APPROACH TO THE SICK CHILD: WHEN TO WORRY AND WHAT TO DO

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"Little Liam is always sick!"

- 3 year old male with recurrent respiratory infections
- Infections occur monthly and linger for 2-3 weeks
- Associated symptoms of fatigue, loss of appetite, hives
- Parents are tired of going to the doctor and being constantly told "it's a virus"
- "Liam's older sisters Emma and Charlotte were never sick like this!"

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1. THE "WORRIED WELL"

3

BIG LOVE

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The BIG-LoVE study

- **B**etter **I**dentification of **G**erms-**Lo**ngitudinal **V**iral **E**pidemiology
- Twenty-six households (108 individuals) provided concurrent weekly symptom diaries and nasal swab data for 4166 person-weeks
- The FilmArray polymerase chain reaction (PCR) platform (BioFire Diagnostics, LLC) was used to detect 16 respiratory viruses.
- Viral illnesses were defined as ≥1 consecutive weeks with the same virus detected with symptoms reported in ≥1 week

Clin Infect Dis. 2015 Oct 15;61(8):1217-24

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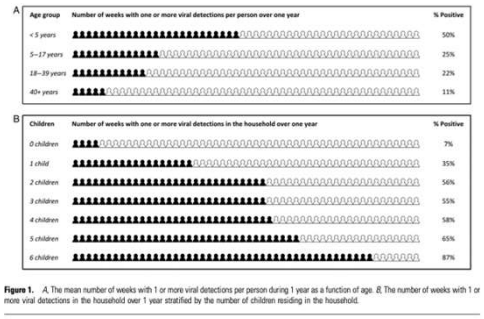

Figure 1. *A*, The mean number of weeks with 1 or more viral detections per person during 1 year as a function of age. *B*, The number of weeks with 1 or more viral detections in the household over 1 year stratified by the number of children residing in the household.

Clin Infect Dis. 2015 Oct 15;61(8):1217-24

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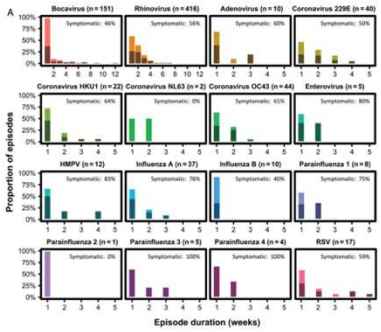

Clin Infect Dis. 2015 Oct 15;61(8):1217-24

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My approach

1. Reassurance ("Yes, Little Liam IS always sick – and it's normal!")
2. If reassurance fails - tests to consider:
   - CBC/diff
   - IgG/A/M/E
   - Skin and/or serum environmental allergen testing (if appropriate)
   - Spirometry
3. If that still is not enough – options to consider:
   - Therapeutic vaccination with 23 valent pneumococcal polysaccharide vaccine (can also be diagnostic) or 20 valent pneumococcal conjugate vaccine

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Therapeutic immunization

- 72 patients with 4+ RTI treated with antibiotics per year, 4+ AOM treated with antibiotics per year or 2+ sinusitis per year
- 57% ages 2-5 years, 43% older

	Patients, N (%)
Preimmunization antibody levels	
Nonprotective	64 (89)
Low-range protective	8 (11)
Antibody response	
Protective	60 (83)
Partial	12 (17)
Clinical and serological response	
Positive clinical response	69 (96)
Positive clinical response with partially protective serology	12 (17)
No clinical response despite protective serology	3 (4)
Patients aged 2–5 yr	41 (57)
Positive clinical response with protective serology	36 (88)
Positive clinical response with nonprotective serology	2 (5)
No clinical response with protective serology	3 (7)
Patients 6 yr and older	31 (43)
Positive clinical response with protective serology	21 (68)
Positive clinical response with nonprotective serology	10 (32)
Patients given PCV7 (3–4 doses)	45 (62)
Positive clinical response with protective serology	37 (82)
Positive clinical response with nonprotective serology	5 (11)
No clinical response with protective serology	3 (7)
Non-PCV7 group	27 (37)
Positive clinical and serological response	20 (74)
Positive clinical response with nonprotective serology	7 (26)

The Pediatric Infectious Disease Journal 35(2):p 205-208, February 2016

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When you hear hoofbeats, think HORSES, not Zebras

- Prof. Theodore Woodward, Univ of Maryland School of Medicine, c. 1948

http://mrzepczynski.blogspot.com/2015/11/assuming-horses-not-zebras-is-good.html
https://quoteinvestigator.com/2017/11/26/zebras/

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"The doctors in the hospital referred us here after discharge"

- 2 mo male with history of neonatal bacterial meningitis
- Full term, no complications, feeding and growing well at home initially
- 10 days of life - cyanosis and respiratory distress so presented to ED - Febrile to 38.2 C, LP + E. coli, imaging with extensive dural venous thrombosis
- Treated with anticoagulation and 6 weeks of IV antibiotics with improvement
- Father with possible immune deficiency

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THE "WORRIED SICK"

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Number of signs present	Sensitivity	Specificity
One sign	100%	26%
Two signs	94%	64%
Three signs	77%	86%

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

Allergy Asthma Immunol Res (2013). 5(2):88-95

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Labs

- WBC 9.43, normal diff
- Hgb 11.3 / Hct 32.1
- CMP normal (normal Tot prot / alb)
- IgG 146.6 (L) (206-601 mg/dl)
- IgA 2.2 (L) (2.8 – 47 mg/dl)
- IgM 20.7 (nl) (17– 105 mg/dl)
- IgE 4.2 (L) (8 – 144 IU/ml)

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My approach

1. Early initiation of antibiotics with any signs of illness pending further workup
2. Labs to consider:
   - Flow cytometry
   - Evaluation of vaccine response
   - Complement studies
   - Evaluation for asplenia (RBC pits, Howell Jolly bodies on smear)
   - Targeted genetic testing panel
3. If indicated: Initiation of prophylactic antibiotics, immunoglobulin replacement therapy (or both!)

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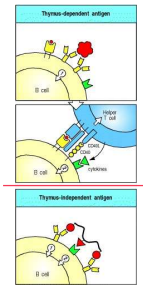
T-cell independent (polysaccharide) and T-cell dependent (protein/conjugated) vaccines



- Pneumococcal conjugate (Prevnar 7, Prevnar 13, Prevnar 20)
- *Haemophilus influenza* B conjugate
- Diphtheria and tetanus

- Pneumococcal polysaccharide (Pneumovax 23)
- ~~Meningococcal polysaccharide (Menomune)~~
- S. typhi polysaccharide (Typhim Vi)

Figure adapted from Janeway's Immunobiology: The Immune System in Health and Disease

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Response to protein/conjugated vaccines

- Impaired typically only in more severe forms of immunodeficiency
- An **absent** response to tetanus (assuming vaccination within 10 years) is **always abnormal**
- Poor antibody response to other vaccines **does not necessarily represent immunodeficiency**
  - Varicella
  - Diphtheria
  - Haemophilus influenzae B
  - Hepatitis B
  - PCV (especially serotypes 6B, 9V, 23F)

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Pneumococcal vaccines

- **Pneumococcal polysaccharide - Pneumovax 23 (PPSV23) (1983)**
- **Pneumococcal conjugate vaccine**
  - Prevnar (PCV7) (2000)
  - Prevnar 13 (PCV13) (2010)
  - Prevnar 15 (PCV15) (2021)
  - Prevnar 20 (PCV 20) (2021) – Now indicated for ages 6 weeks and older
- Know exactly which "pneumonia vaccine" the patient got and when (Request records!)
- You **cannot** interpret pneumococcal titers without knowing this information!

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Comparison of serotypes in pneumococcal vaccines

Conjugate vaccines						Polysaccharide vaccine
PCV7 (Prevnar 7, no longer available)	PCV10[a] (Synflorix)	PCV10[a] (Pneumosil)	PCV13[b] (Prevnar 13)	PCV15[b] (Vaxneuvance)	PCV20[c] (Prevnar 20)	PPSV23[b] (Pneumovax 23)
1	1	1	1	1	1	1
–	–	–	–	–	–	2
–	–	–	3	3	3	3
4	4	–	4	4	4	4
–	5	5	5	5	5	5
–	–	6A	6A	6A	6A	–
6B	6B	6B	6B	6B	6B	6B
–	7F	7F	7F	7F	7F	7F
–	–	–	–	–	8	8
–	–	–	–	–	–	9N
9V	9V	9V	9V	9V	9V	9V
–	–	–	–	–	10A	10A
–	–	–	–	–	11A	11A
–	–	–	–	–	12F	12F
14	14	14	14	14	14	14
–	–	–	–	–	15B	15B
–	–	–	–	–	–	17F
18C	18C	–	18C	18C	18C	18C
–	–	19A	19A	19A	19A	19A
19F	19F	19F	19F	19F	19F	19F
–	–	–	–	–	–	20
–	–	–	–	22F	22F	22F
23F	23F	23F	23F	23F	23F	23F
–	–	–	–	33F	33F	33F

https://www.uptodate.com/contents/image?imageKey=PEDS%2F77274

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Response to pneumococcal conjugate vaccine (PCV-7, PCV-13, PCV-15, PCV-20)

- **The definition of a "normal" response is not well defined** and based on prevention of invasive pneumococcal disease (IPD)
- ? 0.35 or higher to the serotypes contained in the vaccine the patient has received

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Response to pneumococcal polysaccharide vaccine (PPSV-23)

- **The definition of a "normal" response is not well defined** and based on consensus opinion
  - Children < 2 years:
    - Normal responses are not defined
  - Children 2 – 5 years (who have been given PCV and PPSV-23 in the last 8 weeks):
    - Titer ≥1.3 ug/ml to 50% of **non-conjugate vaccine serotypes**
  - Adults 6 - 65 years (who have been given PCV and PPSV-23 in the last 8 weeks):
    - Titer ≥ 1.3 ug/ml to 70% of **non-conjugate vaccine serotypes**
  - Adults > 65 years:
    - ? Probably waning immunity

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Response to pneumococcal polysaccharide vaccine (PPSV-23)

TABLE IV. Summary of PPV23-deficient response phenotypes

Phenotype*	PPV23 response, age >6 y	PPV23 response, age <6 y	Notes
Severe	≤2 protective titers (≥1.3 μg/mL)	≤2 protective titers (≥1.3 μg/mL)	Protective titers present are low
Moderate	<70% of serotypes are protective (≥1.3 μg/mL)	<50% of serotypes are protective (≥1.3 μg/mL)	Protective titers present to ≥3 serotypes
Mild	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 70% of serotypes	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 50% of serotypes	2-Fold increases assume a prevaccination titer of less than cutoff values in Summary Statement 26
Memory	Loss of response within 6 mo	Loss of response within 6 mo	Adequate initial response to ≥50% of serotypes in children <6 y of age and ≥70% in those >6 y of age

*All phenotypes assume a history of infection.

(J Allergy Clin Immunol 2012;130:S1-24.)

Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology

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We are all immune deficient!

- Study of 98 healthy adults (ages 18-92 years) **without** history of recurrent infections
- **20.4% had abnormal response to the PPSV-23** (45% mild, 40% moderate, 15% severe phenotype)

ARTICLE IN PRESS

J ALLERGY CLIN IMMUNOL PRACT
MONTH 2017

Original Article

The Clinical Significance of Specific Antibody Deficiency (SAD) Severity in Chronic Rhinosinusitis (CRS)

Anjeni Kanwani, MD[a], Neha M. Dunn, MD[a], Angelina Mansur, MD[a], Sara Kashani, BA[a], Xavier Bossuyt, MD, PhD[b], Leslie C. Grammer, MD[a], David B. Conley, MD[a], Bruce K. Tan, MD[a], Robert C. Kern, MD[a], Robert P. Schleimer, PhD[a,c], and Anju T. Peters, MD[a] [a]Chicago, IL; and [b]Leuven, Belgium

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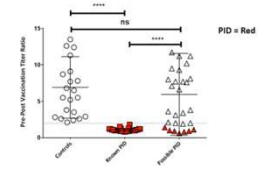
S Typhi IgG Assay (STIGG)

- Newer studies support specificity of assessing immunization response with *Salmonella typhi* PS vaccine to assess antibody response
- Advantages:
  - Neoantigen for most of USA – therefore unlikely to be present in Ig replacement or to have pre-existing antibodies
  - IgG can be readily assessed by EIA sent to MCW immunology lab
  - Ratio post-/pre- IgG ≥2 is normal
- Disadvantages:
  - Cannot be sent by commercial labs or even academic labs without a contract with MCW
  - Insurance coverage for both vaccine and lab is variable

Group	Control (n=22)	Known PID (n=30)	Possible ID (n=29)	p value
% Showing Normal Response	100% (n=22)	0% (n=0)	72.4% (n=21)	<0.0001



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Prophylactic antibiotics as alternative to IgRT

- Double-blind, placebo-controlled randomized trial of azithromycin 250 mg, 3 days a week vs placebo
- 3 year follow-up

J Allergy Clin Immunol 2019;144:584-93

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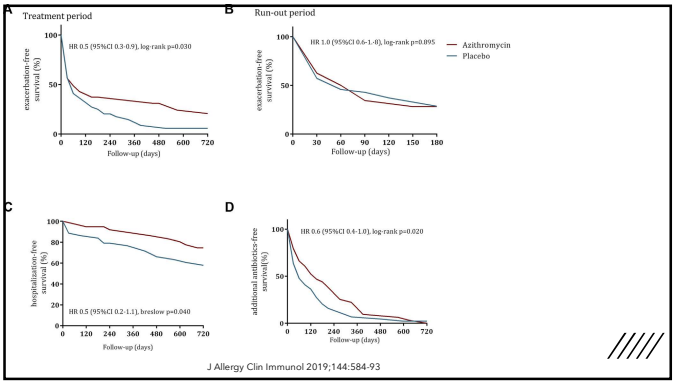

J Allergy Clin Immunol 2019;144:584-93

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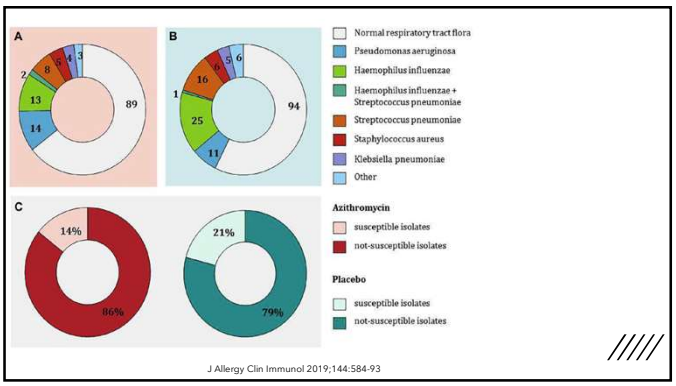

J Allergy Clin Immunol 2019;144:584-93

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TABLE III. Exacerbation, hospitalization, additional courses of antibiotics, colonization, and safety profile by study groups

	Azithromycin (n = 44)	Placebo (n = 45)	*P* value
Serious nonfatal AEs, no.			
Pneumonia	0	6	.010
Neoplasm	0	3	.241
Gastrointestinal tract	0	3	.241
Cardiovascular	0	0	—
Other	3*	5†	.713
Total	3	17	.002
AEs leading to drug discontinuation, no.			
Pneumonia	0	0	—
Neoplasm	0	2	.494
Gastrointestinal tract	0	1	1.000
Cardiovascular	0	0	—
Other	0	1‡	1.000
Total	0	4	.116
Fatal AEs, no.			
Pneumonia	1	1	1.000
Respiratory failure	1	0	.494
Gastric malignancy	0	1	1.000
Parkinson	1	0	.494
Total	3	2	.676

J Allergy Clin Immunol 2019;144:584-93

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TABLE VII. Regimens for prophylaxis of bacterial respiratory tract infections

Antibiotic	Regimen for children	Regimen for adults
Oral agents*		
Amoxicillin (consider with clavulanate, if necessary)	10-20 mg/kg daily or twice daily	500-1,000 mg daily or twice daily
Trimethoprim (TMP)/ sulfamethoxazole (dosing for TMP)	5 mg/kg daily or twice daily	160 mg daily or twice daily
Azithromycin	10 mg/kg weekly or 5 mg/kg every other day	500 mg weekly or 250 mg every other day
Clarithromycin	7.5 mg/kg daily or twice daily	500 mg daily or twice daily
Doxycycline	Age >8 y; 25-50 mg daily or twice daily	100 mg daily or twice daily
Inhaled agents		
Gentamicin	Age >6 y: 80 mg twice daily, 28 days on, 28 days off OR: 21 days on, 7 days off	
Tobramycin	Age >6 y: 300 mg twice daily, 28 days, on 28 days off	

J Allergy Clin Immunol 2015;136:1186-1205

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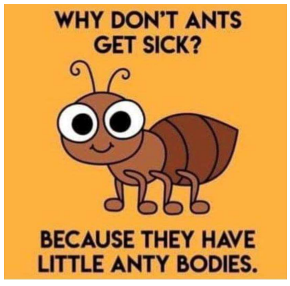

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"I always know when one of her fever episodes is coming!"

- 3 year old female with recurrent fevers since infancy
- Fevers occur monthly with regularity and last 4-5 days
- Fevers usually associated with oral ulcers, pharyngitis, abdominal pain, vomiting/diarrhea
- Given antibiotics on most occasions which sometimes helps and sometimes does not
- Does not attend daycare, no siblings, no smoke exposure and no pets in home

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3.

"SURF'S UP!"

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TABLE I. Categories of fever patterns

Fever type	Definitions*	Considerations for differential diagnosis†
Prolonged fever	Single episode in which duration of fever is longer than expected for clinical diagnosis	Viral syndromes (eg, Epstein-Barr virus mononucleosis) Kawasaki disease
	Single episode in which fever was initially prominent feature but then becomes low-grade or only a perceived problem	Hemophagocytic lymphohistiocytosis/macrophage activation syndrome
Recurrent fever	Episodes during which signs (including fever) and symptoms wax and wane	Infectious causes Viral (eg, Epstein-Barr virus) Bacterial (eg, relapsing fever, rat bite fever, mycobacteria) Fungal (eg, histoplasmosis, coccidioidomycosis) Parasitic (eg, malaria) Dental decay or abscess Malignancy
	Multiple, febrile episodes occurring at irregular intervals involving single organ system (eg, sinopulmonary, urinary tract)	Anatomic defects (eg, vesicoureteral reflux, primary ciliary dyskinesia, central nervous system dysfunction) Environmental causes (allergies, smoking, medications) Primary immunodeficiency Inflammatory bowel disease
	Multiple febrile episodes occurring at irregular intervals involving different organ systems	Viral, bacterial, or fungal infections Primary immunodeficiency Rheumatologic disorders (eg, Behçet's Behçet's, systemic lupus erythematosus)
Fever of unknown origin	Single episode lasting ≥3 wk during which fever is ≥38.3°C on most days, with failure to reach diagnosis after 3 d of inpatient evaluation or ≥2 wk of outpatient visits	Infectious, rheumatologic, oncologic, or gastrointestinal diagnoses, factitious fever
Periodic fever without set periodicity	Recurring episodes of fever lasting days to weeks. Episodes have fever as primary feature with predictable associated signs and symptoms.	Autoinflammatory disorders including mevalonate kinase deficiency, TNF receptor-associated periodic syndrome, familial Mediterranean fever
Periodic fever with set periodicity	Recurring episodes of fever lasting days to weeks. Episodes have fever as primary feature with predictable associated signs and symptoms.	Periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome; mevalonate kinase deficiency; syndrome of undifferentiated recurrent fever

*Fever definitions were adopted from Long.[1]
†Examples but not an exhaustive list.

Clinical Management Review

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome and Syndrome of Unexplained Recurrent Fevers in Children and Adults

J Allergy Clin Immunol Pract 2023;11:1676-87

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PFAPA: The P is for **Set Periodicity**

TABLE II. Modified Marshall's classification criteria[22]

Regularly recurring fevers with early age onset (<5 y)
Constitutional symptoms in absence of upper respiratory infection with at least one of the following clinical signs: • Aphthous stomatitis • Cervical lymphadenitis • Pharyngitis
Exclusion of cyclic neutropenia
Completely asymptomatic interval between episodes
Normal growth and development

J Allergy Clin Immunol Pract 2023;11:1676-87)

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My approach

1. Fever diary for at least 3 months – check fever with same thermometer in the morning, record any "sick" symptoms
2. Labs to consider:
   - At baseline: CBC/diff, ferritin, ESR, CRP, IgG/A/M, serum IL-1b, IL-6, IL-18, sIL2Ra, CXCL9, autoinflammatory syndrome genetic panel
   - During flare: CBC/diff, ferritin, ESR, CRP
3. Trial of prednisone 1 mg/kg at start of fever

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PFAPA: The P is for **Prednisone challenge**

TABLE III. Pharmacologic treatment for periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome

Medication	Dose	Considerations	Advantages	Disadvantages
Prednisone/prednisolone	0.5-2 mg/kg orally at onset of fever	Possible to repeat on day 2 if fever persists	On demand	May increase frequency of episodes
Colchicine	0.6-1.8 mg orally, daily	Slow up-dosing recommended	Reduction or elimination of flares	Possible gastrointestinal side effects
Cimetidine	20-40 mg/kg per day, orally	—	—	Poor efficacy, may require dosing three times per day
Montelukast	4-10 mg/d, orally, based on age	—	—	Possible neuropsychiatric adverse effects
Anakinra	1 mg/kg up to 100 mg, subcutaneously, first day of fever	May repeat on second day	On demand	Injectable, site reactions

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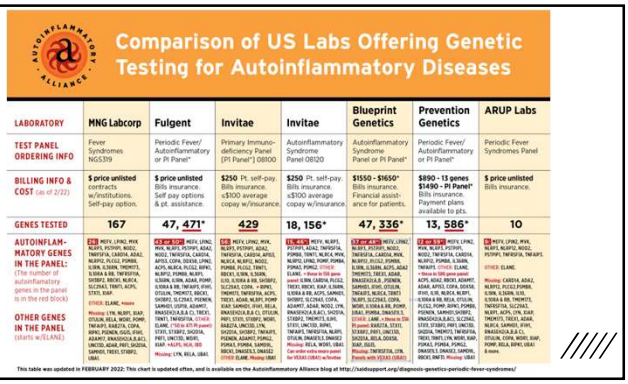

Comparison of US Labs Offering Genetic Testing for Autoinflammatory Diseases

LABORATORY	MNG Labcorp	Fulgent	Invitae	Invitae	Blueprint Genetics	Prevention Genetics	ARUP Labs
TEST PANEL ORDERING INFO	Fever Syndromes NGS319	Periodic Fever/ Autoinflammatory or PI Panel*	Primary Immuno-deficiency Panel [PI Panel*] 08100	Autoinflammatory Syndrome Panel 08120	Autoinflammatory Syndrome Panel or PI Panel*	Periodic Fever/ Autoinflammatory or PI Panel*	Periodic Fever Syndromes Panel
BILLING INFO & COST (as of 2/22)	$ price unlisted contracts w/institutions. Self-pay option.	$ price unlisted Bills insurance. Self pay options & pt. assistance.	$250 Pt. self-pay. Bills insurance. ≤$100 average copay w/insurance.	$250 Pt. self-pay. Bills insurance. ≤$100 average copay w/insurance.	$1550 - $1650* Bills insurance. Financial assist-ance for patients.	$890 - 13 genes $1490 - PI Panel* Bills insurance. Payment plans available to pts.	$ price unlisted Bills insurance.
GENES TESTED	167	47, 471*	429	18, 156*	47, 336*	13, 586*	10
AUTOINFLAM-MATORY GENES IN THE PANEL: (The number of autoinflammatory genes in the panel is in the red block)	167	471	429	156	336	586	10
OTHER GENES IN THE PANEL (starts w/ELANE)	ELANE,						ELANE,

This table was updated in FEBRUARY 2022: This chart is updated often, and is available on the Autoinflammatory Alliance blog at http://saidsupport.org/diagnosis-genetics-periodic-fever-syndromes/

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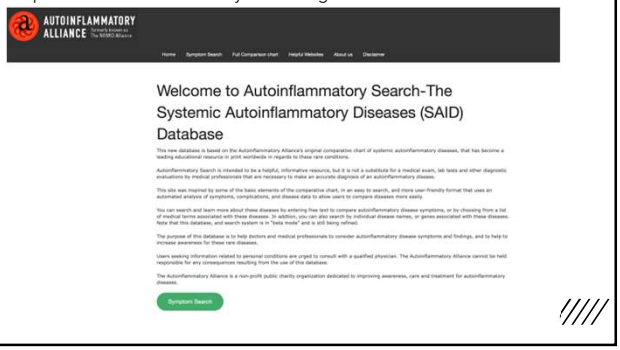
https://www.autoinflammatory-search.org



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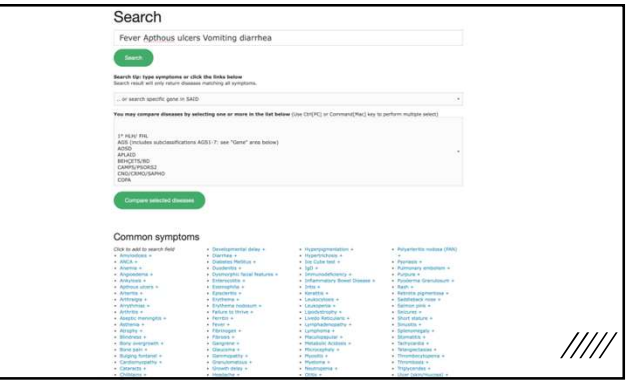

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Search Result

View result in a comparision chart

Ranked by occurance of the search terms

- MKD-mild/moderate (aka HIDS)

Mevalonate Kinase Deficiency-mild/moderate, Hyperimmunoglobulinemia D with Periodic Fever Syndrome

>90% present with symptoms in infancy.

- MA, MKD-severe

Mevalonate Aciduria (MA), Mevalonate Kinase Deficiency-severe

Most present with symptoms at birth, or in early infancy. Most have facial features noted at birth.

New Search

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Comparison Chart

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SURF: **S**yndrome of **U**ndifferentiated **R**ecurrent **F**evers

- Recurrent fevers with set periodicity
- Fail to meet criteria for PFAPA
- No clinical or genetic evidence of a monogenic autoinflammatory syndrome

J Allergy Clin Immunol Pract 2023;11:1676-87)

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SURF'S UP: Now what?

- NSAIDs
- Glucocorticoids 0.5 – 1 mg/kg
- Colchicine 0.6 – 1.8 mg/d orally
  - Start with low dose and increase slowly over weeks
  - Divide dose BID
  - Take without dairy
- Anakinra (once daily injection, can be given on demand)
- Canakinumab (every 4-8 weeks injection)

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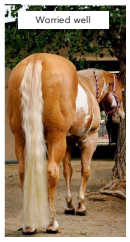
The challenge ….

Telling this …



From this …

Without looking like this …

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