

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

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1

"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!"

2

1.

THE "WORRIED WELL"

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BIG LOVE

HOME > BIG LOVE
 Big Love (2006-2011)
 80%
 Like a typical suburban husband, Bill Dauterive (Bill Hader) has a wife (Halle Berry) who makes money, and a business, fulfilling his dream of connecting with people.
 Starring: Bill Hader, Halle Berry, Tim Allen
 TV Network: HBO
 Premiere Date: 2006
 Genre: Drama
 Executive producers: Tom Haverstick, Tom Schipper

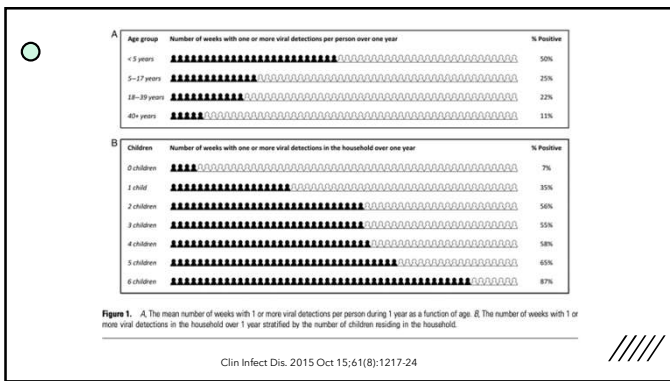
4

The BIG-LoVE study

- Better Identification of **G**erms-**L**ongitudinal **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


5



6

○ When you hear hoofbeats, think HORSES, not Zebras

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



<http://mrazepcyrski.blogspot.com/2015/11/assuming-horses-not-zebras-is-good.html>
<https://quackinvestigator.com/2017/11/26/zebras/>

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10

○ "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

11

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2.

THE "WORRIED SICK"

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12

10^M of Primary Immunodeficiency (PI) cases frequently go undiagnosed until late in life. If you see following Warning Signs, consider PI as a possibility.

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

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

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

13

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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14

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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15

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

- Pneumococcal conjugate (Pevnar 7, Pevnar 13, Pevnar 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

16

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)

17

Pneumococcal vaccines

- **Pneumococcal polysaccharide - Pneumovax 23 (PPSV23) (1983)**
- **Pneumococcal conjugate vaccine**
 - Pevnar (PCV7) (2000)
 - Pevnar 13 (PCV13) (2010)
 - Pevnar 15 (PCV15) (2021)
 - Pevnar 20 (PCV20) (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!

18

Response to pneumococcal polysaccharide vaccine (PPSV-23)

TABLE IV. Summary of PPSV23-deficient response phenotypes

Phenotype*	PPSV23 response, age ≥6 y	PPSV23 response, age <6 y	Notes
Severe	<5 protective titers (>1.3 µg/mL)	<5 protective titers (>1.3 µg/mL)	Protective titers present are low
Moderate	<20% of serotypes are protective (>1.3 µg/mL)	<5% of serotypes are protective (>1.3 µg/mL)	Protective titers present in >5 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 pre-vaccination titer of less than one-half of the minimum 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 ≥20% 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



22

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)

Arjun Khandelwal, MD¹, Nisha M. Datta, MD², Angelika Mariani, MD³, Sara Kachand, BA⁴, Kristen Roseman, MD, PhD⁵, Leslie C. Gorenstein, MD⁶, David B. Conley, MD⁷, Bruce R. Tan, MD⁸, Robert C. Stern, MD⁹, Robert P. Schleimer, PhD¹⁰, and Arjun P. Khandelwal, MD¹¹ (Chicago, IL and London, England)

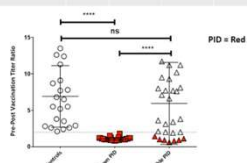


23

S Typhi IgG Assay (STIGG)

- Newer studies support specificity of assessing immunization response with *Salmonella typhi* P5 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



24

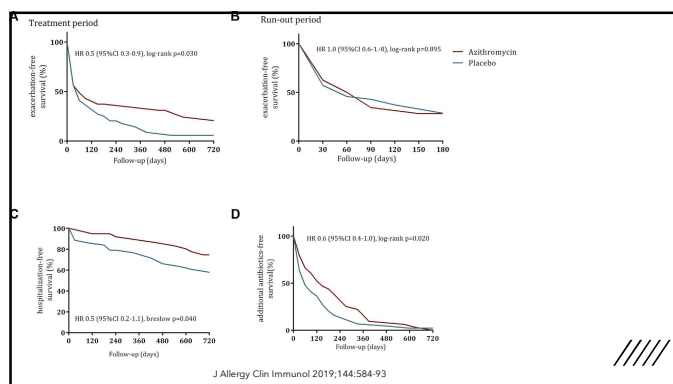
○ Prophylactic antibiotics as alternative to IgRT

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

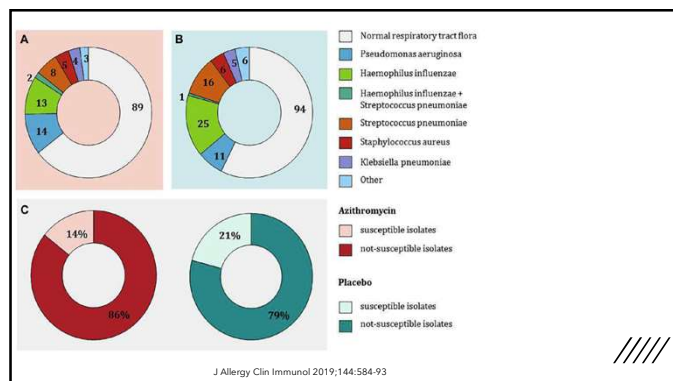
J Allergy Clin Immunol 2019;144:S84-93



25



26



27

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 ^a	5 ^b	.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 ^c	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

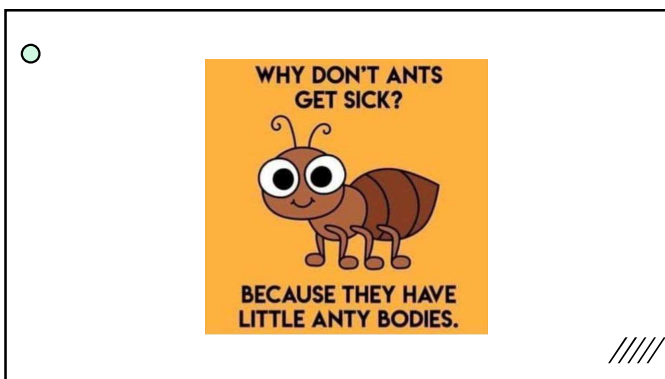
28

TABLE VII. Regimens for prophylaxis of bacterial respiratory tract infections

Antibiotic	Regimen for children	Regimen for adults
Oral agents ^a		
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

29



30

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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

31

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3.

"SURF'S UP!"

32

Fever type	Definition*	Considerations for differential diagnosis
Protracted fever	Single episode in which duration of fever is longer than expected for clinical diagnosis	Viral syndromes (eg, Epstein Barr virus, adenovirus) Kawasaki disease Hemophagocytic lymph-histiocytosis/hemophagocytosis activation syndrome
Recurrent fever	Single episode in which fever was initially prominent but then becomes low grade or only a protracted prodrome Episodes during which signs (including fever) and symptoms wax and wane Multiple, discrete episodes occurring at irregular intervals involving single organ system (eg, sinusitis, otitis media) Multiple, discrete episodes occurring at irregular intervals involving different organ systems	Infectious causes Viral (eg, Epstein-Barr virus) Bacterial (eg, relapsing fever, atypical fever, typhoid fever) Fungal (eg, histoplasmosis, coccidioidomycosis) Parasitic (eg, malaria) Dental decay or abscess Malignancy Autoimmune diseases (eg, vasculitis, rheumatoid arthritis, primary biliary cholangitis, central nervous system demyelination) Environmental causes (allergies, smoking, medications) Primary immunodeficiency Inflammatory bowel disease
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 repeat evaluation or >2 d of continuous care	Viral, bacterial, or fungal infections Primary immunodeficiency Rheumatologic disorders (eg, Behçet's disease, systemic lupus erythematosus) Infections, 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 mevalonic aciduria, familial Mediterranean fever, TRP 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, neovascular keratitis, deficiency syndrome of undifferentiated recurrent fever

*Fever definitions were adapted from Long. Reprinted here with an editorial fix.

33

Clinical Management Review

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

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

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

TABLE II. Modified Marshall's classification criteria²²

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)



34

○ 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



35

○ 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

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



36

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 NGS39	Periodic Fever/Autoinflammatory or PI Panel*	Primary Immunodeficiency Panel (PI Panel)* I18000	Autoinflammatory Syndrome Panel I8020	Autoinflammatory Syndrome Panel or PI Panel*	Periodic Fever/Autoinflammatory Panel or PI Panel*	Periodic Fever Syndromes Panel
BILLING INFO & COST (as of 2/23)	\$ price unlimited contracts w/conditions. Self-pay option.	\$ price unlimited	\$250 PI, self-pay. Bills insurance. c\$500 average copay w/insurance	\$250 PI, self-pay. Bills insurance. c\$500 average copay w/insurance	\$1550 - \$1650* Bills insurance. Financial assistance for patients.	\$890 - 13 genes \$1490 - PI Panel* Bills insurance. Payment plans available to DCs.	\$ price unlimited Bills insurance.
GENES TESTED	167	47, 471*	429	18, 156*	47, 336*	13, 586*	10
AUTOINFLAMMATORY GENES IN THE PANEL: (The number of autoinflammatory genes in the panel is in the red block)	167	47, 471*	429	18, 156*	47, 336*	13, 586*	10
OTHER GENES IN THE PANEL: (GENES w/CLINICAL)	167	47, 471*	429	18, 156*	47, 336*	13, 586*	10

This table was updated in FEBRUARY 2023. This chart is updated often, and is available on the AutoInflammatory Alliance blog at <http://autoinflammatory.org/blog/genetic-testing-periodic-fever-syndromes/>

37

<https://www.autoinflammatory-search.org>

WELCOME TO Autoinflammatory Search-The Systemic Autoinflammatory Diseases (SAID) Database

This new database is based on the AutoInflammatory Alliance's original comparative chart of systemic autoinflammatory diseases, that has become a leading educational resource in gene medicine to help in these rare conditions.

Autoinflammatory Search is intended to be a helpful, informative resource, but is not a substitute for a medical exam, lab tests and other diagnostic measures by medical professionals that are necessary to make an accurate diagnosis of an autoinflammatory disease.

This site was created by some of the field's foremost experts in the comparative field, in an effort to search, and more importantly, to share information that uses an automated analysis of symptoms, complications, and disease data to allow users to compare diseases more easily.

You can search and learn more about these diseases by entering the text to compare autoinflammatory disease symptoms, or by choosing from a list of clinical features and associated diseases. To identify any gene that is associated with the particular disease names, or other associated with these diseases, click on the database, or search results, to view the full list of genes.

The purpose of this database is to help doctors and medical professionals to compare autoinflammatory disease symptoms and findings, and to help to increase awareness for these rare diseases.

Users seeking information related to general conditions are urged to consult with a qualified physician. The AutoInflammatory Alliance cannot be held responsible for any consequences resulting from the use of this database.

The AutoInflammatory Alliance is a non-profit public charity organization dedicated to improving awareness, care and treatment for autoinflammatory diseases.

[Autoinflammatory Search](#)

38

Search

Fever Aphthous ulcers Vomiting diarrhea

Search for these symptoms or click the links below. Search result will only return disease matching all symptoms.

...or search specific genes in SAID

You may compare diseases by selecting one or more in the list below (Use CTRL/CMD keys to perform multiple select)

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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)

J Allergy Clin Immunol Pract 2023;11:1674-87)



43

The challenge

Telling this ...



From this ...



Without looking like this ...



44

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45
