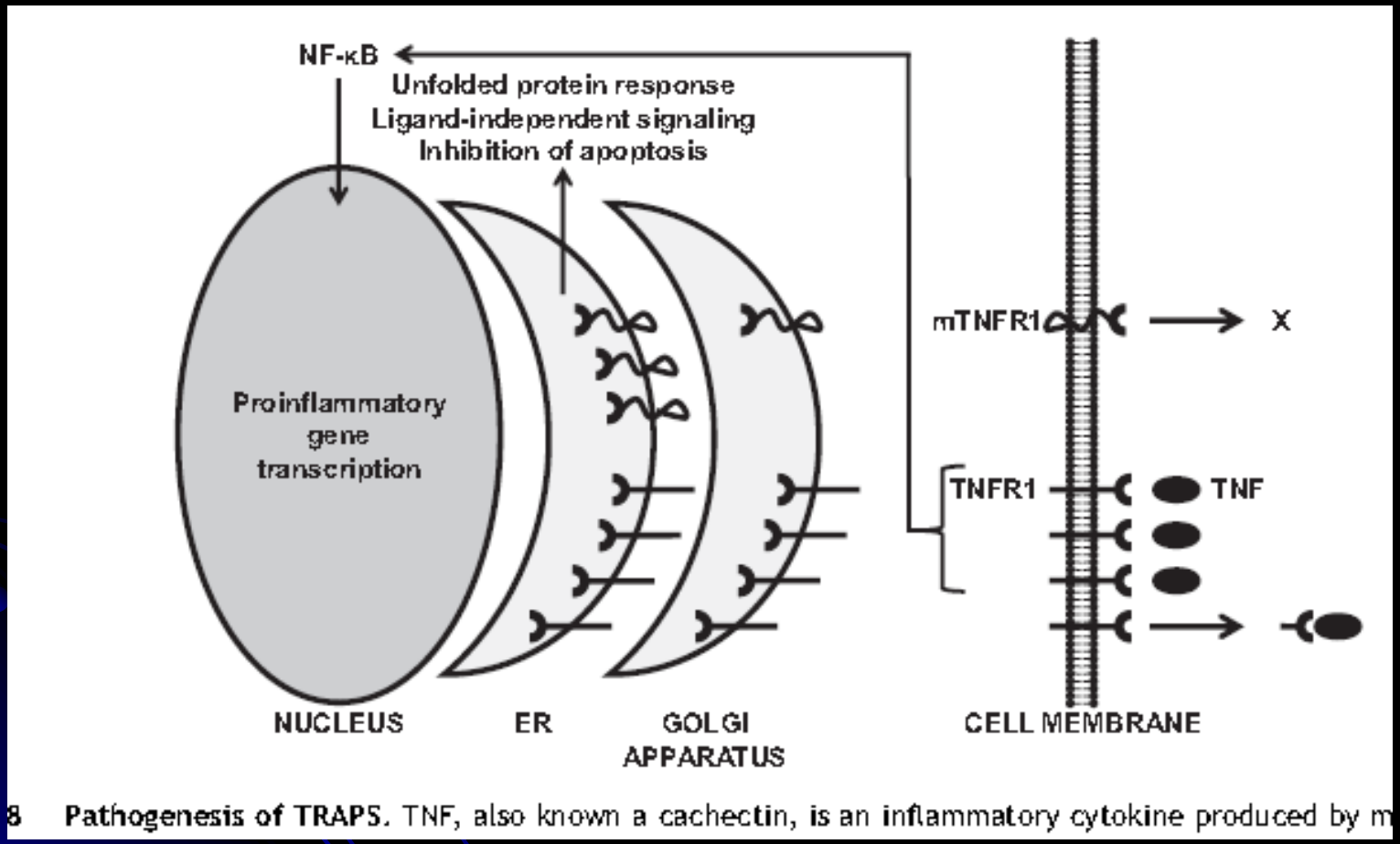
Marshall GS. Prolonged and recurrent fevers in children. J of Infection 2014;68:S83-S93

Fever Patterns



Prolonged and recurrent fevers in children. Marshall GS. J of Infection 2014:68;S83-S93

traps



8 **Pathogenesis of TRAPS.** TNF, also known a cachectin, is an inflammatory cytokine produced by m

Prolonged and recurrent fevers in children.
Marshall GS. J of Infection 2014:68;S83

Table 3 Autoinflammatory diseases.[a]

Feature	Inflammasomopathies					Protein folding disorder
	Intrinsic (Cryopyrin-associated)			Extrinsic		
	FCAS	MWS	NOMID	FMF	HIGDS	TRAPS
Synonyms	FCUS	—	CINCA	—	MKD Etiocholanolone fever	Hibernian fever
Gene defect	*NLRP3*	*NLRP3*	*NLRP3*	*MEFV*	*MVK*	*TNFRSF1A*
Inheritance pattern	Autosomal dominant	Autosomal dominant	Sporadic	Autosomal recessive	Autosomal recessive	Autosomal dominant
Ethnicity	European	European	Any	Mediterranean	European	European
Age at onset	<1 year	<20 years	<1 year	<20 years	<1 year	<20 years
Frequency of attacks	Variable	Variable	Continuous	Variable	2—4 weeks	Variable
Duration of attacks	1—2 days	2—3 days	Continuous	1—3 days	3—7 days	>7 days
Clinical findings	Rash Conjunctivitis Headache Nausea	Rash Conjunctivitis Deafness	Rash Meningitis Arthropathy Deafness Adenopathy Hepatomegaly Splenomegaly	Serositis Splenomegaly Erysipeloid erythema	Rash Adenopathy Serositis Vomiting Diarrhea Arthralgia Headache	Rash Arthritis Conjunctivitis Splenomegaly
Amyloidosis	No	Yes	No	Yes	No	Yes
Treatment modalities	Anti-IL-1	Anti-IL-1	Anti-IL-1	Colchicine	Anti-IL-1 Anti-TNF	Anti-IL-1 Anti-TNF

Prolonged and recurrent fevers in children.
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Table 1
Mechanisms of disease in autoinflammatory syndromes

Mechanism/Pathway	Syndrome	Treatment
IL-1	FMF CAPS PAPA DIRA *NLRP12* MVK	Colchicine/IL-1 inhibitors
TNF-mediated	TRAPS	TNF-α inhibitors
Interferon-mediated	CANDLE SAVI	JAK inhibitors
Unknown	DADA2 (*CECR1*)	TNF-α, IL-1 inhibitors

Abbreviations: CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPS, cryopyrin-associated periodic syndrome; DADA2, deficiency of adenosine deaminase 2; DIRA, deficiency of IL-1 receptor antagonist; FMF, familial Mediterranean fever; IL, interleukin; JAK, Janus kinase; MVK, mevalonate kinase; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; SAVI, stimulator of interferon genes–associated vasculopathy with onset in infancy; TNF, tumor necrosis factor; TRAPS, TNF receptor–associated periodic syndrome.

Verbsky JW. When to Suspect Autoinflammatory/Recurrent Fever Syndromes. Pediatr Clin N Am 64 (2017) 111–125

Case

- 4 ¾ yo Caucasian male with recurrent febrile episodes (8/08, 10/08, 11/08, 12/08, 4/09 and 5/09) associated with cervical adenopathy. LN size decrease between episodes. Fevers usually reach 104^{o}F and last 4-5dys.
- Associated c/o: HA, abdl pain, decr po intake, occ rhinorrhea with episodes. Looks 'miserable' during episodes.
- PMH: Recurrent OM until BMT at 2 yo
- What additional historical information would you like?

Case: Additional Hx & Diagnostic Considerations

- Cervical adenopathy (up to 4 – 5 cm per PCP records)
- Occasional oral ulcers
- **Prodrome:** 'glassy' eyes
- No rash, diarrhea, joint pain/swelling

- Overall good **growth**

- **Exposures**: Travel within state; Petting zoo recently
- **Ancestry**:
- Father Mediterranean; Mother mixed

DDx

- ?
- ?
- ?
- ?

Case: Additional Hx & Diagnostic Considerations

- Cervical adenopathy (up to 4 – 5 cm per PCP records)
- Occasional oral ulcers
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- Overall good growth

- Exposures: Travel within state; Petting zoo recently

- Ancestry:
- Father Mediterranean; Mother mixed

DDx:

- ALPS
- Mononucleosis (recurr EBV)
- Fungal, Behcet's

- PFAPA

- Normal child

- Tick-borne, Brucellosis

- FMF

Case continued

PE:

- General: Alert interactive child, non-toxic
- Afebrile. Wt 90th%ile, Ht 75th%ile
- Lungs: clear
- CV: Nl S1, S2, no murmurs, rubs
- Abdomen: nontender w/o HSM
- Rest of PE unremarkable except for bilateral enlarged, nontender anterior cervical and submandibular nodes (largest 2 – 3cm)
- No conjunctival injection, oral lesions, rash

Case

- Any additional questions?
- What laboratory tests or imaging would you like to order – if any?

Case

Previous W/U:

- Normal CBCs with manual diff
- ESR 30 (8 dys after start of fever), CRP nl
- CMP normal
- EBV VCA IgG +, VCA IgM -, EBNA +
- ANA neg
- No increased dbl negative CD3 cells
- CXR normal

Case: What is your Differential Diagnosis for this child?

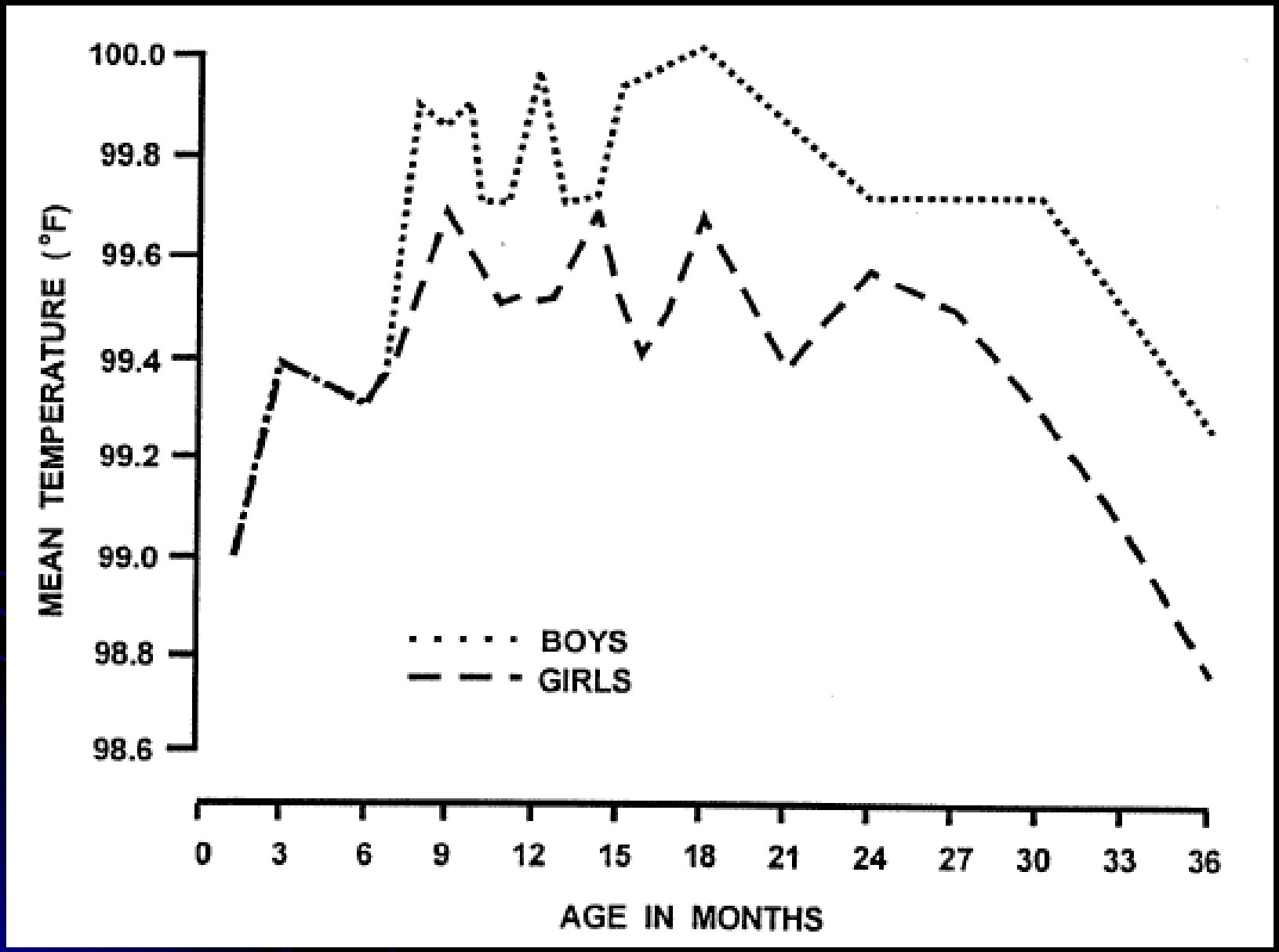
- 4 ¾ yo Caucasian male with c/o of recurrent febrile episodes (8/08, 10/08, 11/08, 12/08, 4/09 and 5/09) with associated cervical adenopathy. Fevers usually reach 104°F.
- Associated c/o: HA, abdl pain, decr po intake, oral lesions, occ rhinorrhea with episodes. Looks 'miserable' during episodes. No rash, diarrhea, joint pain/swelling. Overall good growth; nl development.
- Exposures: Travel within state; Petting zoo recently
- PMH: Recurrent OM until BMT at 2 yo
- Ancestry: Father Mediterranean; Mother mixed

- PE: Alert interactive child, non-toxic. Afebrile. Wt 90th%ile, Ht 75th. Unremarkable except for bilateral enlarged anterior cervical and submandibular nodes (largest 2 – 3cm).
- No conjunctival injection, oral lesions, rash or HSM.
- Previous W/U:
- Normal CBC's, ESR 30 (8 days after start of fever), CRP nl,
- EBV VCA IgG +, VCA IgM -, EBNA +, ANA neg,
- no increase in dbl negative CD3,
- CXR normal

Differential Diagnosis

- Normal Temperatures for Age
- Recurrent Viral / Bacterial Infections: Normal Variant in Young Child
  - Big Love Study
- Infection(s) suppressed by intermittent Antibiotics:
  - URI, Endocarditis, Occult abscess/osteo, etc
- Uncommon Infectious Etiologies:
  - Malaria, Relapsing Fever (*B. recurrentis*), Mycobacteria, Brucella, EBV, etc

Normal Mean Rectal Temperatures for Boys & Girls



Bayley M, Stolz HR. Child Dev 1937;8:195

Differential Diagnosis Continued

- Autoimmune Diseases
  - Autoimmune Lymphoproliferative Syndrome (ALPS)
  - JIA, SLE, Behcet's, etc
  - Inflammatory Bowel Disease
- Neoplasia
  - Doubt - Given duration of S & Sx, fluctuating LN size
- Cyclic Neutropenia
- Periodic Fever Syndrome

Recurrent / Periodic Fevers

- What's normal?
  - ≤ 10 illnesses / year
  - Higher in daycare attendees

- Targeted questions:
  - Prodrome / First Symptoms
  - Peak of fever
  - Duration of fever
  - Cadence
  - Appearance of additional Sx
  - Associated signs & symptoms (mouth/genital ulcers; abdl, joint, chest pain; V/D; rash; mood change; periorbital edema; conj)
  - Duration of Signs & Sx
  - Similarity of Signs & Sx for each episode
  - **Diary**

Long S. Pediatr Clin N Am 2005;52:811

Definitions of Fever Patterns

Recurrent fever:

- single illness in which fever and other signs & symptoms wax and wane (sometimes related to antimicrobial therapy)

or

- Repeated unrelated febrile infections of the same organ system (eg,
- sinopulmonary, urinary tract)

or

- Multiple illnesses with irregular intervals, involving different
- organ systems in which fever is one, variable component

or

- Intermittent fevers without periodic pattern

Periodic fever:

- Recurring episodes of illness wherein fever is the cardinal feature
- Associated symptoms are similar and predictable
- Duration days to weeks with intervening intervals of well-being
- "clockwork" periodicity, occ irregular periodicity

Principles and Practice of Pediatric Infectious Diseases 2008,3rd ed, Chapter 17, Long SS, Edwards KM; p.126

Differential Causes of Recurrent Fevers

- **Infectious diseases** – unusual for single infectious disease to present with recurrent fever over time:
  - Recurrent URI
  - Urinary tract infections
  - Viral infections (EBV, Parvovirus B19, HSV1, and HSV2)
  - Bacterial Infections (Brucella, salmonella, leptospira, TBC, Rat bite fever)
  - Relapsing fever (Borrelia hermsii or recurrentis)
  - Occult Abscess or Osteo
    - Paritally suppressed with intermittent empiric Abx
  - Parasitic diseases (Malaria, toxoplasmosis)
- **Congenital immune defects:**
  - Primary immunodeficiencies
  - Cyclic neutropenia
- **Neoplastic diseases:**
  - Acute lymphoblastic leukemia
  - Acute myeloid leukemia
  - Lymphoma (Pel Epstein fever)
  - Bone tumors
  - Solid organ tumors
- **Inflammatory conditions:**
  - Multifactorial inflammatory diseases
    - Bechet's disease
    - Crohn’s disease
  - Hereditary monogenic fevers
    - Familial Mediterranean Fever
    - Cryopyrin associated periodic syndrome (FCAS, MWS, CINCA/NOMID)
    - TRAPS syndrome
    - Mevalonate Kinase deficiency
  - Idiopathic forms
    - PFAPA syndrome

Periodic Fever Syndromes and Autoinflammatory Diseases

"Recurrences of fever that last from a few days to a few weeks, separated by symptom-free intervals of variable duration"

Causes include recurrent infections, neoplastic disorders, or noninfectious inflammatory disorders.

Drenth JPH, van de Meer JWM. NEJM 2001, 345:24:1748

Historical Descriptions:

- 169 AD Claudius Galen: "fever with phases of the moon"
- 1790 Heberden: Periodic 'fits'
- 1895 Osler
- 1908 Janeway & Mosenthal: 1st patient with periodic fevers described

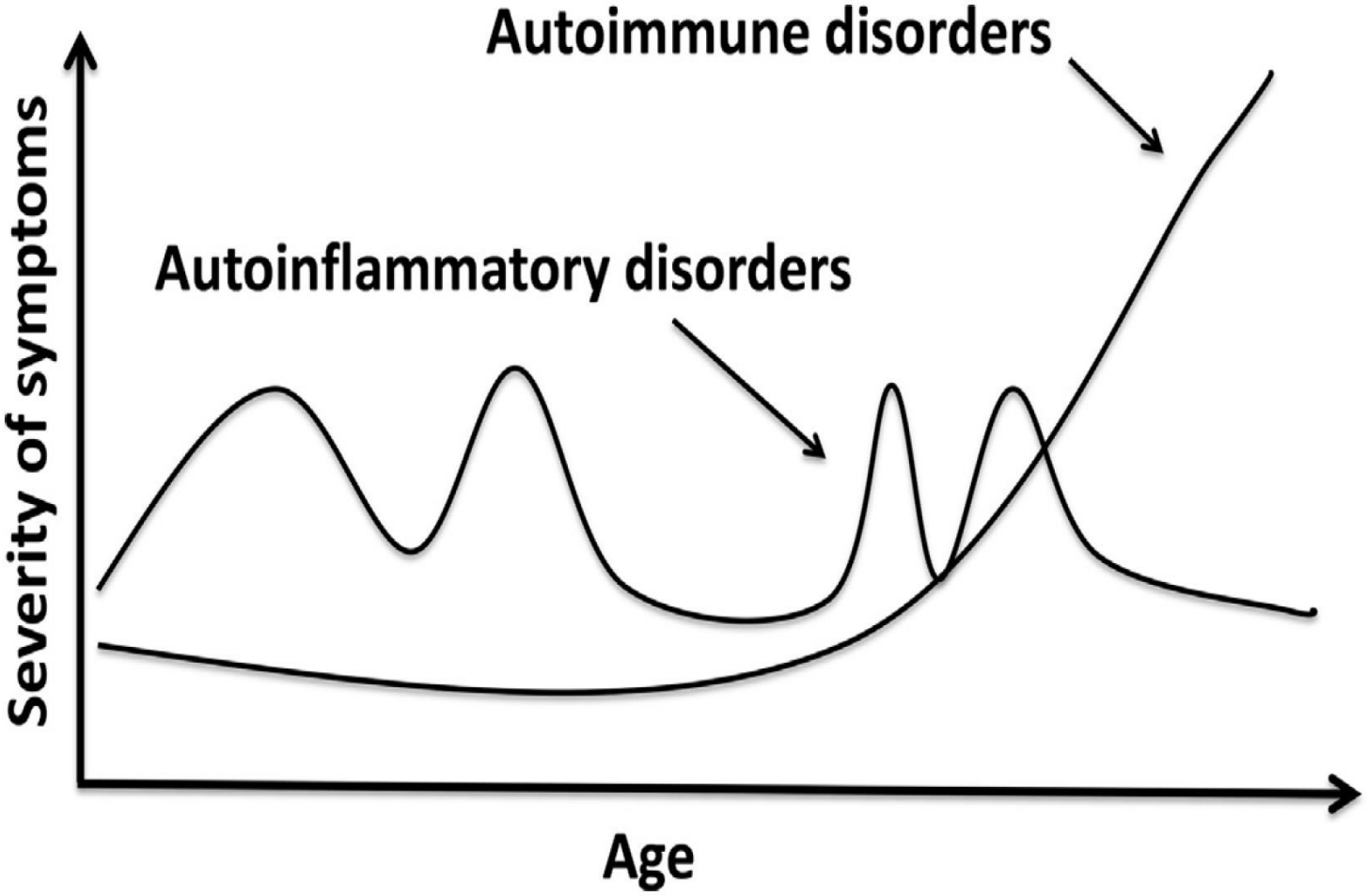


Fig. 1. Graphic representation of symptoms over time of autoinflammatory disorders and autoimmune disorders.

Verbsky JW. When to Suspect Autoinflammatory/Recurrent Fever Syndromes. Pediatr Clin N Am 64 (2017) 111–125

Key Elements in Periodic Fever Syndromes

- Fever as cardinal feature
- Recurrence of episodes
- ***Predictable course for each episode***
- Symptom-free intervals
- Lack respiratory symptoms
- Family Hx of similar Sx
- During episodes: leukocytosis, elevated ESR & CRP
- Triggers: immunizations, minor infections, stress

Long S. Pediatr Clin N Am 2005;52:811

PFAPA

PFAPA

- Periodic Fever
- Aphthous ulcers 65 – 70% (38%)*
- Pharyngitis 65 – 70% (85%)
- Adenopathy [cervical] 75 – 80% (62%)
  - *Marshall G, Edwards K, others*

*HA 44%, V 27%, Abdl pain 41%

Periodic fevers and aphthous ulcers

Other Diagnoses to consider??

** Feder HM, Salazar JC. Acta Pediatrica 2010;99:178*

Periodic fevers and Aphthous ulcers

DDx to consider:

- Cyclic neutropenia, Behcet's, Crohn's, ?SLE

PFAPA

- Clockwork cycle
- Abrupt onset after prodrome
  - “glassy eyes”, clingy, tired
  - then fever > 39^{o}C
  - Mouth ulcers - solitary or scattered; not multiple
- Absent: congestion, conjunctivitis, cough, wheezing
- Last ~3 - 6 dys, cycle every 3 – 8 weeks
- Between episodes
  - completely well, normal growth, fewer routine childhood illnesses
- 80% <5yo at onset
- 62% males
- Parental Hx of unexplained fevers occasionally
- Mild neutrophilia, Increased ESR and CRP

- Diagnosis : Clinical

Marshall G, Edwards K,Butler J, et al JPediatr 1987;110:43
Feder HM, Salazar JC. Acta Pediatrica 2010;99:178

Background: PFAPA

PFAPA is most common periodic fever in children

- Sterotypical febrile episodes first described in 1987
  - **P**eriodic **F**ever - fevers with periodicity which begin typically beginning < 5yo (some reports in adults)
    - Last ~3 - 6 days, cycling every 3 – 8 weeks
  - **A**phthous stomatitis
  - **P**haryngitis
  - **A**denopathy [cervical]
  - Constitutional symptoms
  - Lab abnormalities during episodes:
    - Elevated inflammatory markers that normalize
    - No diagnostic test

Marshall G, Edwards K,Butler J, et al JPediatr 1987;110:43
Feder HM, Salazar JC. Acta Pediatrica 2010;99:178

aphthous ulcers favor PFAPA syndrome.[22] In 2008, Gattorno and colleagues[39] derived and validated a diagnostic score that predicts which children with PFAPA-like symptoms are likely to test positive for one of the heritable periodic syndromes (Table 5). This score may be useful for guiding diagnostic work-ups in the clinical setting.

The prognosis in PFAPA syndrome is good. In a longitudinal study, 50 of 59 patients had complete resolution of

Table 5 Gaslini score.[a]

Variable	Code[b]		Coefficient		Value
Age at onset	Months	X	−0.067	=	a
Abdominal pain	0 = Never 2 = Sometimes or often 3 = Always		1.494		b
Aphthous ulcers	0 = Never 1 = Sometimes or often 2 = Always		−1.504		c
Thoracic pain	0 = Absent 1 = Present		1.958		d
Diarrhea	0 = Never 1 = Sometimes 2 = Often 3 = Always		0.901		e
Family history	0 = Negative 1 = Positive		1.503		f

For each variable, multiply the code number (e.g., 0, 1, 2, etc.) by the corresponding coefficient to obtain the value. Add the values (a + b + c + d + e + f) to obtain the total score. In a validation set, a score >1.32 identified children who were positive for heritable periodic fever syndromes with 87% sensitivity and 72% specificity).

[a] Named for the Giannina Gaslini Institute in Genoa, Italy, the principal investigators' home institution.

[b] Codes apply during each episode of fever and not during interval periods.

Data from Gattorno et al.[39]

Prolonged and recurrent fevers in children. Marshall GS. J of Infection 2014:68;S83

PFAPA Treatment Options

- No intervention, except antipyretics & patience
- Corticosteroids (0.6 – 2 mg/kg) x 1 at start of typical fever
  - Intervals can decr
- Cimetidine x 6 months
- Tonsillectomy
- Adjunct – Vitamin D (preliminary study)

- Spontaneous resolution
  - Variable duration, Mean 4.5 yrs
  - Frequently heralded by lengthening of intervals

Prospective, Randomized Controlled Trial of Tonsillectomy in PFAPA patients (19 T & A; 20 Controls)

Garavello W, et al. J Pediatri 2009;155:250

Table II. Number and characteristics of PFAPA episodes during 18 months after entry

	Surgery group	Controls	P
Number of episodes			
None (complete resolution)	12 (63%)	1 (5%)	< .001
1 to 3	7 (37%)	2 (10%)	< .001
4 to 6	0 (0%)	7 (35%)	< .001
7 to 12	0 (0%)	6 (30%)	< .001
> 12	0 (0%)	4 (20%)	< .001
Characteristics			
Total number of episodes	12	179	-
Duration of symptom-free period, weeks	18.6 (8 to 26)	7.5 (3 to 19)	< .001
Mean duration of episode, days	1.7 (2 to 4)	3.5 (2 to 5)	< .001
Maximum temperature, °C	39.1 (38.6 to 40.3)	39.5 (38.7 to 41.0)	NS
Corticosteroid treatment	50%	88%	.004
Aphthous stomatitis	58%	64%	NS
Pharyngitis	100%	98%	NS
Cervical adenopathy	83%	86%	NS

NS, not significant.

Data refer exclusively to patients experiencing new episodes after study entry. Data are reported as mean (range) or number (%), as appropriate.

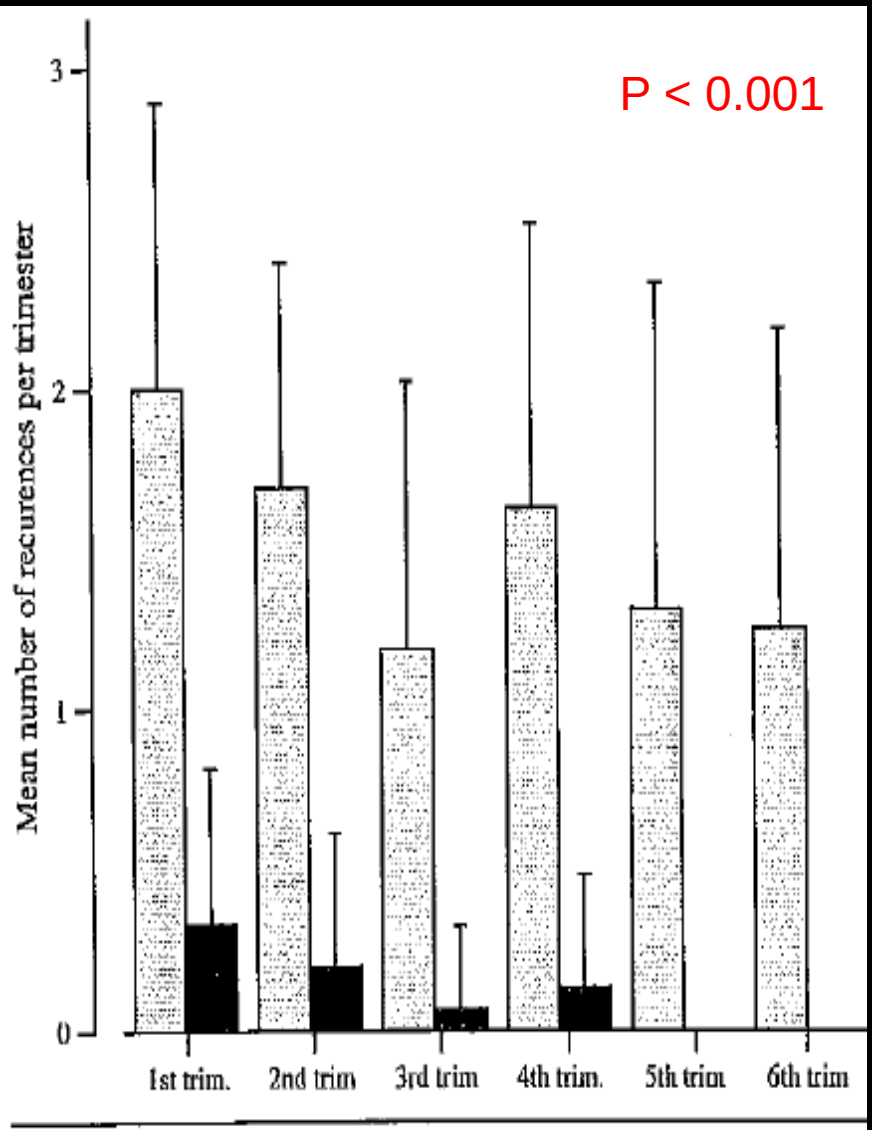


Figure. Number of PFAPA episodes according to study

VITAMIN D LEVELS AND EFFECTS OF VITAMIN D REPLACEMENT IN CHILDREN WITH PERIODIC FEVER, APHTHOUS STOMATITIS, PHARYNGITIS, AND CERVICAL ADENITIS (PFAPA) SYNDROME

INTERNATIONAL JOURNAL OF PEDIATRIC OTORHINOLARYNGOLOGY 78 (2014) 964–968

Stefano Stagi, Federico Bertini, Donato Rigante, Fernanda Falcini

Health's Sciences Dept, Anna Meyer Children's University Hospital and Dept of BioMedicine, Section of Rheumatology, University of Florence, Italy and Institute of Pediatrics, Universita Cattolica Sacro Cuore, Rome, Italy

Objective:

- To assess serum 25-hydroxyvitamin D [25(OH)D] concentrations in children with PFAPA syndrome and longitudinally evaluate the effect of wintertime vitamin D supplementation on their disease course

Patients

- Consecutive evaluation of 25 Italian children
- All fulfilled the Euro-Fever PFAPA criteria
  - Between September 2009 and August 2013 (4 winters)
  - 19 males; 6 females
  - Mean age: 3.6 $\pm$ 0.9 years (range 2.4 – 5.3 years)
  - Attending pediatric hospitals in Tuscany

Results: Vita D Levels

- 25(OH)D levels:
  - No patients with PFAPA syndrome had sufficient 25(OH)D levels
  - 5 (20%) patients with insufficient levels (20 - 30 ng/mL)
  - 20 (80%) with deficient levels (<20 ng/mL)
  - A similar breakdown was not provided for Controls

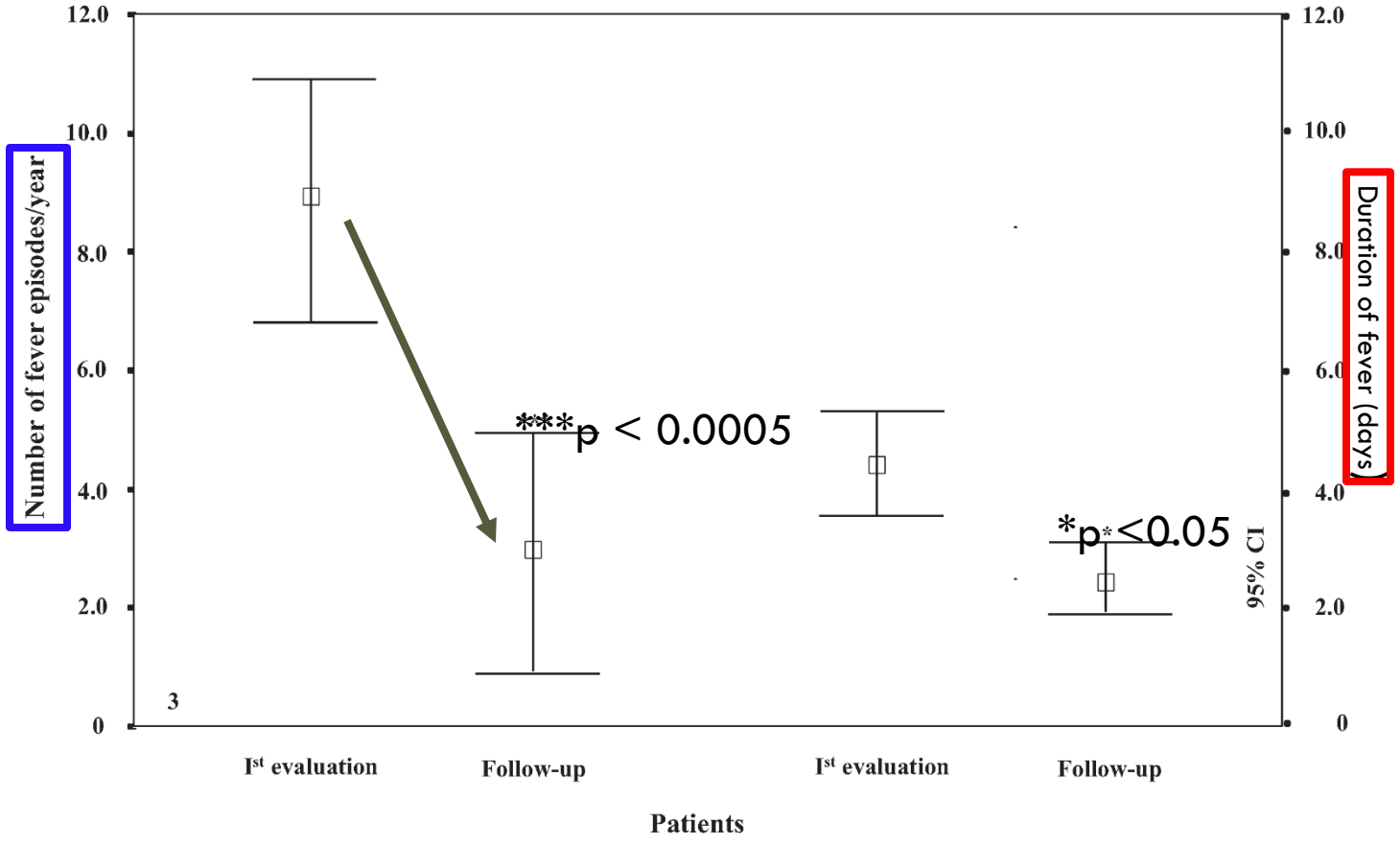
- Correlation between 25(OH)D levels and age, sex, seasons, episodes of fever (number), CRP, calcium, phosphate, BMI, and height:
  - 25(OH)D levels were
    - inversely correlated with fever episodes ($r = 0.42$, $p < 0.005$)
    - directly correlated with CRP values ($r = 0.39$, $p < 0.005$)

Results: After vitamin D supplementation

Vitamin D supplementation (for a mean of 7.4 ± 1.1 mo, range 5.9–9.4 mo),

- Longitudinal evaluation
- After mean F/U of 12.3 months (range 10.1-14.3 mo):
  - 9 PFAPA patients (36.0%) reached sufficient vita D levels
  - 14 (56.0%) had insufficient levels
  - only 2 (8.0%) remained deficient

Significant decrease in number of Fever episodes/yr and in Duration of fever (dys) before and after Vita D supplementation



Limitations

- Small number of patients
- All from one region in Italy
- Case Control study not RTC

Conclusions: Vitamin D levels and effects of Vitamin D replacement in children with PFAPA syndrome

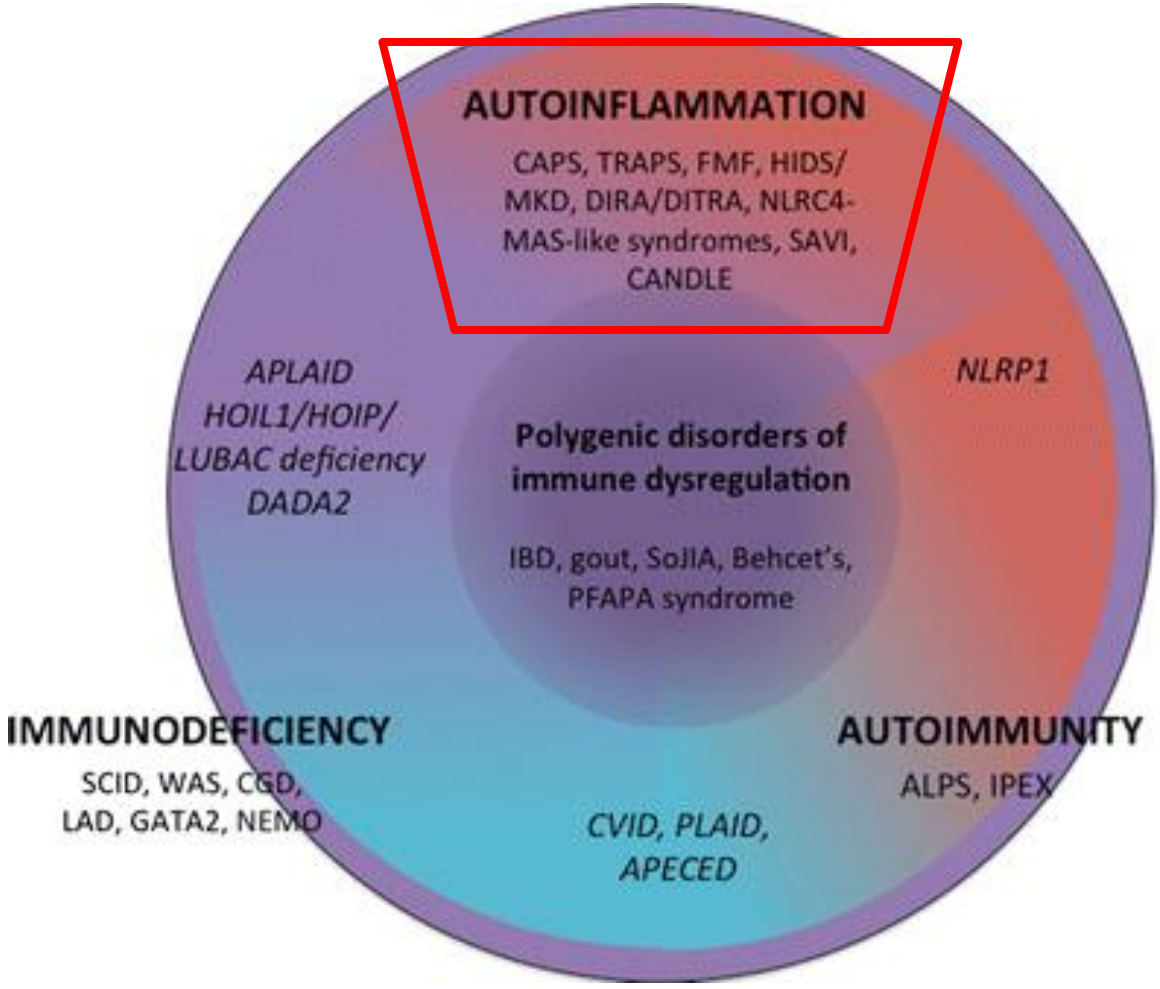
- Deficient or insufficient vitamin D serum levels found in most children with PFAPA syndrome in this study
- Hypovitaminosis D might be a significant risk factor for PFAPA flares
- Vitamin D supplementation seems to significantly modify PFAPA episodes
  - reduced both the duration and frequency of flares
  - Intriguing but definitive conclusions regarding Vitamin D's role on PFAPA flares will require an RCT or large intervention studies to confirm findings

Autoinflammatory Diseases (AKA Hereditary Fever Syndromes or Recurrent Fever Syndromes)

- "Rare group of diseases characterized by recurrent episodes of seemingly unprovoked inflammation"
  - Characterized by fevers, rash, arthritis, &/or other organ-specific inflammation
- Without significant levels of autoantibodies or autoreactive T cells (distinct from autoimmune disease)
- Over last 13 yrs, genetic basis identified for many of the autoinflammatory diseases
  - Disorders of the innate immune system
    - *Defects in gene families & pathways regulating innate immunity*
    - *Most genetic causes derive from defects in proteins of innate immunity*

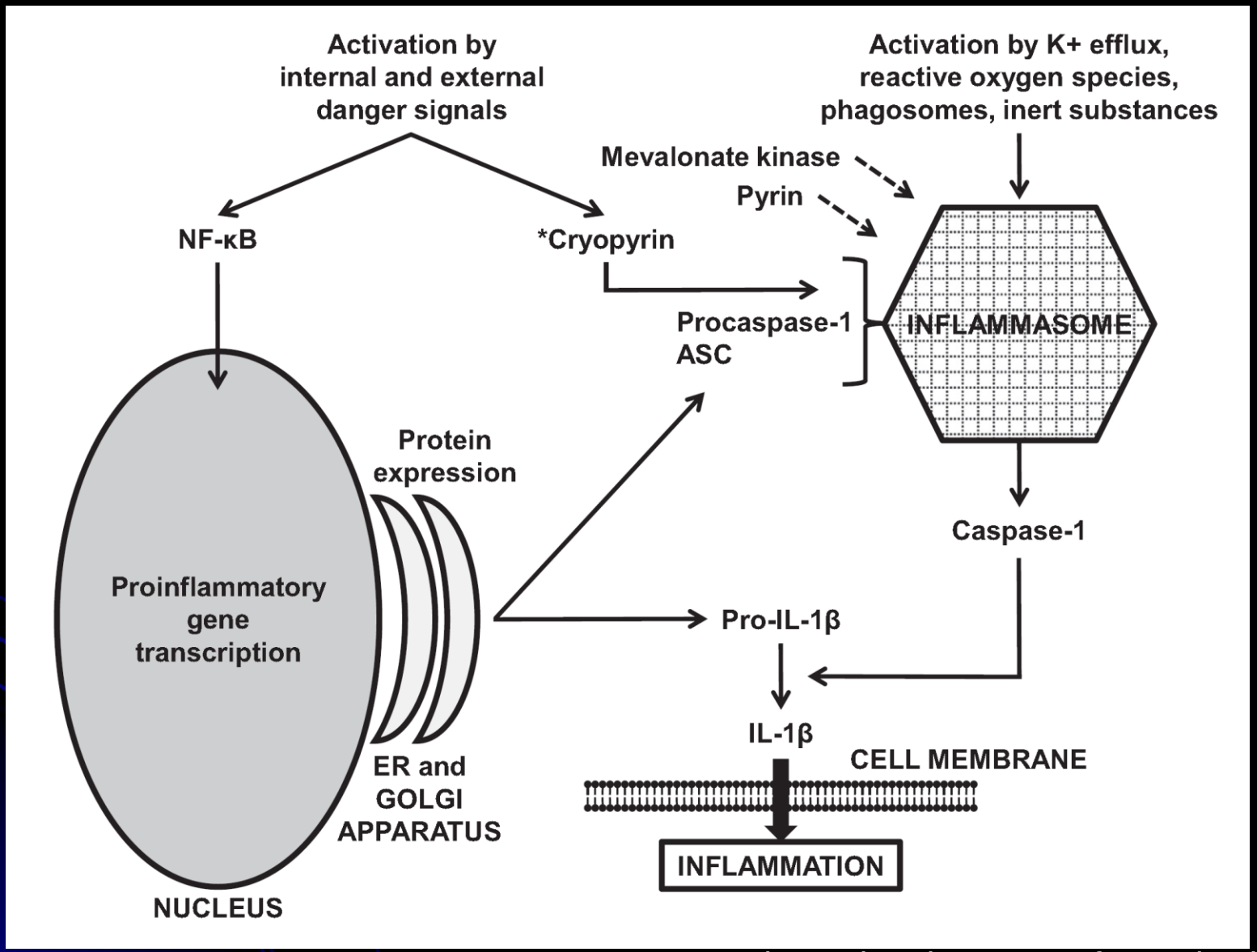
Hull, Shoham, Kastner, et al. Curr Opinion Rheum 2003

Immune Dysregulation



UNC HEALTH CARE
Children's

Inflammasome - activates inflammatory cascade



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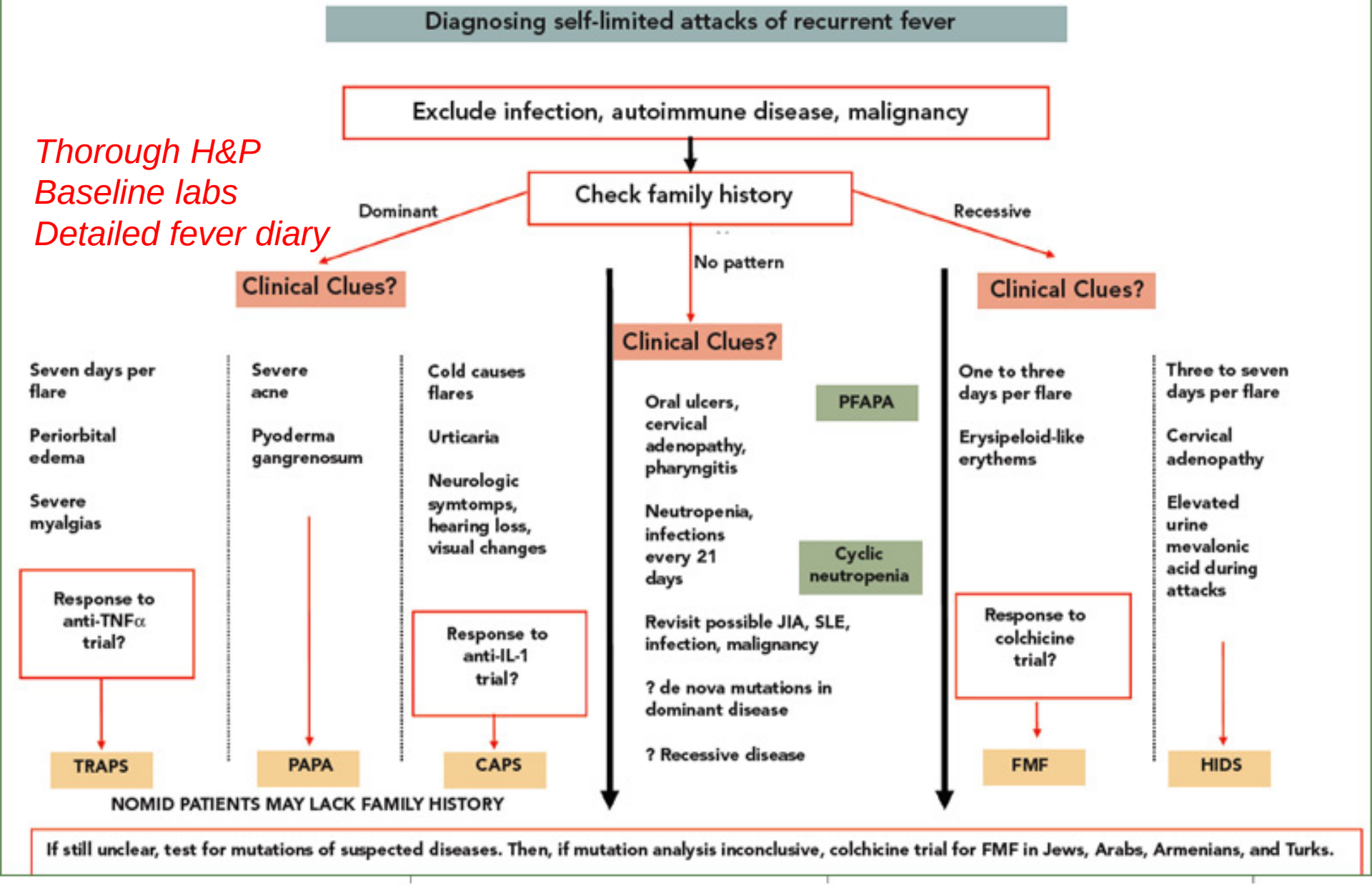
Can you name 4 of the “Autoinflammatory Diseases”?

Hereditary Fever Syndromes (Autoinflammatory Disorders)

- Familial Mediterranean Fever (FMF)
- Hyperimmunoglobulinemia D Syndrome (HIDS)
- TNF Receptor-associated Periodic Fever Syndrome (TRAPS)
- Cryopyrin-Associated Syndromes (CAPS)

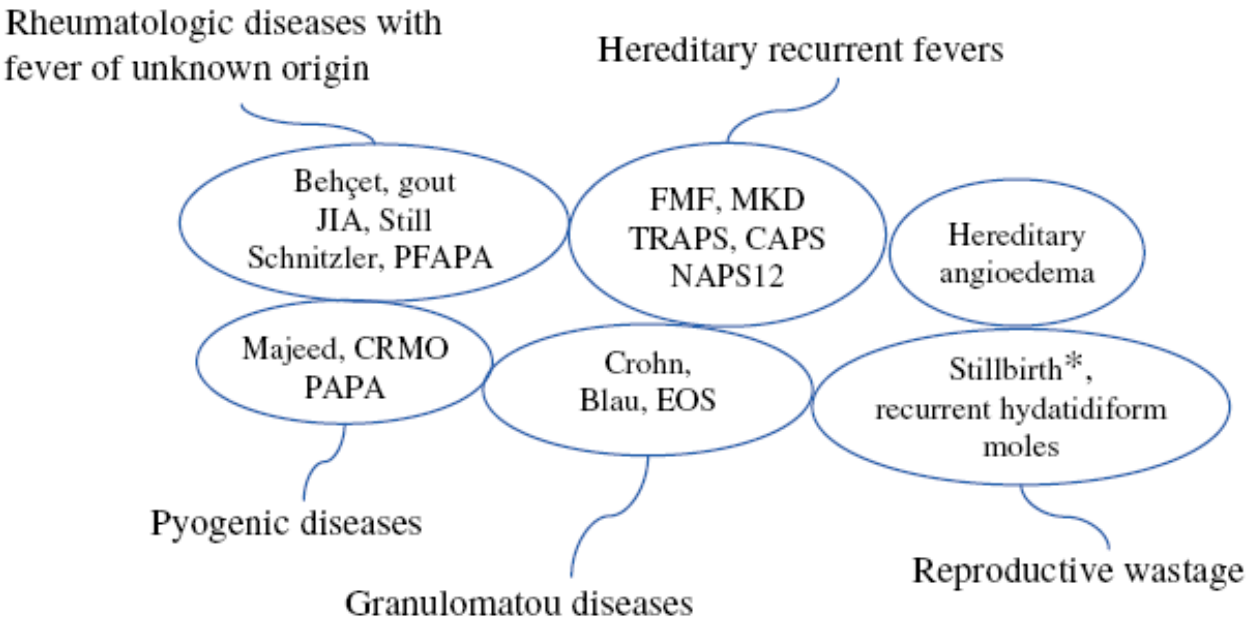
ALGORITM FOR DIAGNOSING A PATIENT'S RECURRENT FEBRILE ATTACKS



Thorough H&P
Baseline labs
Detailed fever diary

CURR OPIN RHEUMATOL. 2006;18:108-117.

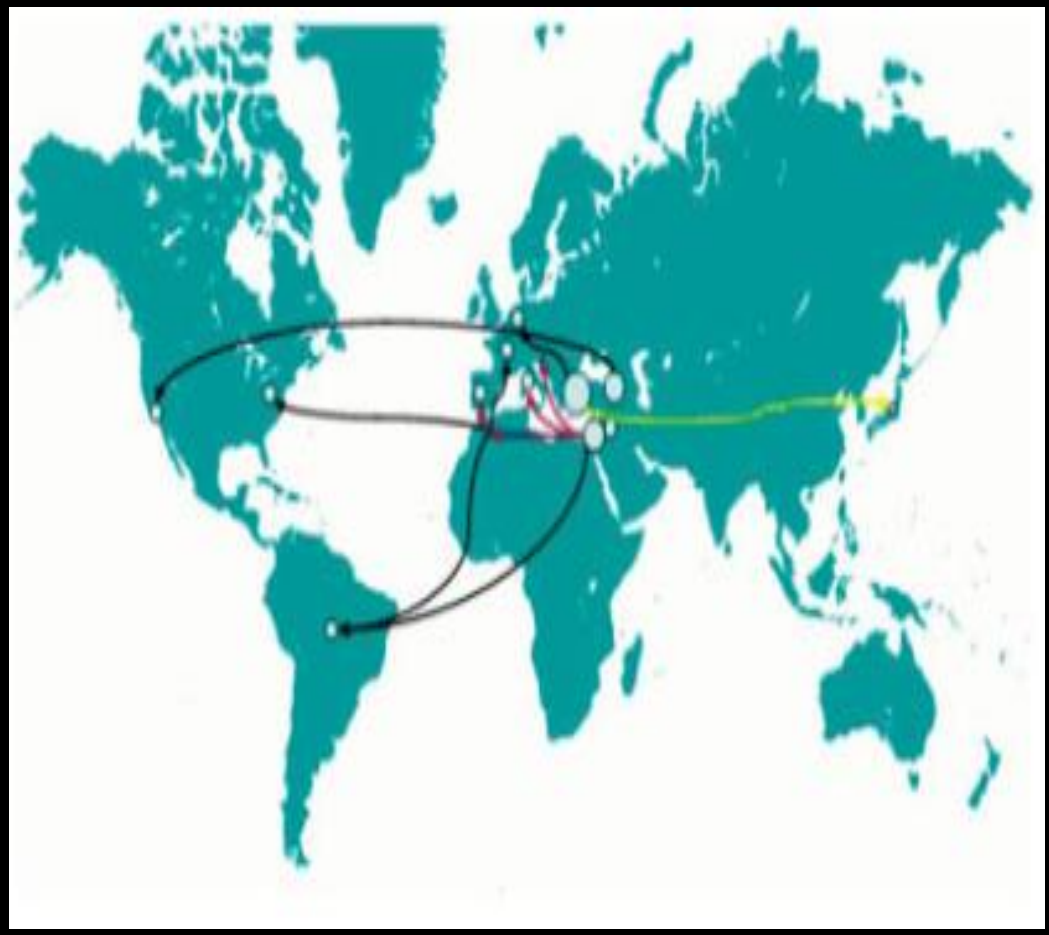
Expanding Spectrum of Autoinflammatory Diseases



Touitou I, Kone-Paut. Best Practice & Rsch Clin Rheum;22:811

Familial Mediterranean Fever (FMF)

- Described in 1908 by Janeway and Mosenthal
- Individuals from the Mediterranean basin
  - Turkish, Armenian, Jewish, Italian, Arabian
  - Now in other groups: Greek, East Asian
- Autosomal recessive
- Most prevalent periodic fever syndrome

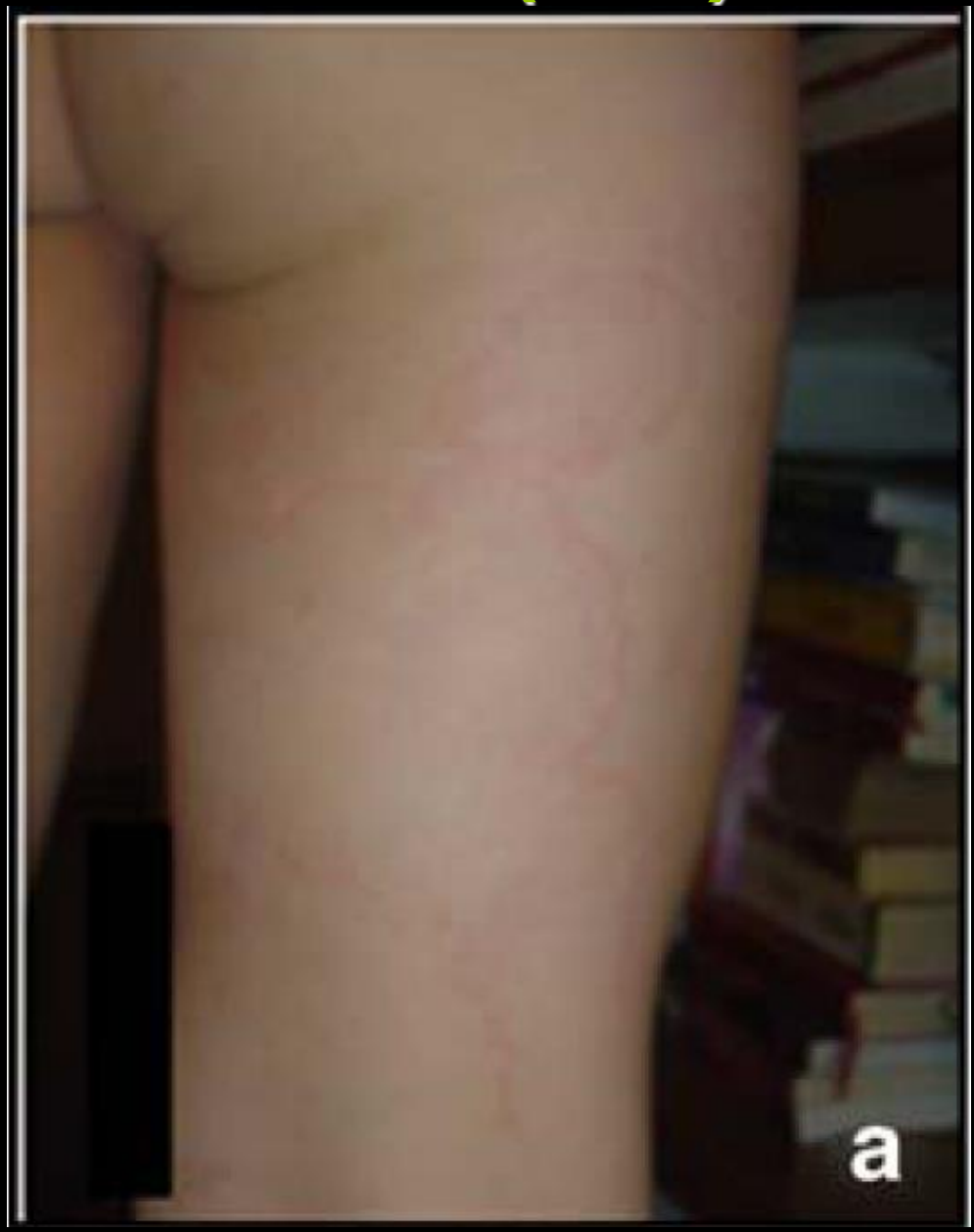


Ben-Cherit, Touitou. Arthr and Rheumatism 2009;61

Familial Mediterranean Fever (FMF)

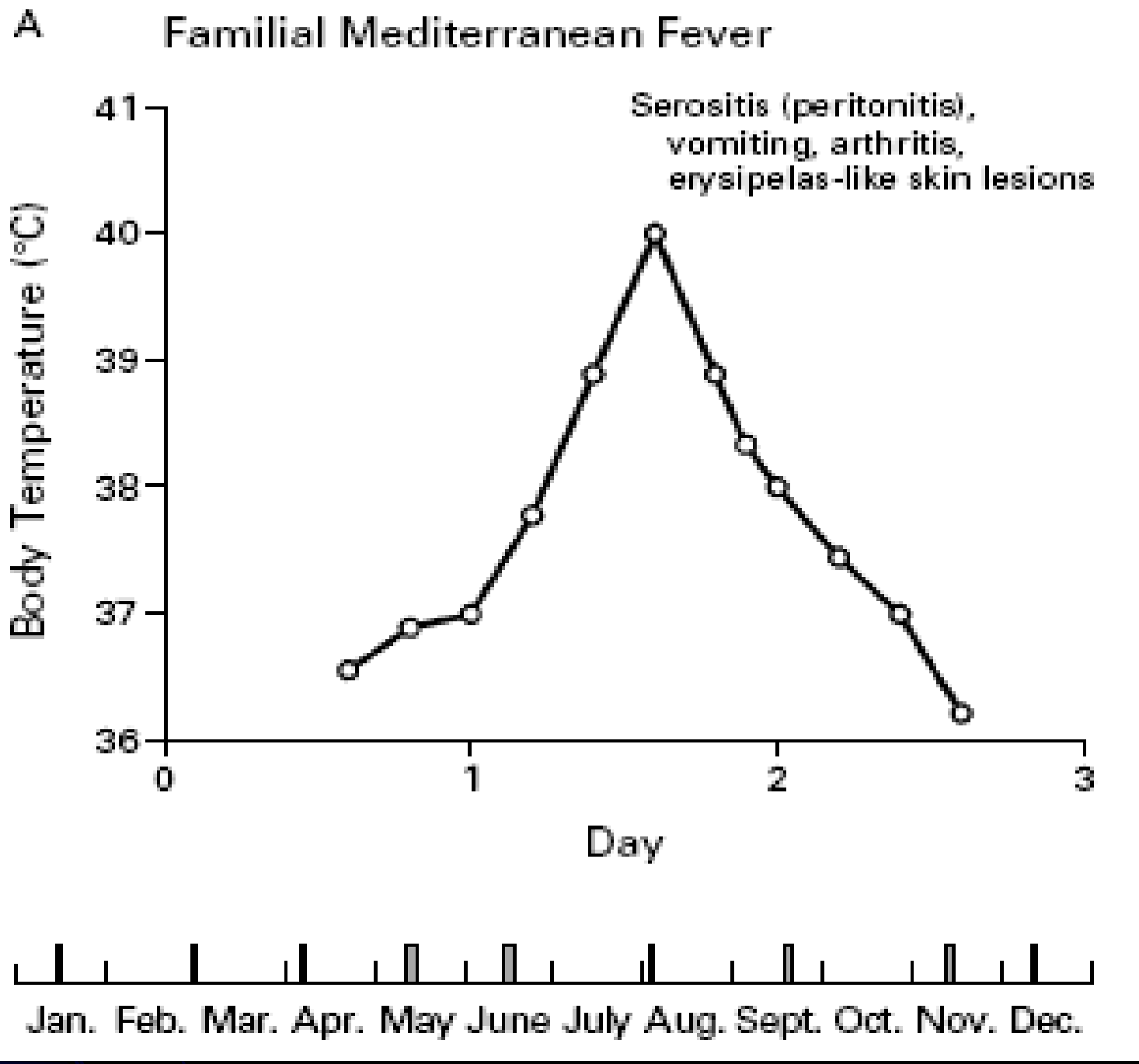
Clinical manifestations:

- Short attacks of fever and serositis
- Most < 20 yo on presentation
- Sudden onset, usua last 6-96 hrs
- Localized inflammation of serosal membranes, joints, skin
  - Severe abdl pain, peritonitis, pleuritis, arthritis, rash (erysipeloid erythema), less commonly pericarditis
- Subclinical inflammation may persist
  - Predisposed to amyloidosis (kidneys, GI, Liver/spleen)



Gattorno M, et al. J Clin Immunol 2008;28:S73

FMF Presentation in Patient



Drenth JPH, van de Meer JWM. NEJM 2001, 345:24:1748

FMF: Diagnosis

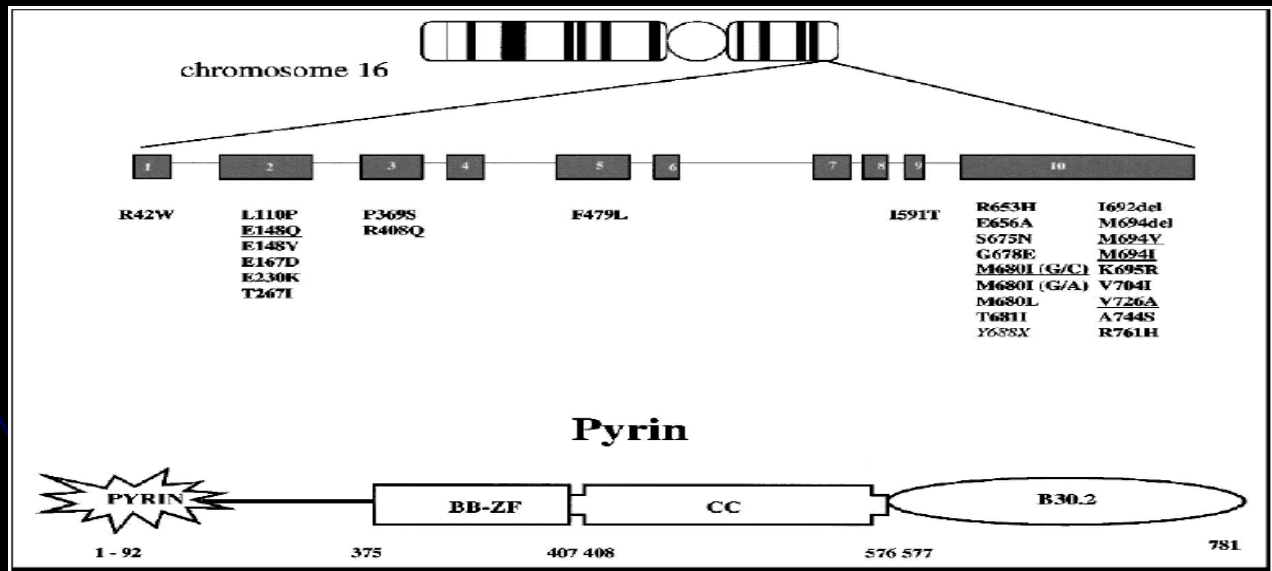
Major criteria
Typical attacks
1. Peritonitis (generalized)
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
Minor criteria
1-3. **Incomplete** attacks involving one or more of the following sites:
1. Abdomen
2. Chest
3. Joint
4. Exertional leg pain
5. Favorable response to colchicine
Supportive criteria
1. Family history of FMF
2. Appropriate ethnic origin
3. Age <20 years at disease onset
4-7. Features of attacks:
4. Severe, requiring bed rest
5. Spontaneous remission
6. Symptom-free interval
7. Transient inflammatory response, with one or more abnormal test result(s) for the white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibronogen
8. Episodic proteinuria/hematuria
9. Negative laparotomy or removal of normal appendix
10. Consanguinity of parents

Familial Mediterranean Fever (FMF)

- Laboratory
  - Increased inflammatory mediators:
    CRP, Serum amyloid A
- Pathology of affected tissues:
  massive infiltration by PMNs

Familial Mediterranean Fever (FMF) Mutation

- Mutations in the MEFV gene (MEd FeVer gene)
  - Identified on Chromosome 16p in 1997
  - > 100 mutations reported
  - Encodes Pyrin protein (Marenostrin)
  - Pyrin expressed mainly in neutrophils and monocytes
    - Member of the death fold superfamily
    - PYRIN domain interacts with ASC (apoptotic speck protein)
      - Regulator of NFkB activation, IL-1 beta secretion and apoptosis
      - Mutated pyrin ineffectively downregulates inflammatory response
    - Pyrin-deficient mice with defective apoptosis



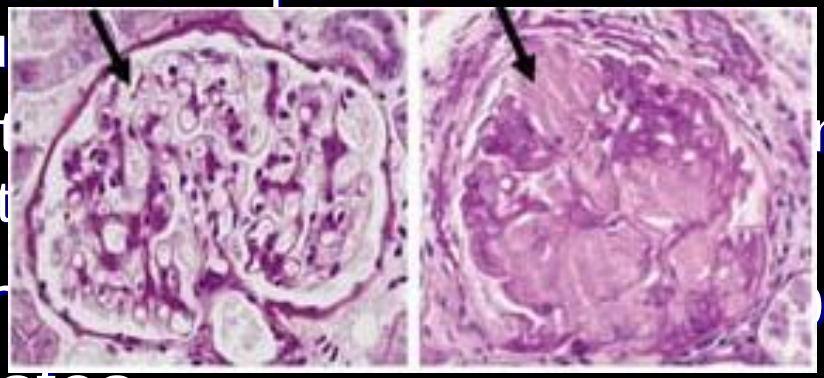
FMF: Treatment / Prognosis

- Colchicine
  - Inhibits neutrophil chemotaxis
  - Prevents febrile attacks in ~60%
  - Significant attack reduction in another 20–30%
  - Improved QOL
- Some success with other modulators

- Prognosis determined by development of secondary Amyloidosis

Secondary Amyloidosis

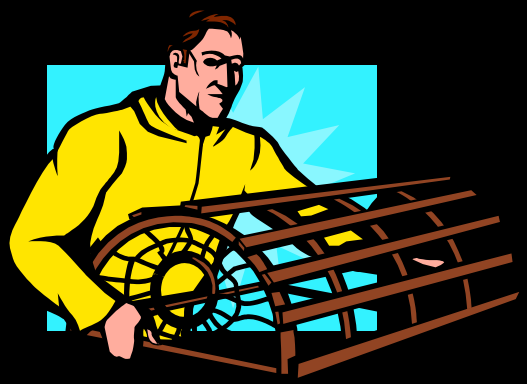
- Derived from the inflammatory protein serum amyloid A
- Major cause of morbidity and mortality
  - Kidney deposition results in end stage renal disease
    - Early indicator of impaired renal function is microalbu
    - Colchine t n kidney transplant
  - Deposition leen, heart, thyroid, testes



- Risk increases with FHx of amyloidosis, male gender, alpha alleles of SAA1, and poor compliance

Tumor Necrosis Factor Receptor-associated Periodic Fever Syndrome (TRAPS)

- Described in 1982 by Williamson
  - AKA Familial Hibernian Fever
  - Original description in large Irish-Scottish family
    - Now many ethnic backgrounds
- Autosomal dominant



TRAPS Clinical Manifestations

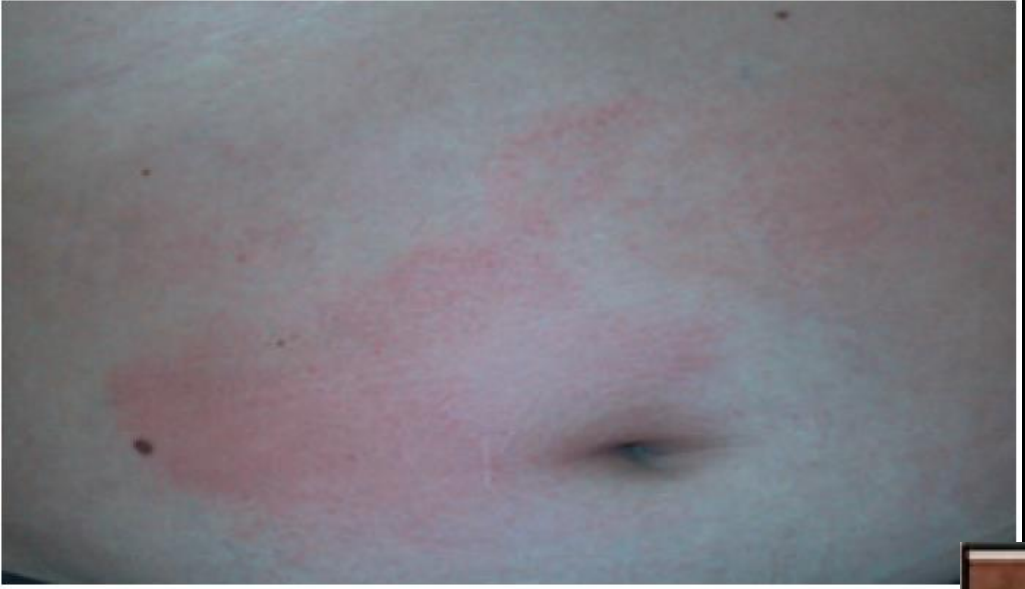
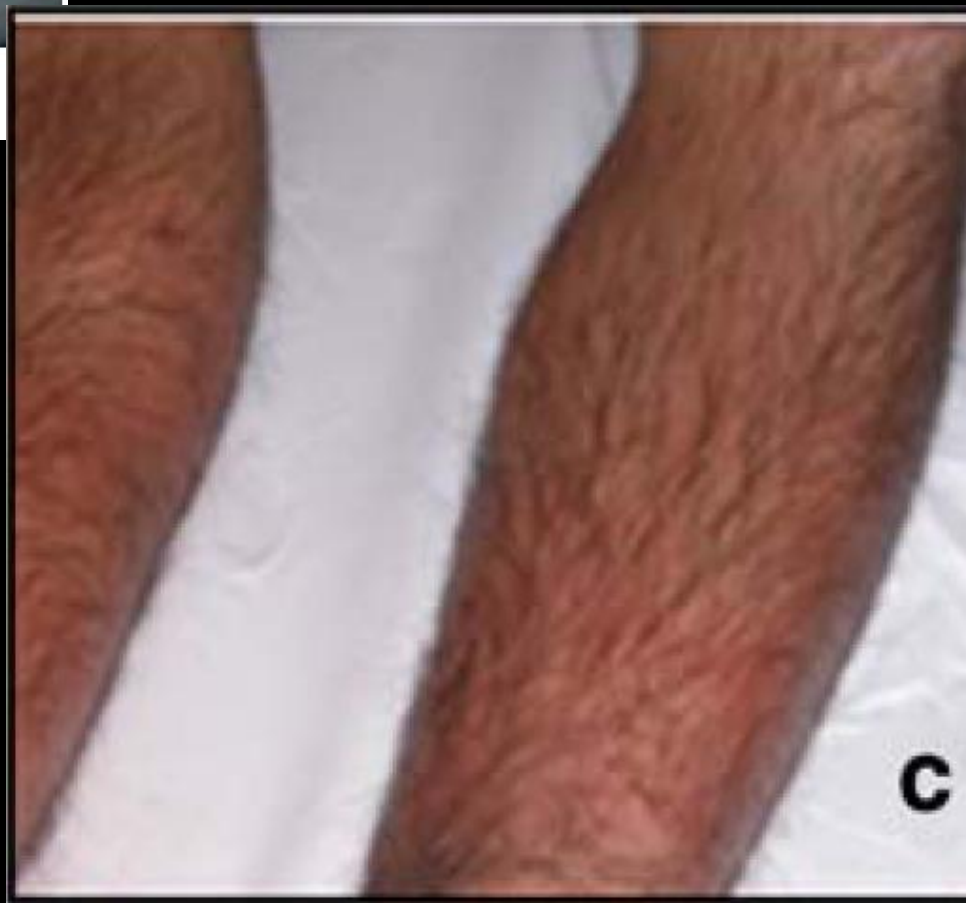


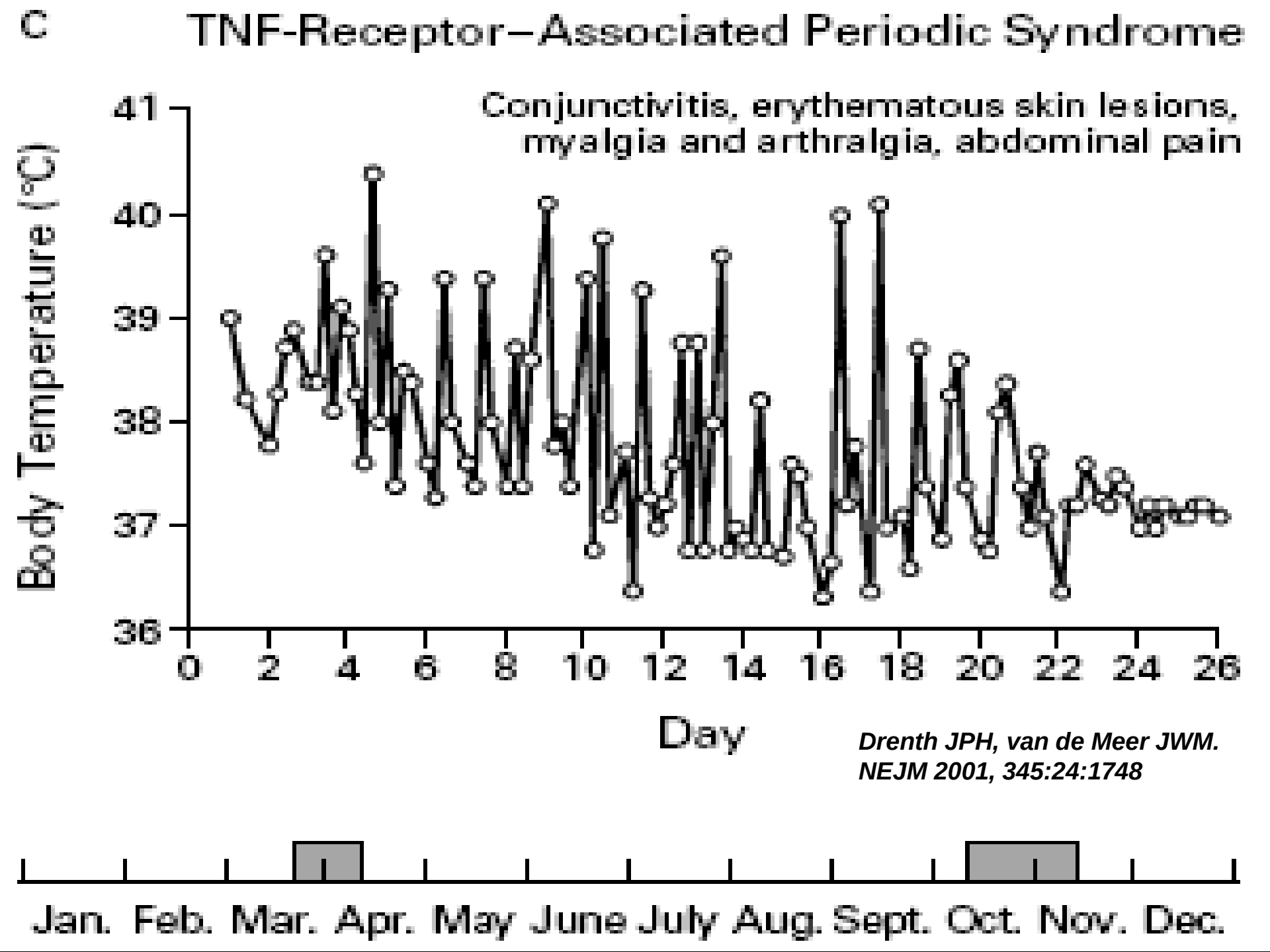
Fig 2. Migratory erythematous rash in TRAPS.

Bodar EJ, et al. Brit J of Haematology;144:279

Gattorno M, et al. J Clin Immunol 2008;28:S73

- Longer duration of attacks (> 1 wk)
- Irregular intervals
- Fever, abdominal pain, pleurisy, ocular inflammation (conjunctivitis, periorbital edema), arthralgia >>arthritis
- Centrifugally migrating myalgia & erythematous rash
  - Monocytic fasciitis




C
TNF-Receptor–Associated Periodic Syndrome
Conjunctivitis, erythematous skin lesions,
myalgia and arthralgia, abdominal pain
Body Temperature (°C)
41
40
39
38
37
36
0
2
4
6
8
10
12
14
16
18
20
22
24
26
Day
Drenth JPH, van de Meer JWM.
NEJM 2001, 345:24:1748
Jan.
Feb.
Mar.
Apr.
May
June
July
Aug.
Sept.
Oct.
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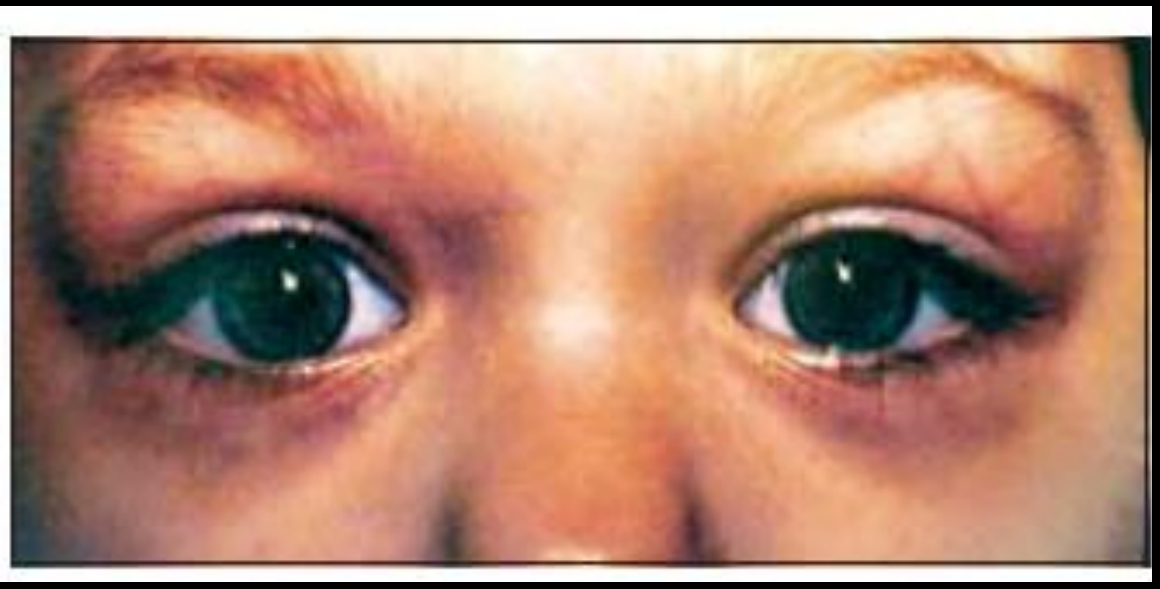
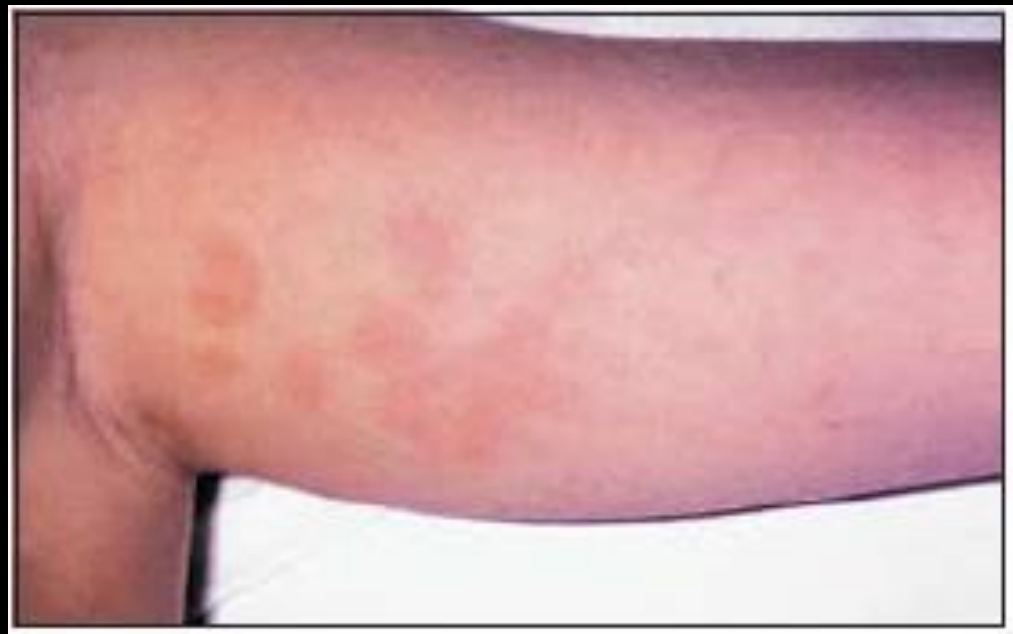
Dec.

Manifestations of TRAPS



Farasat, Aksentijevich; Toro.
Arch Dermatol 2008;144: *392*



TNF Receptor-Associated Periodic Syndrome (TRAPS)

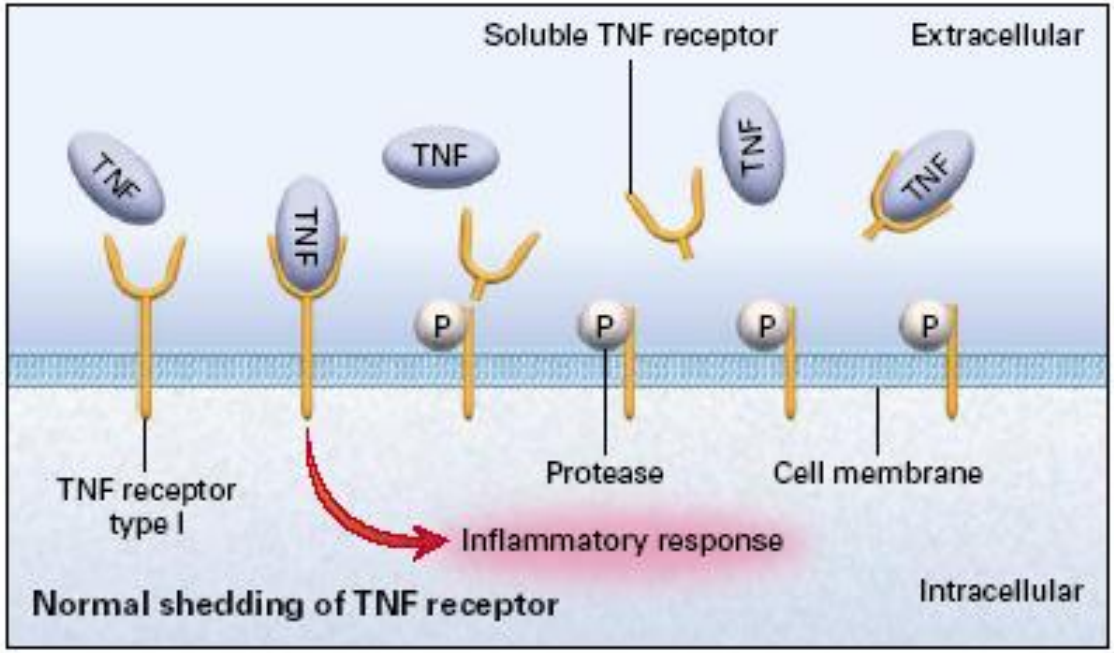
Laboratory

- Incr WBC, CRP, mild complement activation
- Polyclonal Ig levels, esp IgA, may be elevated
  - IgD may be elevated, rarely > 100 IU/ml
- Diagnostic:

Low serum levels of soluble type 1 TNF receptor between attacks

Mutations in TNFRSR1A (gene for Type 1 TNF receptor)

- Chromosome 12
- >80 mutations reported
- Encodes 55 kd protein Mutations affect 3 domains of receptor
- TNFRSF1A accumulates intracellularly



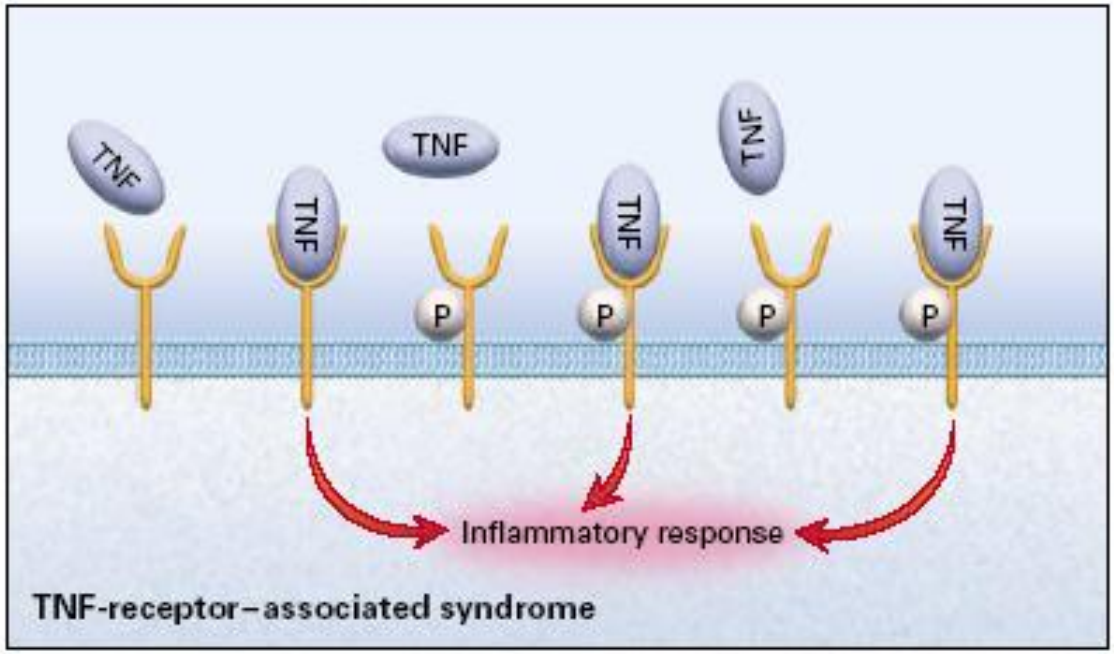


Figure 5. Hypothesized Pathogenesis of the Tumor Necrosis Factor (TNF) Receptor–Associated Periodic Syndrome.

Pathogenesis of TRAPS?

- Decreased TNF-induced apoptosis of neutrophils
- Misfolded receptors retained in the ER
- Lower levels of soluble TNFRSF1?
  - Less soluble receptor available to bind TNF
- Less able to stop inflammatory response

Drenth JPH, van de Meer JWM. NEJM 2001, 345:24:1748

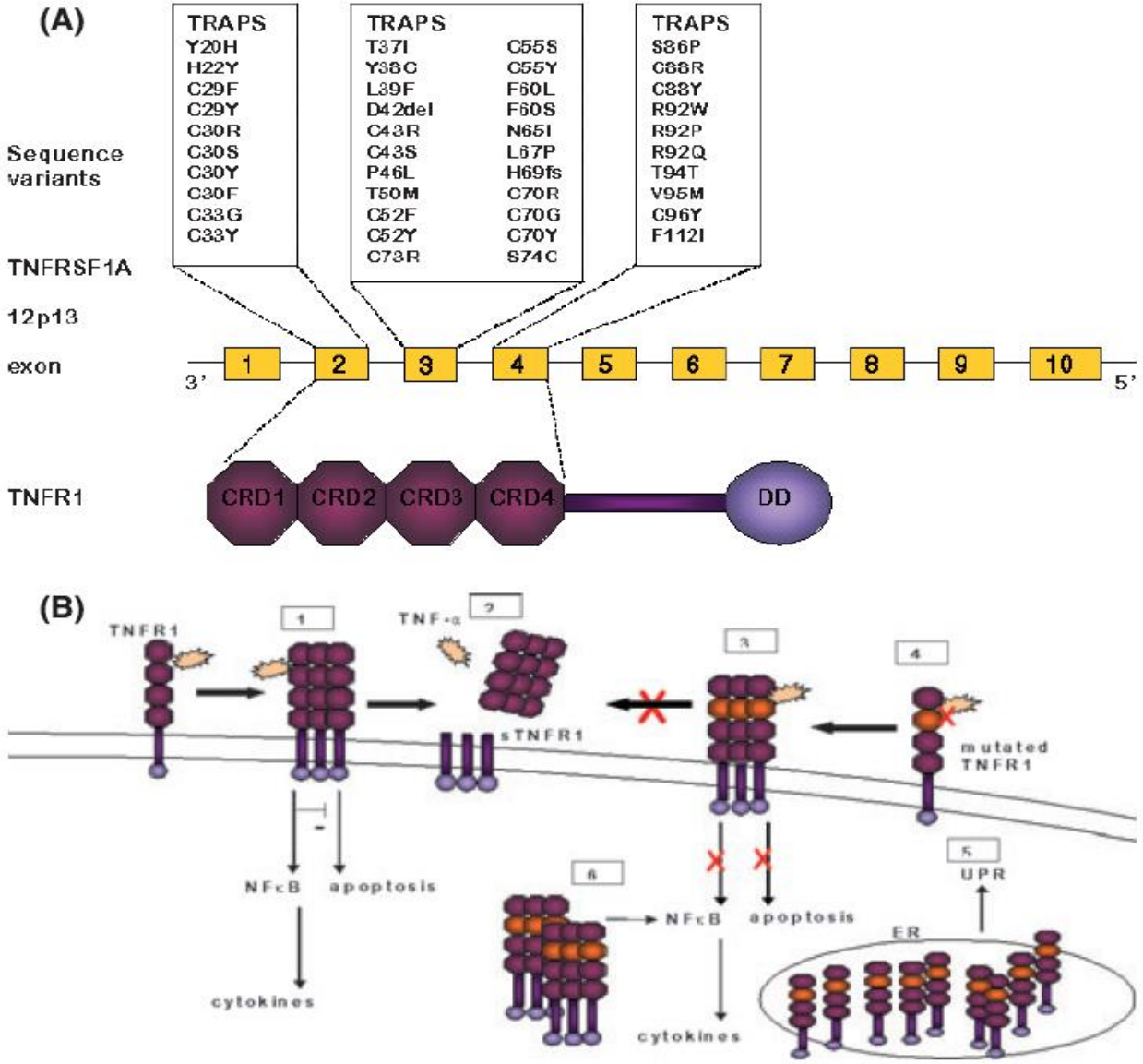


Fig 5. TNFR1. (A) Disease-causing sequence variants in *TNFRSF1A* and their location related to exons. The encoded protein TNFR1 and its domains are shown at the bottom of the figure. (B) 1: Trimerization after TNF-α binding leads to activation of the NFκB and apoptosis pathways. 2: After activation the extracellular part is shed from the cell surface and acts as a competitive inhibitor of TNF-α. 3: Shedding is reduced in the mutated TNFR1 in some patients resulting in less TNF-α inhibition. 4: TNF-α binding and activation of the NFκB and apoptosis pathways was shown to be reduced in some studies. 5: Accumulation of the mutated protein in the endoplasmatic reticulum (ER) might lead to an unfolded protein response (UPR). 6: Accumulation of the mutated protein in the cytoplasm might lead to spontaneous trimerization and activation.

Treatment for TRAPS

- NSAIDS
- Corticosteroids - short term high dose
  - response may wane
- Etanercept trial
  - Binds soluble and bound TNF-alpha
  - Demonstrated significant decrease in frequency, duration and severity of episodes
    - Attack score 100% to 30% with 3x/wk Etanercept
    - Decreased CRP and SAA

    McDermott, et al
  - ?Decreased efficacy after longer use
  - ? Effect on disease course
- Anti-IL1 agent, anakinra – recent use

- Prognosis: dependent on development of amyloidosis
  - Up to 25% of families affected

Case

14 mo boy presenting with Hx of almost monthly fevers since 6 months of age; a few times has had OM or URI Sx. Tired with decreased po during episodes.

Mother also states he seems to have belly pain, red eyes, and with recent fever, would not bear weight on one leg (new walker).

Only travel was to visit family in Paris.

On PE, 15th %ile for weight and 25th for Ht.

Normal otherwise

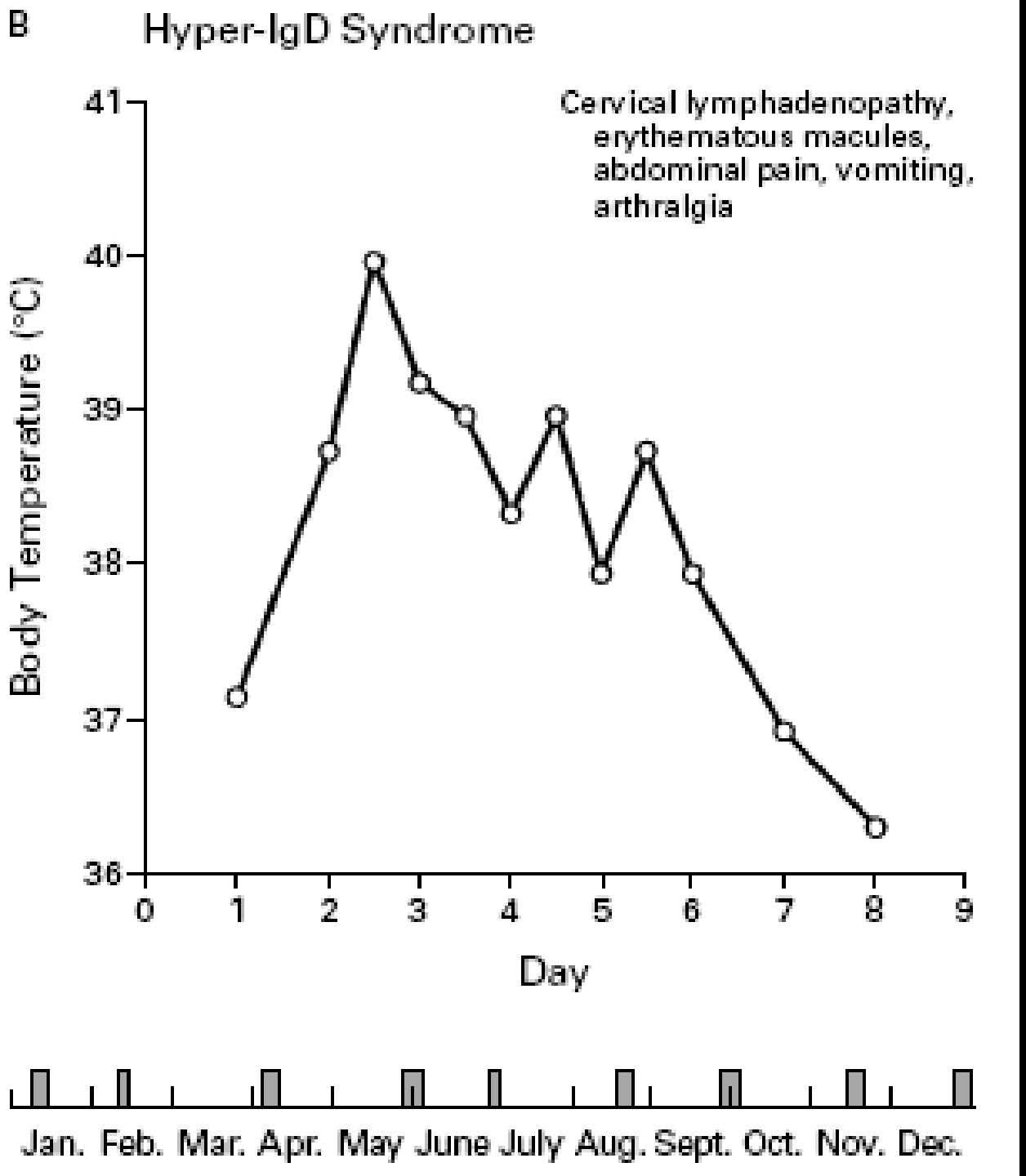
Thoughts??

Hyper IgD Syndrome (HIDS)

- Described in 1984
- Most affected individuals are Western European
  - >60% Dutch or French extraction
- Rare, Autosomal recessive

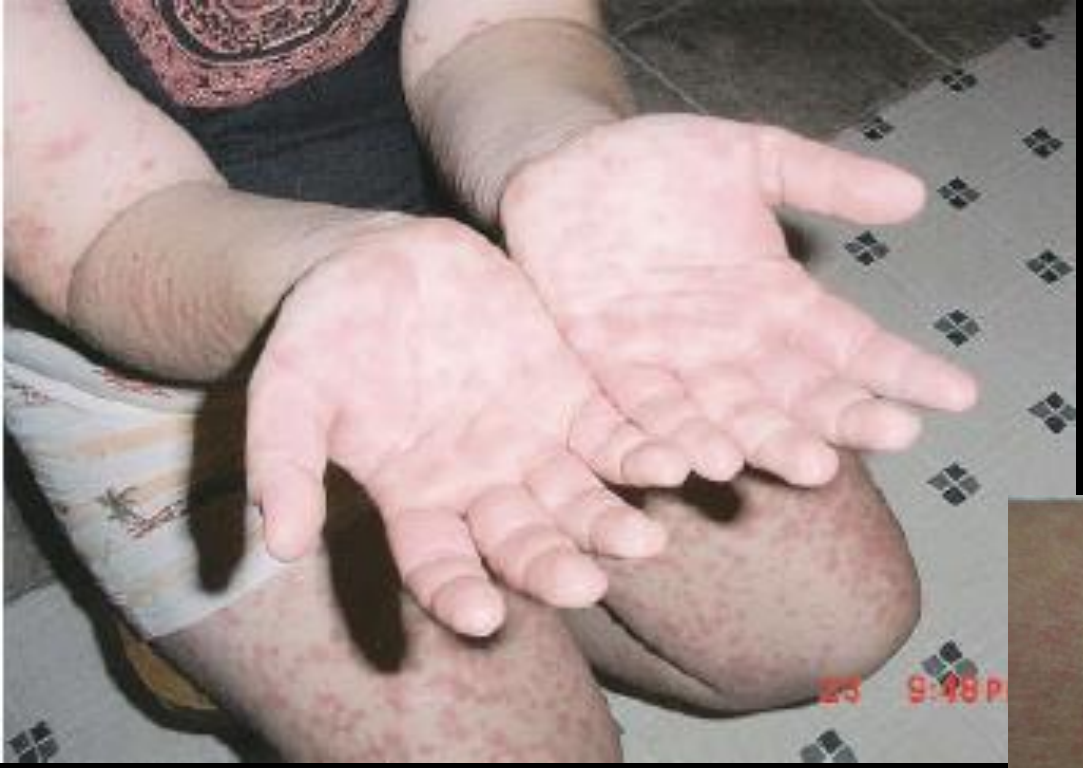
Hyper IgD Syndrome (HIDS)

- Clinical manifestations
  - Median age onset 6 months
  - Recurrent episodes of unexplained high fever, chills, cervical adenopathy, abdominal pain, diarrhea, vomiting
  - HSM, HA, arthralgia/arthritis (large jts), rash
  - Minority with painful oral/vaginal aphthous ulcers
  - Precipitating events:
    - vaccination, minor trauma, surgery, stress
  - Last 3 – 5 dys; Recur q4 – 6 wks (range 2 – 12wks)

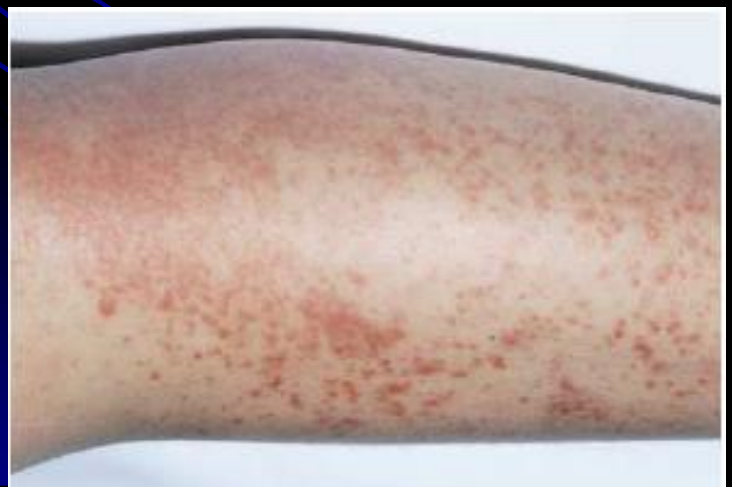


Drenth JPH, van de Meer JWM. NEJM 2001, 345:24:1748

Hyper IgD Syndrome



Erythematous macules and papules,
Occ patehiae and purpura
Takada, Kastner et al. ARTHRITIS & RHEUMATISM, 2003;48:2645



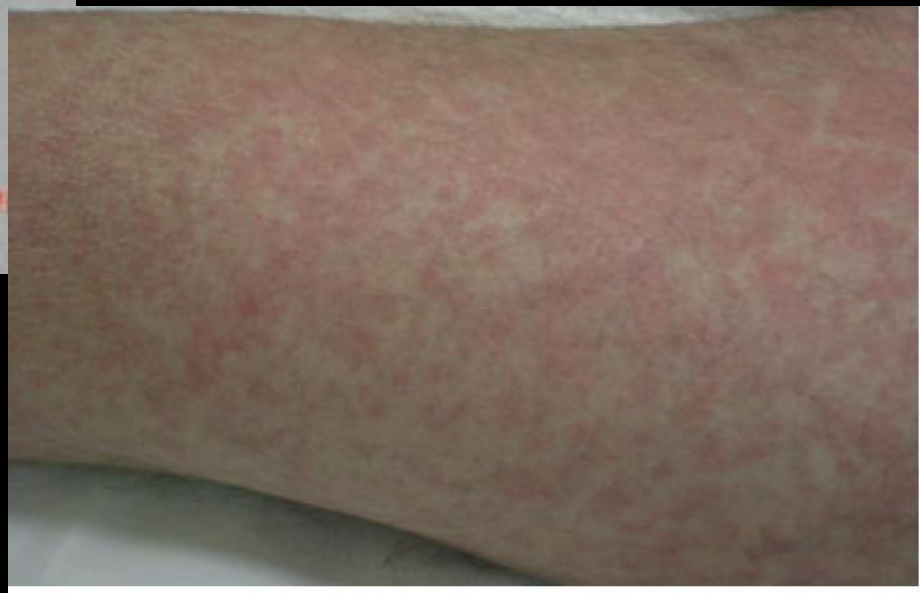


Fig 3. Maculopapular rash in HIDS.

Bodar EJ, et al. Brit J of Haematology;144

Drenth JPH, van de Meer JWM. NEJM 2001, 345:24:1748

Hyper IgD Syndrome

- Unique Laboratory Features
  - IgD level continuously elevated
    - usua > 100 IU/ml (0 – 5300 range in adults)
    - may be normal in < 3 year olds
  - IgA elevated in 80%
  - Urinary mevalonate elevated during attacks

- Genetic Defect
  - Mutations in Mevolonate Kinase (MVK) gene
    - Chromosome 12q
    - Key enzyme in cholesterol metabolic pathway
    - 1 – 10% residual Mevalonate kinase activity
      - < 0.3% activity in mevalonic aciduria

Immunoblots of cell lysates: HIDS vs Controls

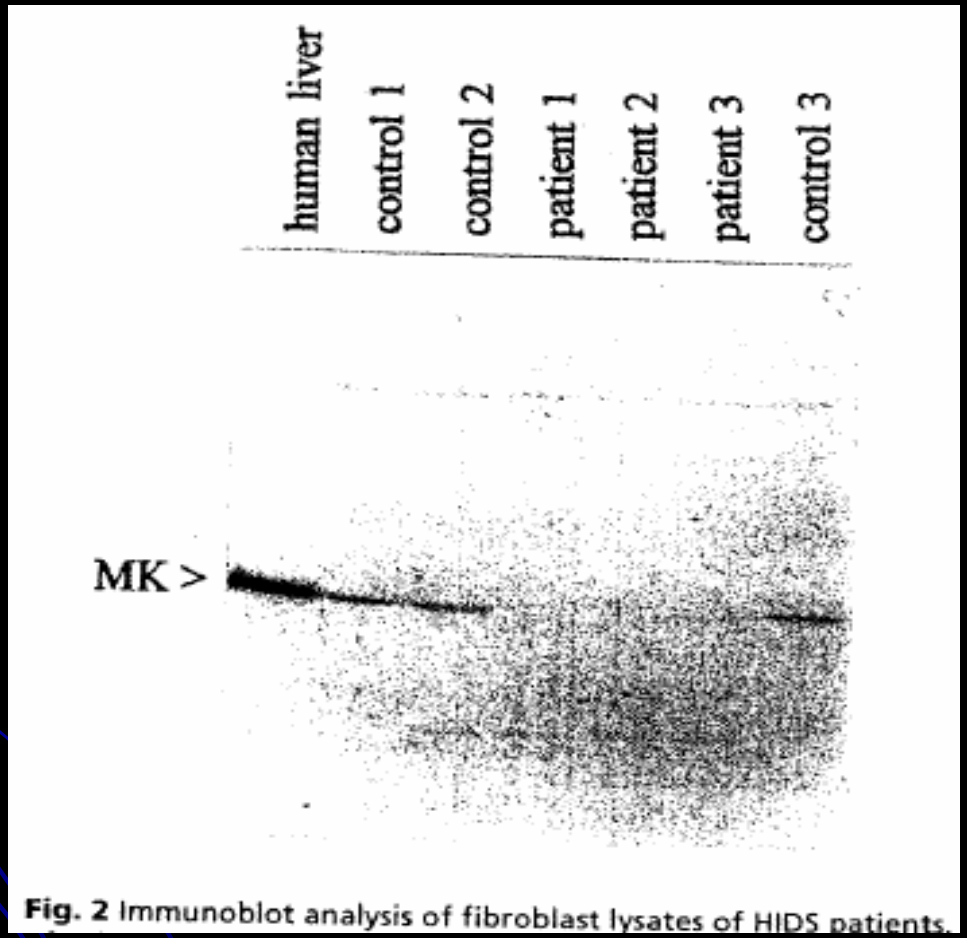


Fig. 2 Immunoblot analysis of fibroblast lysates of HIDS patients.

Houton Sm, et al. Nature Genetics 1999;22:175

Mevolanate metabolism and Cholesterol Biosynthesis

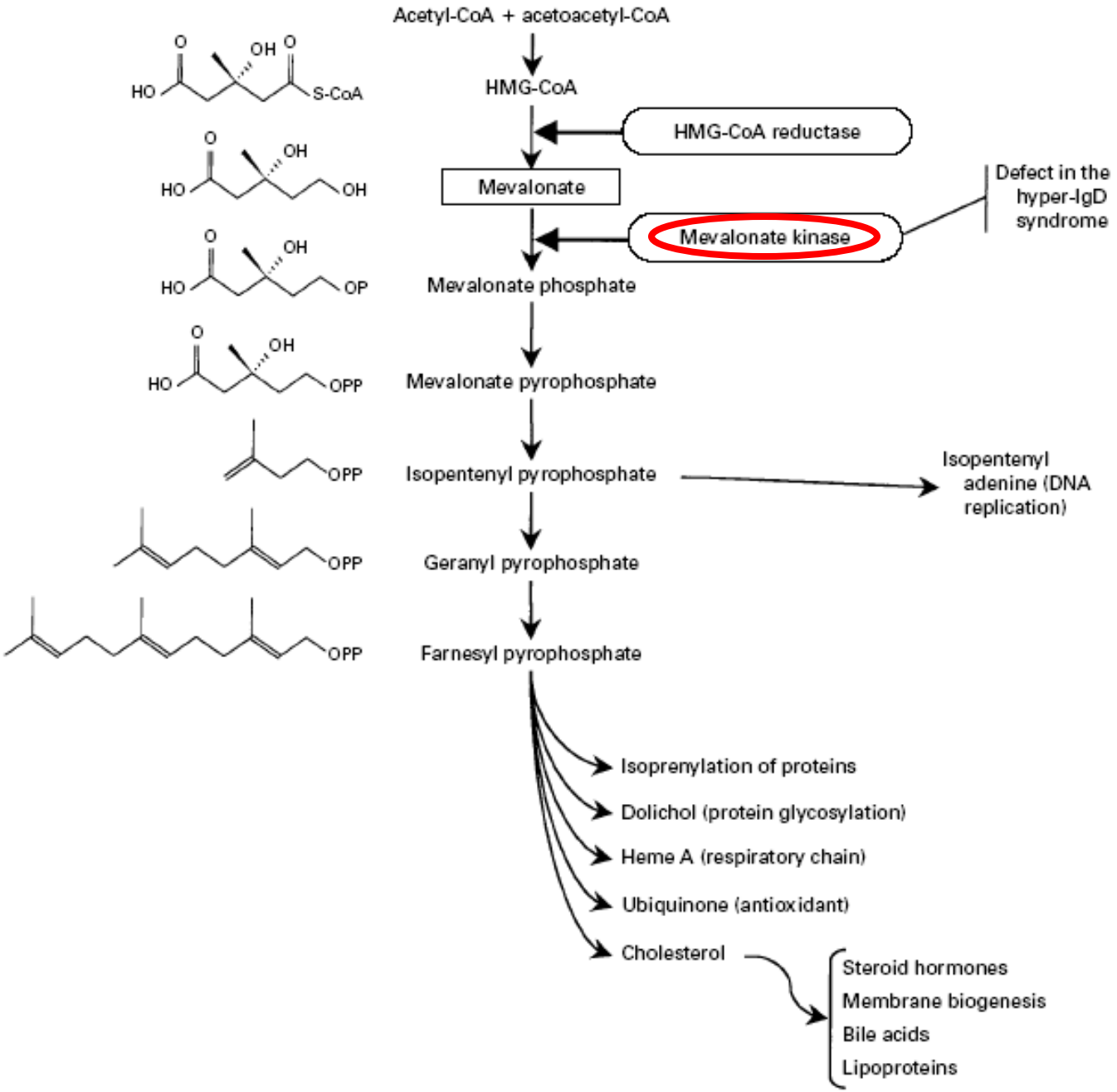
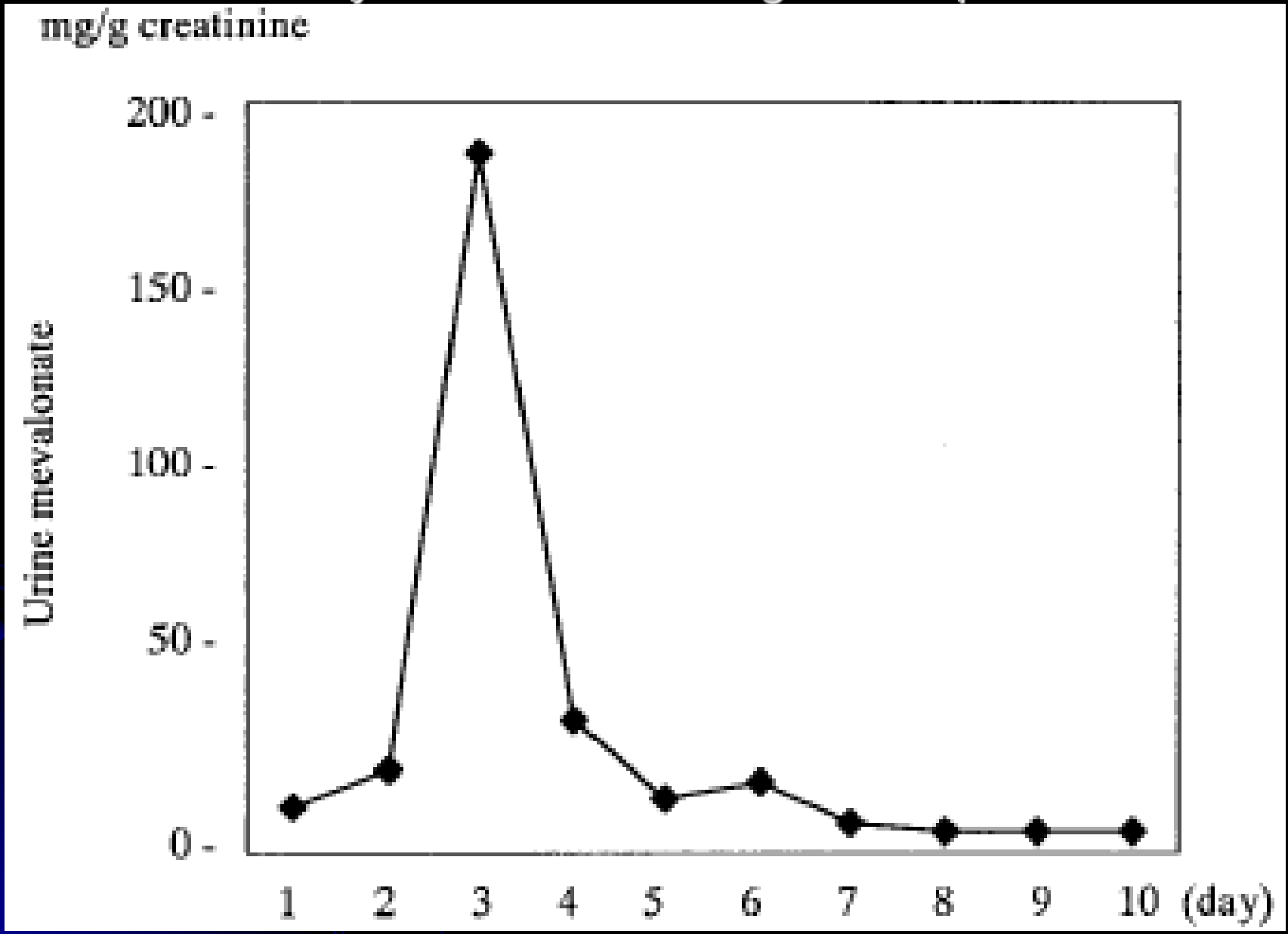


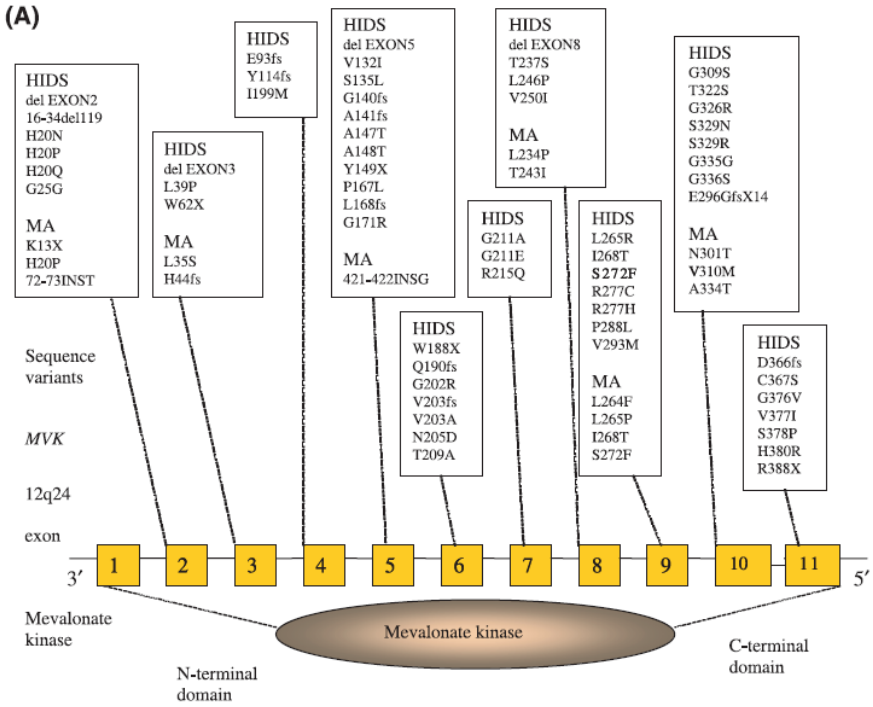
Figure 4. Metabolism of Mevalonate and Biosynthesis of Cholesterol in Mammalian Cells.

Drenth JPH, van de Meer JWM. NEJM 2001, 345:24:1748

Urinary Mevalonate during HIDS episode



Takada, Kastner et al. ARTHRITIS & RHEUMATISM, 2003;48:2645



British Journal of Haematology, **144**, 279–302

Fig 9. Isoprenoid metabolism. (A) Disease-causing sequence variants in *MVK* and their location related to exons. The encoded protein mevalonate kinase is shown at the bottom of the figure. (B) Overview of the isoprenoid metabolism. The broad black arrows indicate the subsequent enzymatic transformations. The yellow stars indicate two key enzymes in the pathway. The red arrows point to the end products and the thin black arrows indicate negative feedback on the pathway by SREBs. Reduced mevalonate kinase activity leads to increased mevalonate upstream and low normal-reduced end products.

HIDS

- Why episodic?
  - 1 – 10% baseline activity
  - 1 – 2% activity during attacks

- Etiology for inflammation?
  - Accumulation of substrate (Mevalonate)

  Or shortage of substrates distal to mevalonate
  - Isoprenoid shortage leads to ???
    - Pro-caspase to Caspase converting Pro-ILbeta to IL beta, resulting in Inflammation
  - MK-deficient cells secrete more IL-1beta than controls

HIDS Treatment Trials and Prognosis

- Maximum doses of NSAIDS for 4-7 dys - ? benefit
- Oral glucocorticoids (1mg/kg for 4-7 dys)
- Treatment Trials:
  - Simvastatin (HMG-CoA reductase inhibitor) Placebo controlled cross-over trial
  - Thalidomide ineffective in double-blind placebo controlled trial
  - Reduce Cytokine signaling
    - Etanercept
    - IL-1-receptor antagonist (Anakinra)-4 case reports of success
- Prognosis
  - Attacks throughout life, highest frequency in childhood and adolescence
  - Amyloidosis very uncommon

Muckle-Wells Syndrome, Familial Cold Autoinflammatory Syndrome, Neonatal Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurologic Cutaneous and Articular Syndrome (CINCA)

- Dominant inheritance
- Now thought to be spectrum of illnesses, rather than distinct entities
  - FCAS mildest; NOMID/CINCA most severe
  - Onset usually infancy
  - Clinical features: nonpuritic, urticarial rash (Bx: PMN & Lymph infiltrate)
    - FCAS -rash precipiated by cold
    - MWS & NOMID with CNS manifestations:

    SNHL, Optic nerve elevation, Chr aseptic meningitis

Muckle-Wells Syndrome, Familial Cold Autoinflammatory Syndrome, NOMID / CINCA

- Disorders of the Pyrin family of Proteins
  - Located on Chromosome 1q, CIAS1 gene
  - Encodes Cryopyrin protein, in PMNs and monos
    - Increases NK-kB signalling, proinflamm effect
    - mediate Caspase-1 activation

    with IL-1 production and fever
    - Recent report of elevated IL-1beta expression in monocytes of NOMID pt
- Treatment: IL-1 antagonist???

Best Practice & Research Clinical Rheumatology
Vol. 22, No. 5, pp. 811–829, 2008

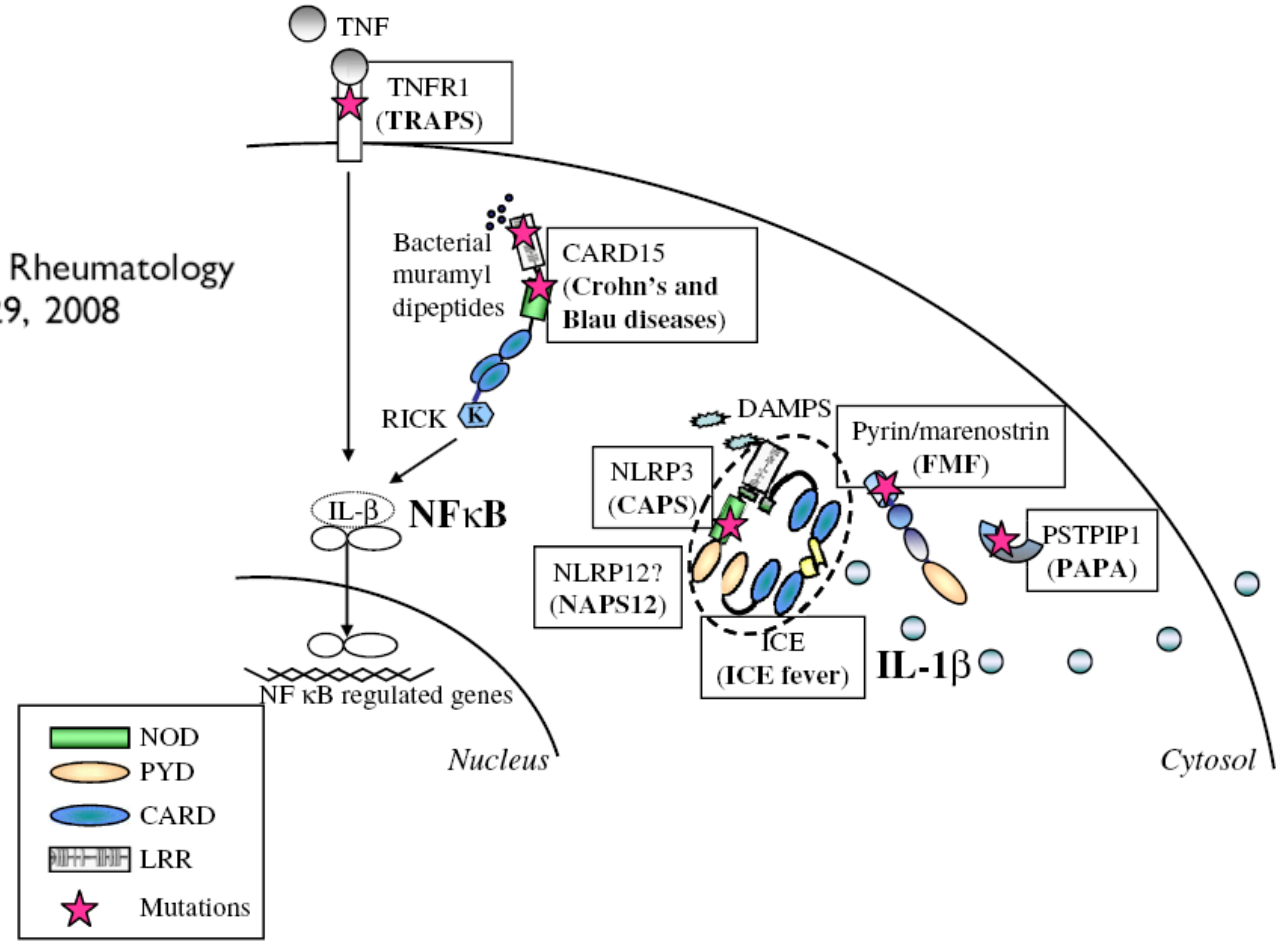
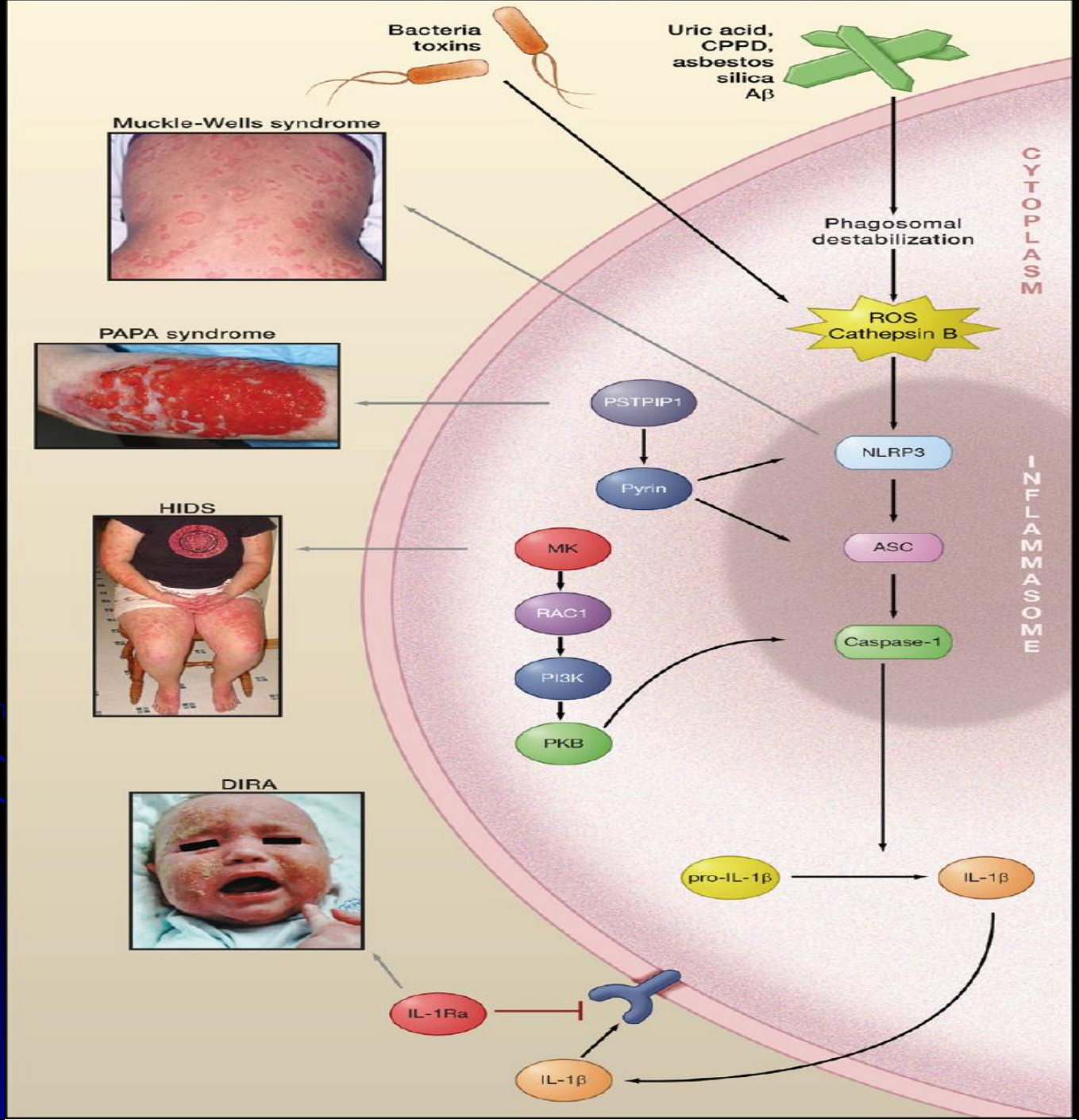


Figure 4. Presumed pathophysiological events in autoinflammatory disorders with identified genes. TRAPS and CARD15-associated diseases are due to altered NFκB regulation, whereas the other represented diseases are caused by a direct (NLRP3 and 12?, ICE fever) or indirect (FMF, PAPA, MKD) deregulation of IL-1β activation. Molecular oligomerization of TNFR1 and NLRP3 is not represented for simplicity. The dotted line represents the NLRP3 inflammasome as described in Figure 3. The NLRP12 hypothetical inflammasome is depicted by a question mark. CAPS, cryopyrin-associated periodic syndrome; CARD15, caspase recruitment domain 15; FMF, familial Mediterranean fever; ICE, interconvertin enzyme; IL-1, interleukin-1; LRR, leucine-repeat rich; MKD, mevalonate kinase deficiency; NAPS12, NLRP12-associated periodic disease; NLRP12, NLR family, pyrin domain containing 12; NOD, nucleotide-binding oligomerization domain; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum and acne; PSTPIP1, proline serine threonine phosphatase interacting protein; PYD, pyrin domain; TNF, tumor necrosing factor; TRAPS, TNF-receptor-associated periodic syndrome

The Inflammasomopathies: IL-1β-Mediated Disorders



Diagnostic Clues in the Clinical Presentation of Periodic Fever Syndromes

- History
  - Onset, periodicity
  - Signs and Symptoms
  - Ancestry +/- helpful
- PE
  - Rash
  - Conjunctival injection
  - Oral lesions
  - Adenopathy, HSM

Distinguishing Clinical Features

- PFAPA
  - Clockwork periodicity
  - Prodrome
- FMF
  - Short attacks of fever and serositis
- HIDS
  - Onset early in life
  - Diarrhea, Ulcers
- TRAPS
  - Longer duration of attacks
  - Conjunctivitis and localized myalgias
  - Periorbital edema

Predictors of a Positive Gene Analysis in pts presenting with clinical PFAPA

228 children with periodic fevers

Independent correlates for positive gene analyses

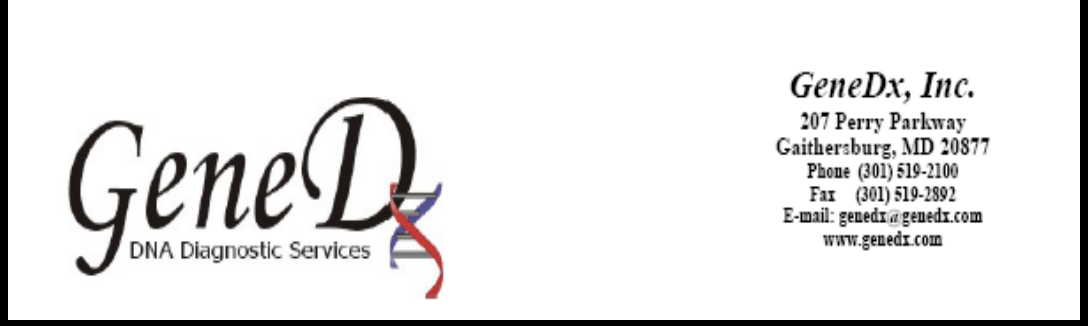
Gattorno, et al

- Young age at onset
- Positive FHx of PF
- Thoracic pain
- Abdominal pain
- Diarrhea
- Oral aphthosis

Laboratory Evaluation

- CBC / morph, ESR, CRP
  - when afebrile and febrile
- Urinalysis
- Immunoglobulin levels, incl IgD & IgA
- Urinary Mevalonate when febrile
- GeneDx
  - Consent; Refer to specialist for DNA testing
- Dan Kastner, MD @ NIAMS
  - Periodic Fever Cohort
- INFEVER European Cohort

GeneDx, Inc.
207 Perry Parkway
Gaithersburg, MD 20877
Phone (301) 519-2100
Fax (301) 519-2892
E-mail: genedx@genedx.com
www.genedx.com



Identifiable Mutations in TNFRSF1A

- Familial = ___%
- Sporadic cases=___%

FMF ?

HIDS ?

Clinical Feature	FMF	TRAPS	HIDS	FCAS	MWS	NOMID/CINCA
Usual ethnicity	Turkish, Armenian, Arab, Jewish, Italian	Any ethnicity	Dutch, other Northern European	Mostly European	Mostly European	Any ethnicity
Duration of attacks	12-72 hours	Days to weeks	3-7 days	12-24 hours	2-3 days	Continuous, with flares
Abdominal	Sterile peritonitis, constipation	Peritonitis, diarrhea or constipation	Severe pain, vomiting, diarrhea, rarely peritonitis	Nausea	Abdominal pain	Not common
Pleural	Common	Common	Rare	Not seen	Rare	Rare
Arthropathy	Monoarthritis, rarely protracted arthritis in knee or hip	Arthritis in large joints, arthralgia	Arthralgia, symmetric polyarthritis			
Polyarthralgia	Polyarthralgia, oligoarthritis, clubbing	Epiphyseal overgrowth, contractures, intermittent or chronic arthritis, clubbing				
Cutaneous	Erysipeloid erythema on lower leg, ankle, foot	Migratory rash, underlying myalgia	Diffuse maculopapular rash, urticaria	Cold-induced urticarial rash	Urticaria-like rash	Urticaria-like rash
Ocular	Rare	Conjunctivitis, periorbital edema	Uncommon	Conjunctivitis	Conjunctivitis, episcleritis	Uveitis, conjunctivitis, progressive vision loss
Neurologic	Rarely aseptic meningitis	Controversial	Headache	Headache	Sensorineural deafness	Sensorineural deafness, chronic aseptic meningitis, mental retardation, headache
Lymphatic	Splenomegaly, occasional lymphadenopathy	Splenomegaly, occasional lympadenopathy	Cervical adenopathy in children	Not seen	Rare	Hepatosplenomegaly, adenopathy
Vasculitis	Henoch-Schönlein purpura (HSP), polyarteritis nodosa	HSP, lymphocytic vasculitis	Cutaneous vasculitis common, rarely HSP	Not seen	Not seen	Occasional
Systemic amyloidosis	Risk depends on *MEFV* and *SAA* genotypes; more common in Middle East	Occurs in ~10%; risk increased with cysteine mutations	Rare	Rare	Occurs in ~25%	May develop in some patients, usually in adulthood

	PFAPA	Cyclic Neutropenia	Familial Mediterranean Fever	HIDS	TRAPS
Onset < 5 years	Expected	Usual; often < 1 year old	Common; peak onset middle of first decade	Expected; often < 1 year old	Variable
Length of fever episode	4 days	5–7 days	1–3 days	3–7 days	2 days–weeks
Periodicity of episodes	q3–6 weeks; typically q28 days	q2–8 weeks; q21 days in > 90%	Irregular intervals: weekly, q3–4 months or less often	q4–8 weeks or irregular	Irregular intervals; varies weeks to years
Associated symptoms/ signs	Pharyngitis 65–70%; aphthous stomatitis 65–70%; cervical adenopathy 75–85%	Ulcers, lingering gingivitis and periodontitis; recurrent otitis media and sinusitis; rare peritonitis; rare gram-negative bacillary or *Clostridium septicum* septicemia	Severe abdominal pain; erysipelas-like rash; scrotal pain and swelling; polyserositis	Abdominal pain, diarrhea in young; headache; arthralgia; diffuse maculopapular rashes; aphthous ulcers; splenomegaly; mood swings; immunizations trigger	Abdominal pain; migratory pseudocellulitis and myalgia; periorbital edema; scrotal pain; polyserositis
Ethnicity/geography	None; rare in siblings	No ethnicity	Most common among Jewish, Armenian, Turkish, Arab, Italian, but cases from worldwide ancestry	Predominantly northern European ancestry	Variable ancestry
Inheritance	None; parent may have history of excessive high fevers as child	Autosomal dominant	Autosomal recessive	Autosomal recessive	Autosomal dominant
Laboratory findings	Mild neutrophilia; ESR elevated < 60 mm/ hour during episode only	Absolute neutrophil count < 200 cells/mm^3 for 3–5 days	Elevated acute-phase reactants	Elevated acute-phase reactants; variable ↓ serum cholesterol; variable ↑ IgA and IgD (> 100 IU/mL) or may not be ↑ (especially < 3 years)	Elevated acute-phase reactants
Etiology/diagnosis	Unknown; clinical diagnosis	Chromosome 19p; *ELA2* mutations leading to mutant neutrophil elastase; apoptosis marrow myeloid cells	Chromosome 16p; *MEFV* missense mutations; PYRIN domain; dysregulation inflammation and apoptosis	Chromosome 12q; *MVK* mutations leading to ↓ mevalonate kinase and isoprenoids; mevalonic aciduria during attacks	Chromosome 12p; *TNFRSF1A* mutations; ↓TNFR-1; complex TNF pathophysiology in binding intracellular trafficking and leukocyte apoptosis
Treatment	None established (see text)	Recombinant G-CSF; aggressive periodontal care; aggressive treatment suspected septicemia	Colchicine	Simvastatin (investigational); etanercept (investigational); allogeneic bone marrow transplant (single case)[103]	Corticosteroid; etanercept (investigational)
Sequelae	None established	Dental problems; infection	Amyloidosis	Amyloidosis case reports	Amyloidosis 10%

Summary

- Periodic Fevers
  - Historical and Exam clues
  - Extensive Differential Diagnosis
  - PFAPA
  - Familial Hereditary Fever syndromes (Autoinflammatory syndromes)
    - Unique group of dzs with permanent genetic defects but intermittent clinical syndromes
    - Rare

Approach to the Child with Prolonged, Recurrent or Periodic Fever

- Extensive History
  - Fever: how obtained, duration, pattern
  - Detailed Review of Systems
  - Exposures
  - Genetic background
- Detailed Physical Examination
  - Growth chart
  - Thorough general examination
  - Identification of target organ abnormalities
  - Notation of mouth ulcers, exanthem, joint abnormalities, lymph nodes

Screening Laboratory Tests and Imaging in Children with Prolonged, Recurrent or Periodic Fever

Laboratory:

- CBC with manual differential *
- ESR and CRP*
- Screening serum chemistry (uric acid/LDH if prolonged fever)
- Urinalysis and Urine culture
- Blood culture (if prolonged fever)
- Additional lab tests
  - targeted to specific organs per Hx, PE or prioritized DDx

Imaging

- Chest X-ray (if prolonged or recurrent fever)
- Other imaging only as directed by examination

Labs and Imaging rarely establish unexpected Dx

- Use to confirm or support a Dx

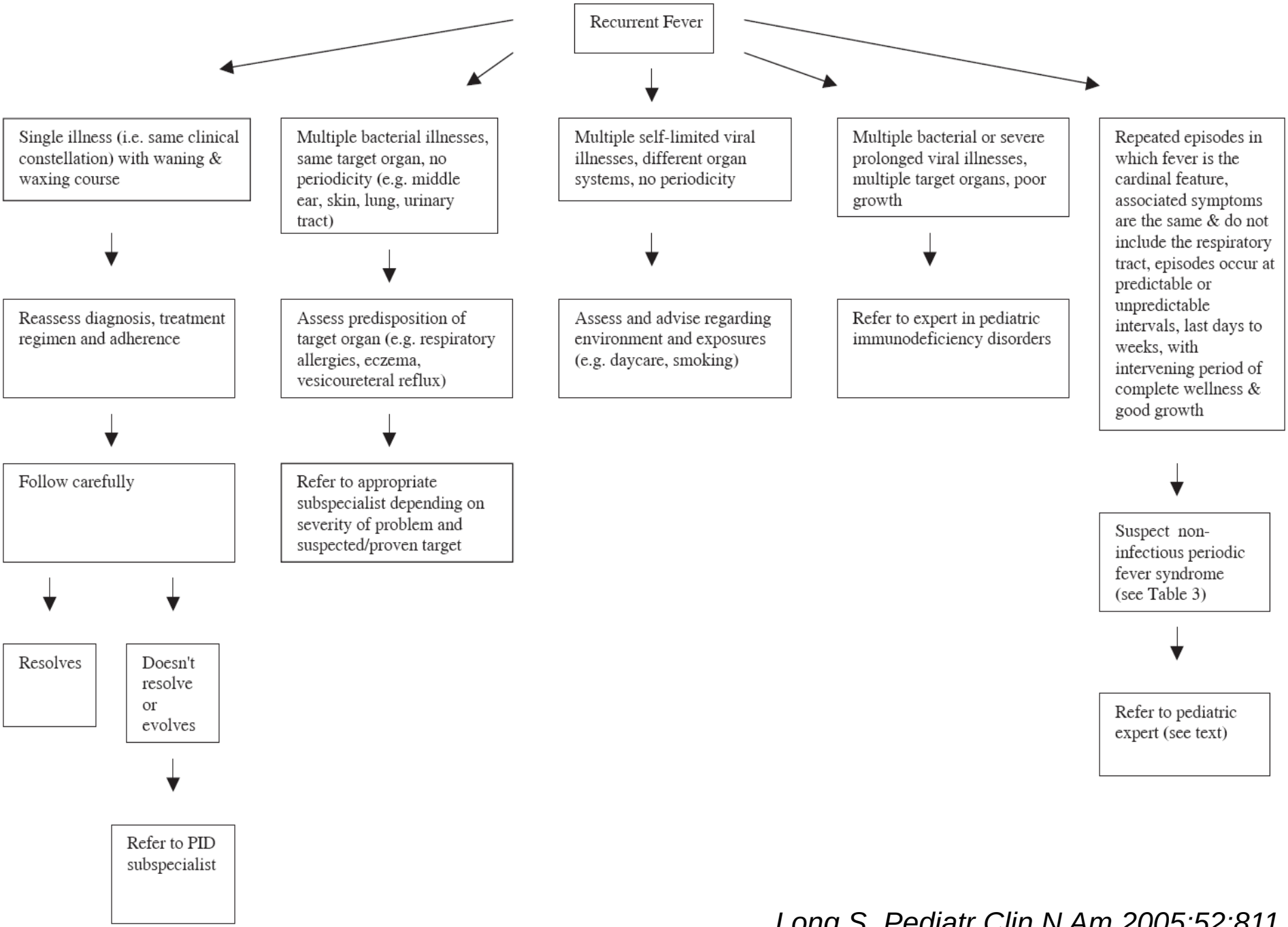
or to establish "wellness" of organ systems

*Perform during episode and interval if periodic fever.

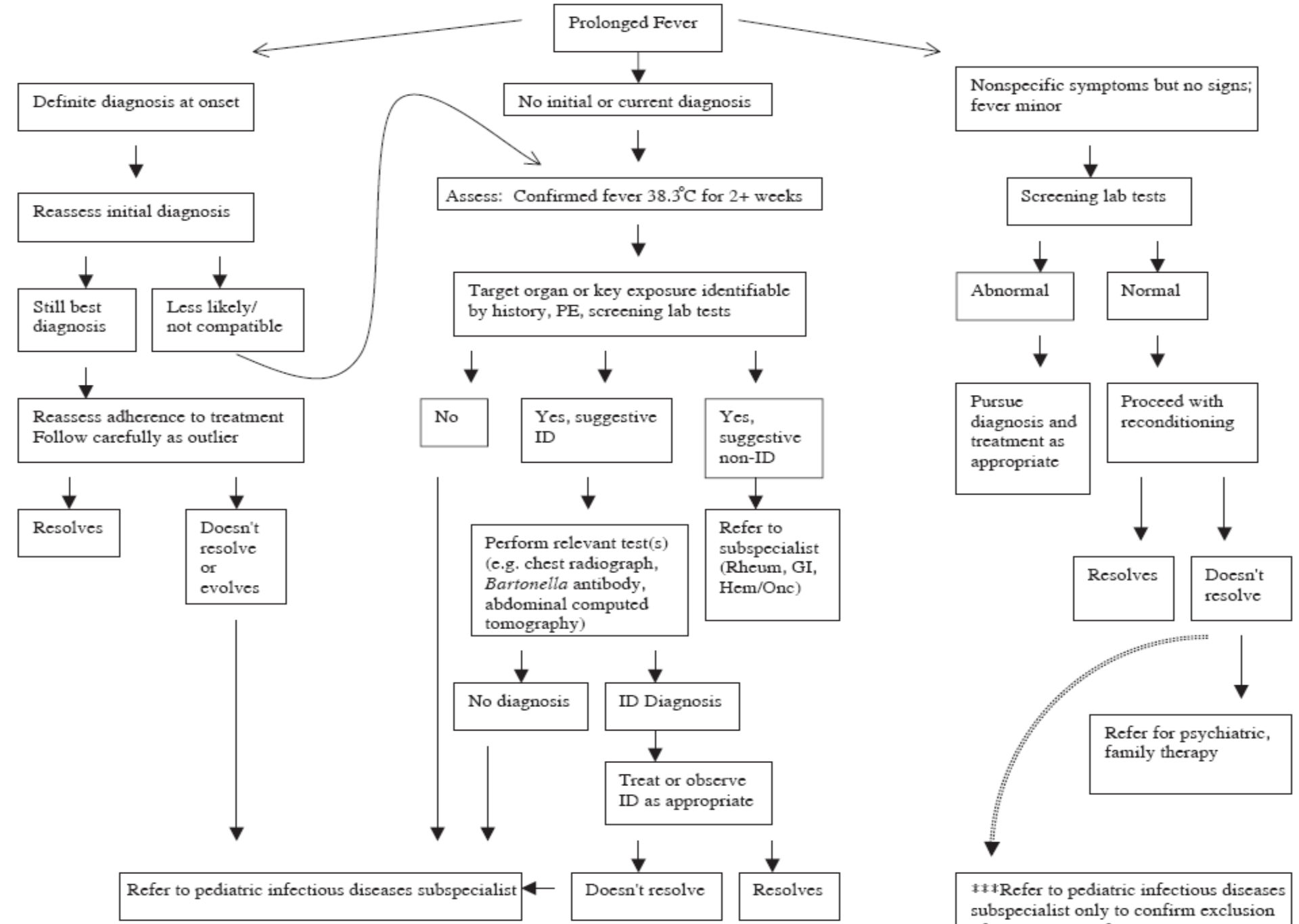
Principles and Practice of Pediatric Infectious Diseases 2008,3rd ed, Chapter 17, Long SS, Edwards KM; p.126

KEY: Close Follow-up

- Repeated History with Serial Physicals
- Directed Laboratory Testing and Imaging
- Wait for diagnostic clues to emerge
- Use Fever Diary to track pattern
- UNLESS:
  - progressive weight loss
  - toxic appearance
  - abnormalities on PE or screening tests



Long S. Pediatr Clin N Am 2005;52:811



Long S. Pediatr Clin N Am 2005;52:811

HIDS Patients' and Relatives' Mutations

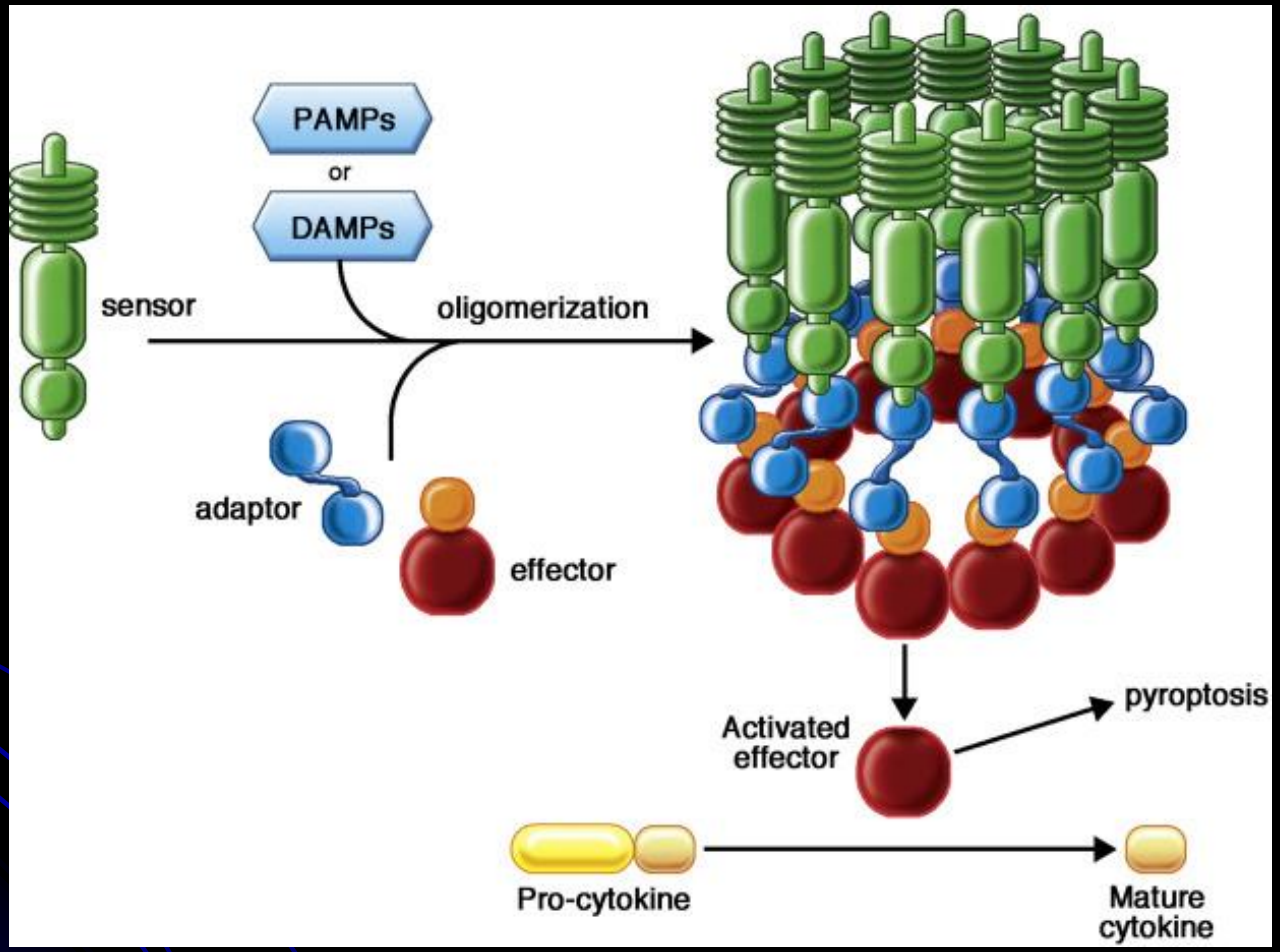
Table 2 • Biochemical data and mutations of HIDS patients and their relatives

Individual	Urinary mevalonic acid[a]	MK activity in lymphocytes[b]	Mutation	Coding effect
control subjects	0.08–0.3	95.8±17.0	–	–
HIDS patient 1	8.3–9.6	2.0 (2.1%)	59A→C	H20P
			1129G→A	V377I
mother	ND	21.1 (22%)	59A→C	H20P
father	ND	44.0 (46%)	1129G→A	V377I
sister	ND	30.5 (32%)	1129G→A	V377I
brother	ND	117 (122%)	no mutation	–
HIDS patient 2	6.4	1.3 (1.2%)	59A→C	H20P
			1129G→A	V377I
mother	ND	24.1 (25%)	ND	–
father	ND	38.7 (41%)	ND	–
HIDS patient 3	5.3–27.8	1.9 (2%)	803T→C	I268T
			1129G→A	V377I
mother	ND	31.0 (33%)	ND	–
father	ND	25.4 (27%)	ND	–
HIDS patient 4	ND	3.3 (3.4%)	1129G→A	V377I

[a]mmol/mol creatinine. [b]pmol/min/mg protein. ND, not determined.

Houton Sm, et al. Nature Genetics 1999;22:175

The Inflammasome



DIAGNOSTIC CRITERIA FOR FAMILIAL MEDITERRANEAN FEVER (FMF)[a]

Major Criteria: Recurrent Attacks of:

1. Fever (1–3 days).
2. Peritonitis (1–3 days).
3. Pleuritis (unilateral) or pericarditis (1–3 days).
4. Monoarthritis (hip, knee, ankle) (1–30 days).

Minor Criteria: Incomplete Attacks Involving:

1. Abdomen.
2. Chest.
3. Joint (e.g., not a typical location).
4. Exertional leg pain.
5. Favorable response to colchicine.

Supportive Criteria

1. Family history of FMF.
2. Appropriate ethnic origin.
3. Age <20 years at disease onset.

4–6. Features of the attack (severe, spontaneous resolution, symptom-free interval).

7. Transient inflammatory, acute-phase response.
8. Episodic proteinuria or hematuria.
9. Unproductive laparotomy.
10. Consanguinity of parents.

[a]Diagnosis of FMF requires the satisfaction of ≥1 major criteria, or ≥2 minor criteria, or 1 minor criterion plus ≥5 supportive criteria, or 1 minor criterion plus ≥4 of the first 5 supportive criteria.[81]