Fever of unknown origin

Martin Rodriguez
UAB

No comercial disclosures to report related to this activity

- *Humanity has but three great enemies: fever, famine, and war; of these by far the greatest, by far the most terrible, is fever.*

  William Osler

Fever

Case

- 76 yo woman with ESRD on HD, HTN, CHF DM, comes in with temp of 100 several nights a week for 2-3 months
- Feels tired in particular late in the day
- Other ROS and exam stable from before
- Does she have fever?
- Does she have FUO?

Case

- 26 yo man comes with report of chronic fever, states his temp reaches 100 several nights a week for the last 2-3 months, when he started checking it because he felt tired
- A lot of stress in school, tired in particular late in the day, not sleeping well
- Other ROS and exam normal
- Does he have fever?
- Does he have FUO?

REVIEW ARTICLE

Concepts of Fever

Philip A. Mackowiak, MD

If asked to define fever, most physicians would offer a thermal definition, such as "fever is a temperature greater than. . . ." In offering their definition, many would ignore the importance of the anatomic site at which temperature measurements are taken, as well as the diurnal oscillations that characterize body temperature.[1] If queried about the history of clinical thermometry, few physicians could identify the source or explain the pertinacity of the belief that 98.6°F (37.0°C) has special meaning vis-à-vis normal body temperature. Fewer still could cite the origin of the thermometer or trace the evolution of modern concepts of clinical thermometry. Although many would have some knowledge of the fundamentals of thermoregulation and the role played by exogenous and endogenous pyrogens in the induction of fever, few would have more than a superficial knowledge of the broad biological activities of pyrogenic cytokines or know of the existence of an equally complex and important system of endogenous cryogens. A distinct minority would appreciate the obvious paradoxes inherent in an enlarging body of data concerned with the question of fever's adaptive value. The present review considers many of these issues in the light of current data.

Arch Intern Med. 1998;158:1870-1881

The eldest known written reference to fever exists in Akkadian cuneiform inscriptions from the sixth century BC, which seem to have been derived from an ancient Sumerian pictogram of a flaming brazier that symbolized fever and the local warmth of inflammation.[2] Theoretical constructs concerned with the pathogenesis of fever did not emerge until several centuries later, when Hippocratic physicians proposed that body temperature, and physiologic function in general, involved a delicate balance among 4 corporeal humors—blood, phlegm, black bile, and yellow bile.[3] Fever, it was believed, resulted from an excess of yellow bile, a concept consistent with the fact that many infections of that era were associated with fever and jaundice. During the Middle Ages, demonic possession was added to the list of mechanisms believed responsible for fever. By the 18th century, Harvey's discovery of the circulation of blood and the birth of microbiology led iatrophysicists and iatrochemists to hypothesize, alternatively, that body heat and fever result from friction associated with the flow of blood through the vascular system and from fermentation and putrefaction occurring in the blood and intestines.[4] Ultimately, thanks to the work of the great French physiologist, Claude Bernard, the metabolic processes occurring within the body finally came to be recognized as the source of body heat. Subsequent work established that body temperature is tightly controlled within a narrow range by mechanisms regulating the rate at which such heat is allowed to dissipate from the body.

The origin of the practice of monitoring body temperature as an aid to diagnosis is shrouded in uncertainty. The oldest known references to devices used

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This article is also available on our Web site: www.ama-assn.org/internal.

Mackowiak PA. Arch Intern Med 1998; 138 p 1870

Fever

- What is the normal body temperature?
- Fever is a temperature greater than….?
- Where is the temperature taken from?
- When in the day is it being obtained?
- Have things changed over time? Are we using obsolete definitions?
- Does it matter if the patient has symptoms or not?

Fever

- In 1868 Carl Wunderlich published “Das Verhaltenb der Eigenwarme in Krankenheiten” (the course of temperature in diseases)
  - 1 million observations in 25K individuals
  - Normal body temperature 98.6 F (37 C), range (97.2-99.5), established 100.4 F (38 C) as the upper limit of normal
  - Recent tests with one of his thermometers suggests miscalibration and higher readings of as much as 2.6-4 F), also most were axillary
  - Life expectancy 38, many had chronic infections at the time

Fever

- Oral
  - Respiratory rate (tachypnea may increase 1-1.5 F), hot or cold meals/liquids, smoking, failure to keep mouth closed
  - Less of an issue with new probes
- Axillary
  - Inaccurate, reported to be 0.5 F lower than oral
- Rectal
  - Usually 1 F higher than oral
- Ear
  - 0.5-1 F higher than oral
- Forehead
  - 0.5-1 F lower than oral

Fever, is the definition accurate?

- Study of 700 readings in 148 individuals in the 90s
  - Mean oral temp 98.2, ULN 98.9 in AM and 99.9 in PM
- Compilation of 27 studies
  - 35K individuals
  - Mean oral temp 97.9 F (36.6 C), range 96.2-99.1
  - Lower temp with age, comorbidities

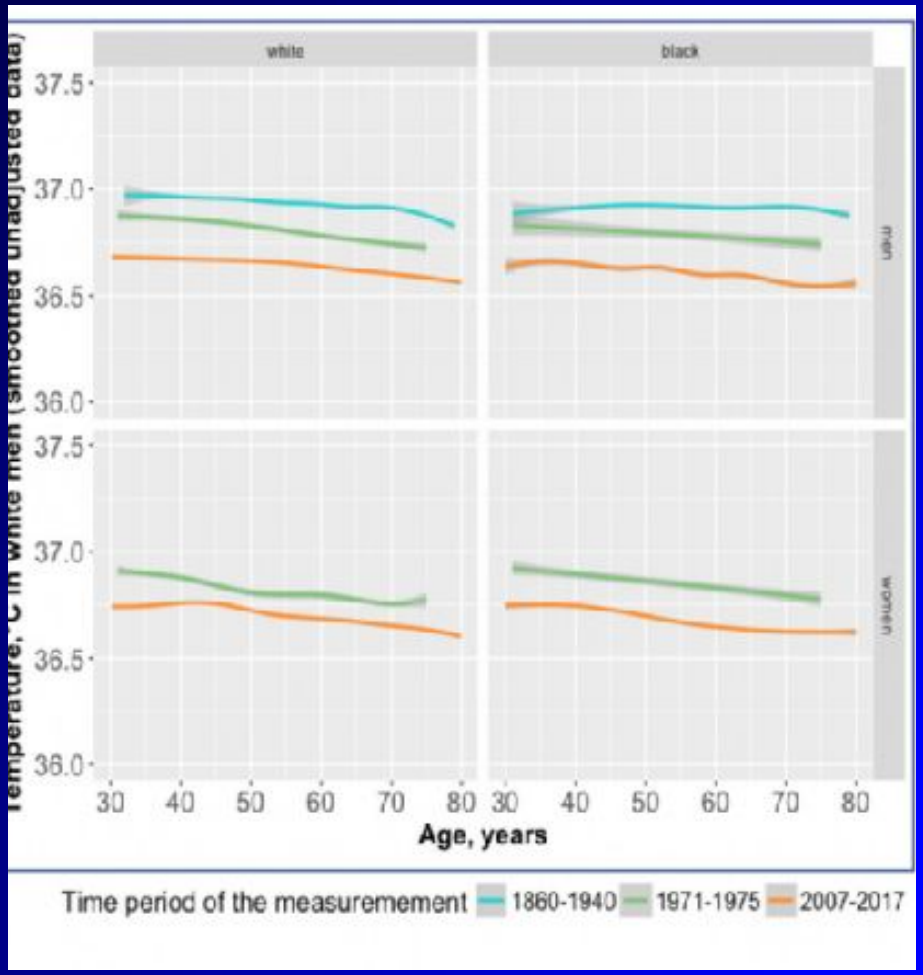
Sapira's Art and Science of Bedside Diagnosis.
Obermeyer Z, et al. BMJ 2017; 359 j5468

Fever, is the definition accurate?

- Measurements in 3 cohorts over time, 67K measurements
  - Union Army Veterans of the Civil War (23K, 1860-1940)
  - NHANES (15K 1971-1975)
  - Stanford Translational Research database (150K 2007-2017)
- Mean body temperature has decreased 0.05 F per decade (1.1 F lower than in 19th century)
- Basal metabolic rate has decreased
  - Decrease in chronic infections, physical activity

Protsiv M, et al. eLIFE 2020; 9 e49555

Normal temperature since 1860



Fever

- Diurnal variation
  - Highest 4-9 PM
  - Lowest 2-8 AM
- Variations with age and sex
  - Elderly average 1 F less than young people
  - Women have slightly higher temps

Fever

- What is fever?
- Individualize the definition using clinical judgement

Fever of unknown origin

Fever of unknown origin (FUO)

- Petersdorf and Beeson in 1961
  - Fever higher than 100.9 (38.3 C) on several occasions for 3 weeks or longer without an identifiable cause and with one week of study in the hospital
- Definition changed overtime
  - Different groups have used different temps and durations of work up (2-3 weeks)
  - Not required to be in the hospital (or only 3 days or 3 outpatient visits), just an appropriate diagnostic evaluation

Fever of unknown origin (FUO)

Table 1. Fever of Unknown Origin Definitions

Type	Definition
Classic	Temperature >38.3°C (100.9°F) recorded on several occasions occurring for >3 weeks in spite of investigations on 3 outpatient visits or 3 days of stay in the hospital or 1 week of invasive ambulatory investigations.
Nosocomial	Temperature >38.3°C (100.9°F) recorded on several occasions in a hospitalized patient who is receiving acute care and in whom infection was not manifest or incubating on admission. Three days of investigations including at least 2 days incubation of cultures is the minimum requirement for this diagnosis.
Neutropenic	Temperature >38.3°C (100.9°F) on several occasions observed in a patient whose neutrophil count is <500/μL or expected to fall to that level in 1–2 days. This diagnosis should be considered for investigations including at least 2 days of incubation of cultures. This is also called immunodeficient FUO.
HIV-associated	Temperature >38.3°C (100.9°F) on several occasions found over >4 weeks or >3 days for hospitalized patients with HIV infection. This diagnosis is considered if appropriate investigations over 3 days, including 2 days of incubation of cultures, reveal no source.

Adapted from Durack and Street [10].

Abbreviation: FUO, fever of unknown origin.

Wright WF. OFID 2020

Fever of unknown origin (FUO)

- Over 200 causes, 7-50% remain undiagnosed
- Infections
- Malignancies
- Autoimmune
- Miscellaneous
- Undiagnosed

REV ASSOC MED BRAS 2019; 65(8):1109-1115. Wright WF. OFID 2020

Etiology of FUO

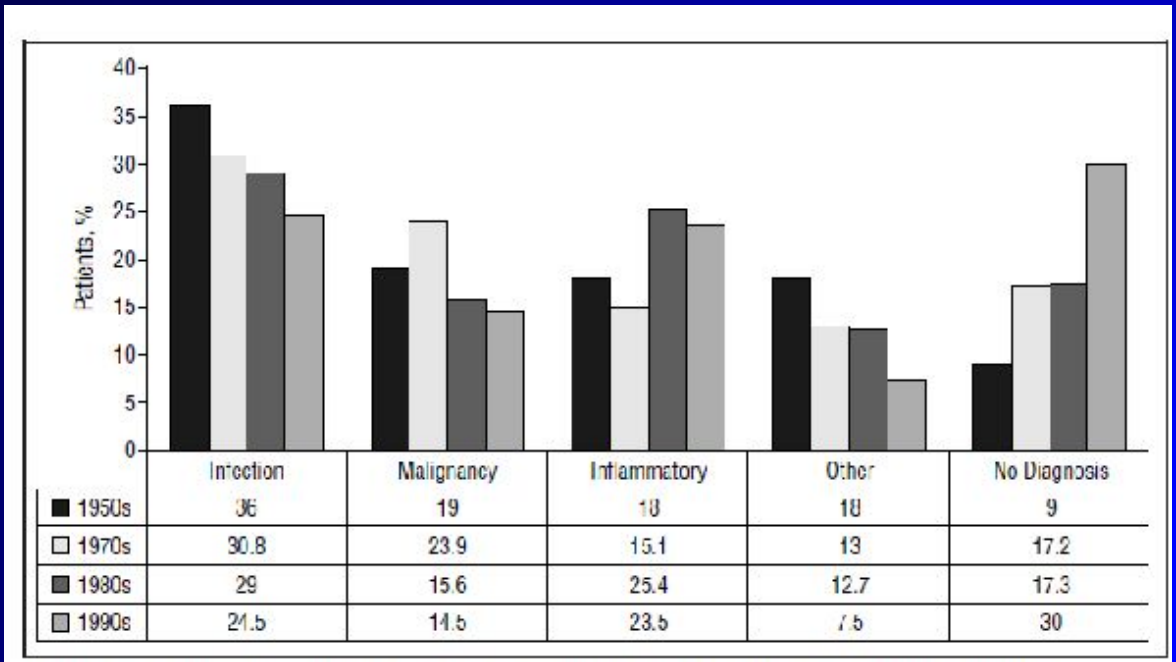
Less common diagnoses of fever of unknown origin

Infections	Malignancies	Systemic inflammatory diseases	Miscellaneous
Abscesses (especially intra-abdominal)	Aleukemic leukemia	Allergic granulomatous angiitis	Disorders of temperature regulation (neurologic and dermatologic)
African tick bite fever*	Atrial myxoma	Antiphospholipid syndrome	Drug fever$^{\Delta}$
Amebic liver abscess*	Colon cancer	Behçet's disease	Environmental (metal and polymer fume fevers)
Anaplasmosis/ehrichiosis*	**Hepatocellular carcinoma** or other tumors metastatic to the liver	Cryoglobulinemia	Factitious fever
Babesiosis*	Kaposi's sarcoma	**Giant cell arteritis**	Familial Mediterranean fever
Brucellosis*	**Leukemia**	Granulomatosis with polyangiitis (formerly Wegener's disease)	Inflammatory bowel disease
Castleman's disease	Lung cancer	Granulomatous hepatitis	Neuroleptic malignant syndrome
Chikungunya*	**Lymphoma, especially non-Hodgkin's**	Hypersensitivity vasculitis	Periodic fever
Chronic active hepatitis	Mesothelioma	Inflammatory bowel disease	Pulmonary emboli
Culture-negative endocarditis¶	Multiple myeloma	Panaortitis	Retroperitoneal hematomas
Cytomegalovirus	Myelodysplastic syndromes	**Polyarteritis nodosa**	Chronic fatigue syndrome
Dental abscesses	**Renal cell carcinoma**	Polymyalgia rheumatica	Thyroiditis
Dengue*	Sarcoma	Reactive arthritis (formerly Reiter's syndrome)	
Diskitis		Sarcoidosis	
Epididymitis		Still's disease	
Fascioloiasis*		Systemic lupus erythematosis	
Filariasis*		Takayasu's arteritis	
Gonococcal arthritis			
Herpes simplex encephalitis			
Infectious mononeucleosis			
Kala azar (visceral leishmaniasis)*			
Kikuchi's disease			
Lassa fever*			
Leptospirosis*			
Lyme disease*			
Osteomyelitis			
Prostatitis			
Pyelonephritis			
Pyometria			
Q fever*			
Relapsing fever (*Borrelia recurrentis*)*			
Rheumatic fever			
Sinusitis			
Toxoplasmosis			
Typhoid fever*			
Tuberculosis			
Whipple's disease			
Zika virus*			

More common causes are in **bold type**.

* Travel and environmental exposure histories are especially relevant.
¶ Causes include *Actinobacillus* spp, *Bartonella* spp, *Brucella* spp, *Cardiobacterium* spp, *Chlamydia* spp, *Coxiella burnetii*, *Eikenella* spp, *Haemophilus* spp, *Histoplasma capsulatum*, *Kingella* spp, *Legionella* spp, *Mycoplasma* spp, *Tropheryma whipplei*, and marantic endocarditis.
Δ Antimicrobials (especially sulfonamides and penicillins), antiepileptic, antithyroid, and nonsteroidal anti-inflammatory drugs.

Fever of unknown origin (FUO) over time



	Infection	Malignancy	Inflammatory	Other	No Diagnosis
1950s	36	19	18	18	9
1970s	30.8	23.9	15.1	13	17.2
1980s	29	15.6	25.4	12.7	17.3
1990s	21.5	14.5	23.5	7.5	30

Figure 1. The percentage of patients with fever of unknown origin by cause over the past 40 years.

Mourad O, et al. Arch Intern Med 2003; 163:545

Fever of unknown origin (FUO)

- Changes in epidemiology, lower prevalence of some chronic infections
  - Local epidemiology
- Availability of imaging
  - Liver abscess and malignancies
  - Endocarditis
- Availability of labs
  - CTD
  - Chronic infections
  - PCR

Fever of unknown origin (FUO), initial evaluation

- History, history, history, and repeat the history
  - Symptoms, very extensive ROS
  - PMH, FH, meds, exposures, social history, trips, pets
- Exam and repeat the exam
  - Eyes, nails, mouth, LN, skin, liver, spleen, genitals
- Initial imaging and labs
  - Labs: routine and history guided, UA, CTD, inflammatory markers, ferritin, HIV
  - Micro: history guided, blood cultures?
  - Chest and abd/pelvis imaging, LE Doppler?, TTE?
  - Pre-test probability and false positives
- Presence of diagnostic clues

What is that miscellaneous category again?

- Drugs
- Factitious
- Endocrine
- Thromboembolic disease
- Sarcoidosis, granulomatous hepatitis
- HLH/MAS
- Lymph node processes (Kikuchi)
- Central
- Hematoma
- Auto-inflammatory syndromes
  - Familial periodic fevers
  - Other

Table 3. Medications that Can Cause Fever of Unknown Origin

Anticonvulsants	**Cardiovascular drugs**
Barbiturates*	Captopril (Capoten)
Carbamazepine (Tegretol)	Hydralazine
Phenytoin (Dilantin)	Hydrochlorothiazide
Antihistamines	Methyldopa
Cimetidine (Tagamet)	Nifedipine (Procardia)
Ranitidine (Zantac)	Procainamide
Antimicrobials	Quinidine
Carbapenems*	**Nonsteroidal anti-inflammatory drugs**
Cephalosporins*	Ibuprofen
Erythromycin	Salicylates
Isoniazid	Sulindac (Clinoril)
Minocycline (Minocin)	**Others**
Nitrofurantoin (Furadantin)	Allopurinol (Zyloprim)
Penicillins*	Heparin
Rifampin	Meperidine (Demerol)
Sulfonamides*	Phenothiazines

Hersch EC, et al. Am Fam Physician 2014; 90: 91

Fever of unknown origin (FUO), further evaluation

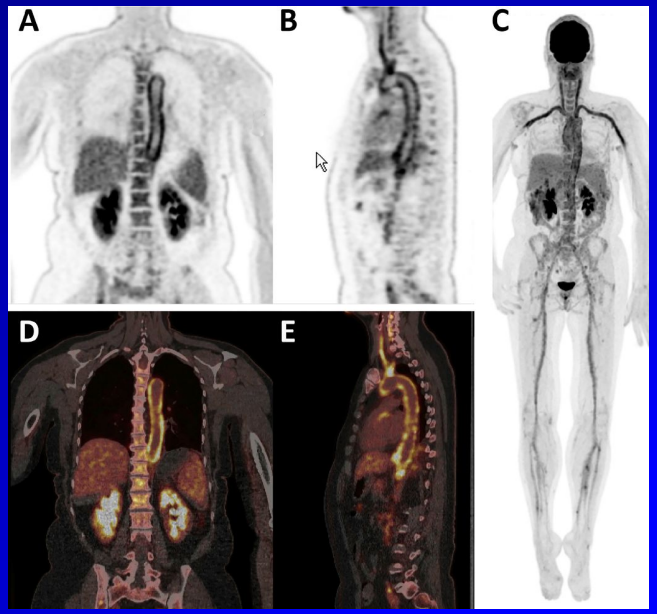
- Repeat the history and exam
- Labs
  - Micro, PCRs, serologies (routine?, exposure-guided?)
  - SPEP/IFE/FLC, Ig levels, CTD serologies, cryoglobulins, complement, peripheral smear, TFTs
- Echo
- Nuclear scan and/or PET
- Tissue
  - Directed
  - Temporal artery
  - Laparotomy
  - Liver bx
  - Bone marrow biopsy

Fever of unknown origin (FUO), further evaluation

- Repeated periodic evaluations
  - Clues may appear over time, leading to further tests or ideas
- Consult with other people
- Consider genetic and/or autoinflammatory causes
- Empiric treatments?
  - NSAIDs
  - Other
- No diagnosis

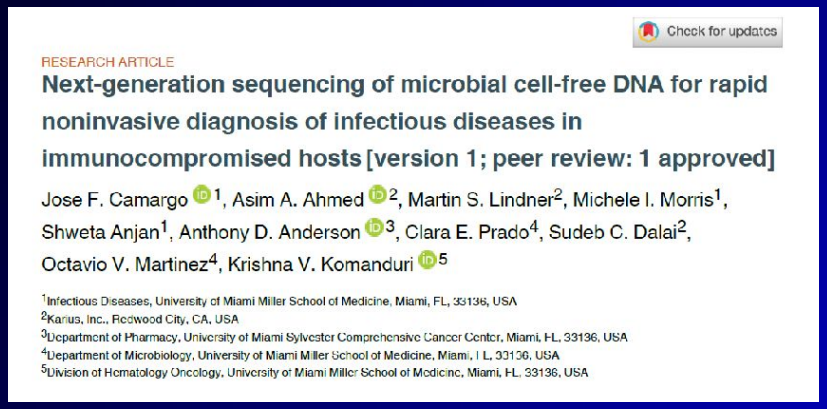
FUO and PET

- Increasingly being used for evaluation, helpful in 15-70% of patients
- In particular for patients without diagnostic clues, may help localize biopsy site or find organ involvement not obvious in history/exam, labs, or other imaging
- Better yield in those with elevated CRP and older age
- Infections (including prosthetic material), malignancy, inflammatory conditions



Schönau V, et al. Ann Rheum Dis 2018;77:70. Kouijzer IJE, et al. Semin Nucl Med 2017; 48:100

FUO and new molecular diagnosis tools



Check for updates

RESEARCH ARTICLE

Next-generation sequencing of microbial cell-free DNA for rapid noninvasive diagnosis of infectious diseases in immunocompromised hosts [version 1; peer review: 1 approved]

Jose F. Camargo [1], Asim A. Ahmed [2], Martin S. Lindner[2], Michele I. Morris[1], Shweta Anjan[1], Anthony D. Anderson [3], Clara E. Prado[4], Sudeb C. Dalai[2], Octavio V. Martinez[4], Krishna V. Komanduri [5]

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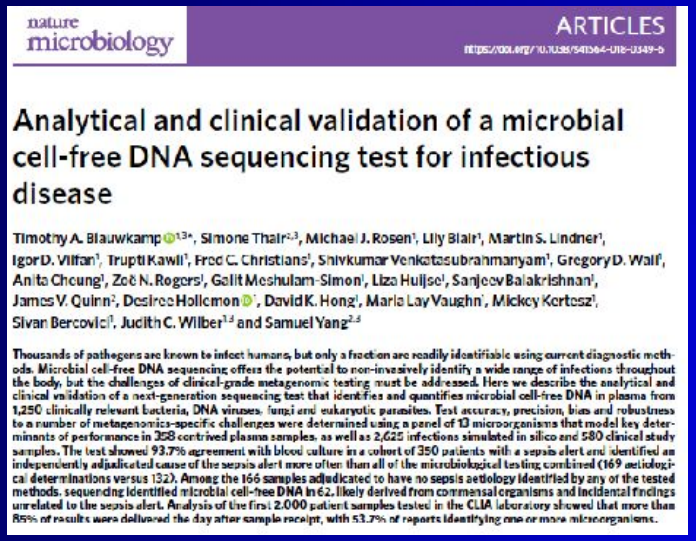


nature microbiology

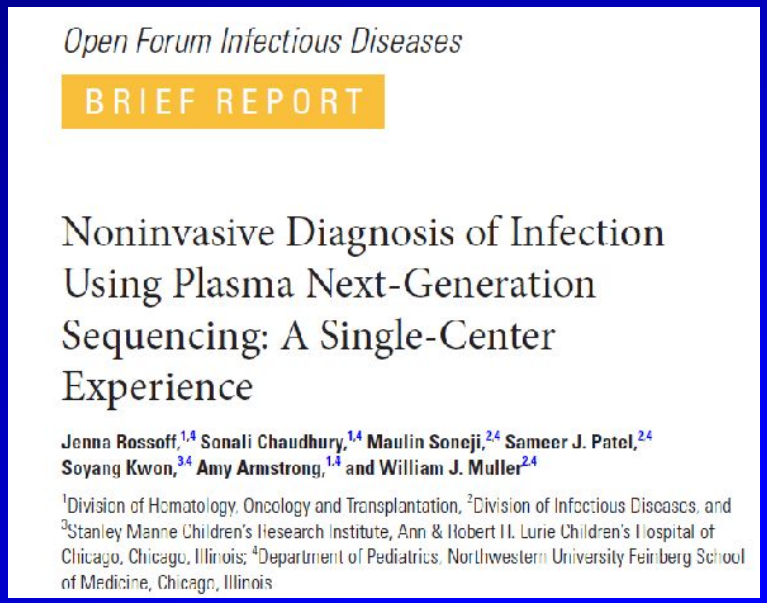
ARTICLES

https://doi.org/10.1038/s41564-018-0349-6

Analytical and clinical validation of a microbial cell-free DNA sequencing test for infectious disease

Timothy A. Blauwkamp[1,3*], Simone Thair[2,3], Michael J. Rosen[1], Lily Blair[1], Martin S. Lindner[1], Igor D. Vilfan[1], Trupti Kawli[1], Fred C. Christians[1], Shivkumar Venkatasubrahmanyam[1], Gregory D. Wall[1], Anita Cheung[1], Zoë N. Rogers[1], Galit Meshulam-Simon[1], Liza Huijse[1], Sanjeev Balakrishnan[1], James V. Quinn[2], Desiree Hollemon[1], David K. Hong[1], Maria Lay Vaughn[1], Mickey Kertesz[1], Sivan Bercovici[1], Judith C. Wilber[1,3] and Samuel Yang[2,3]

Thousands of pathogens are known to infect humans, but only a fraction are readily identifiable using current diagnostic methods. Microbial cell-free DNA sequencing offers the potential to non-invasively identify a wide range of infections throughout the body, but the challenges of clinical-grade metagenomic testing must be addressed. Here we describe the analytical and clinical validation of a next-generation sequencing test that identifies and quantifies microbial cell-free DNA in plasma from 1,250 clinically relevant bacteria, DNA viruses, fungi and eukaryotic parasites. Test accuracy, precision, bias and robustness to a number of metagenomics-specific challenges were determined using a panel of 13 microorganisms that model key determinants of performance in 358 contrived plasma samples, as well as 2,625 infections simulated in silico and 580 clinical study samples. The test showed 93.7% agreement with blood culture in a cohort of 350 patients with a sepsis alert and identified an independently adjudicated cause of the sepsis alert more often than all of the microbiological testing combined (169 aetiological determinations versus 132). Among the 166 samples adjudicated to have no sepsis aetiology identified by any of the tested methods, sequencing identified microbial cell-free DNA in 62, likely derived from commensal organisms and incidental findings unrelated to the sepsis alert. Analysis of the first 2,000 patient samples tested in the CLIA laboratory showed that more than 85% of results were delivered the day after sample receipt, with 53.7% of reports identifying one or more microorganisms.



Open Forum Infectious Diseases

BRIEF REPORT

Noninvasive Diagnosis of Infection Using Plasma Next-Generation Sequencing: A Single-Center Experience

Jenna Rossoff,[1,4] Sonali Chaudhury,[1,4] Maulin Soneji,[2,4] Sameer J. Patel,[2,4] Soyang Kwon,[3,4] Amy Armstrong,[1,4] and William J. Muller[2,4]

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A few cases

Case

- 81 yo man with CHF, CAD, DM, presents with 2 months of fevers, 101-101.5
- ROS positive for bilateral shoulder and hip pain
- PCP gave him azithromycin without improvement
- On exam febrile, tender to palpation in shoulders and hips

- ESR 89, CRP 233.5, albumin 2.8

- Diagnosed with GCA and started on steroids with rapid improvement
- Given MTX as steroid sparing agent on follow up and did well

Giant cell arteritis

- Consider the diagnosis in older than 50, incidence increases after that
- Less common in minorities, female:male 2-3:1
- PMR in 50%: morning stiffness, aching in shoulders and hips
- Fever, headache, jaw claudication, visual symptoms, mild anemia and elevation of LFTs, high ESR and CRP
- Sometimes isolated to large vessels
- If GCA suspected get TA biopsy

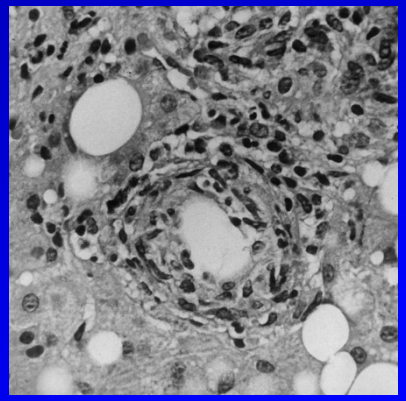
Case

- 62 yo man comes as a transfer. He presented to an OSH with 3 weeks of fevers, fatigue, mild headache. Exam normal except for fever. Found to have WBC 7300 (55% L), AST 220, ALT 254, alk phos 205. TTE, cultures negative. CT mild hepatomegaly
- He undergoes liver biopsy that is read “doughnut granulomas”, then transferred here

- Q fever negative
- CMV serologies and PCR positive, improves without treatment while waiting for results

CMV

- Mono-like
  - EBV, CMV, toxoplasmosis, acute HIV, viral hepatitis, drugs
- CMV second most common cause after EBV
  - Seroprevalence 40-100% of population, increases with age, varies with demographics. In the US 36% in 6-11, 91% in > 80
  - Less likely to have LAP and sore throat
  - In immunocompetent patients: fever and fatigue, occasional rash, rarely GI, CNS, heart
  - Atypical lymphocytes, lymphocytosis, hepatitis



- Doughnut granulomas aka fibrin ring granuloma
  - Q fever
  - CMV, EBV, toxoplasmosis, HAV, leishmaniasis, Hodgkin, GCA, allopurinol

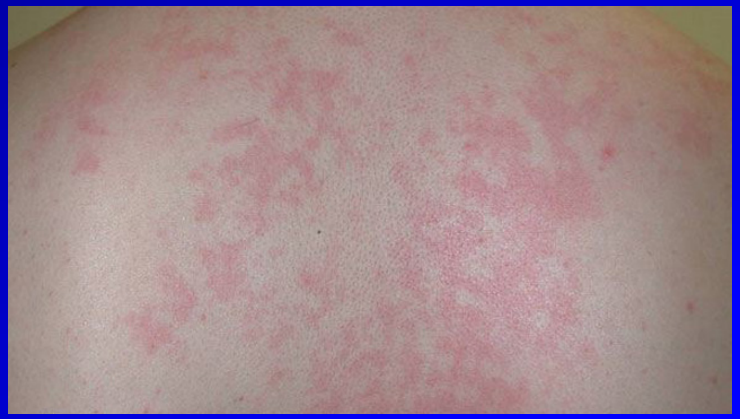
Case

- 41 yo woman, no PMH, admitted with 3 months of fever, also transient rash, nausea, and vomiting, fatigue, joint pain, sore throat, mild cough, on and off since then
- On exam shotty cervical LAP, hepatomegaly
- That night she spikes and the intern notes a salmon color rash in the chest

- WBC 17K, high ESR and CRP, ferritin 3500. Negative CXR and cultures, negative ANA and RF
- After appropriate work up including micro and imaging diagnosed with Adult onset Still's disease (AOSD), treated with steroids followed by tocilizumab

AOSD, Yamaguchi criteria

- Major
  - Fever > 102.2F for at least a week
  - Arthralgias or arthritis for ≥ 2 weeks
  - Nonpruritic macular or maculopapular rash
  - WBC ≥ 10K and ≥ 80% granulocytes
- Minor
  - Sore throat
  - LAP
  - Hepatomegaly or splenomegaly
  - Abnormal LFTs
  - Negative ANA and RF
- 5 including 2 major, exclude other dx



Case

- 35 yo man with IgA nephropathy on azathioprine presents with fevers of 103.2 for 2 weeks. Also sore throat, cough, chills, malaise. At OSH pancytopenia, AKI requiring HD, blood cultures negative, no response to atb. 2 toddlers at home, trip to Argentina last year (Buenos Aires). Exam unremarkable.

- WBC 3.2 (17% N, 66 L), Hb 7, plt 90, alk phos 328, ALS 91, AST 112, ferritin 4952, Alb 1.6, albumin 2.8

- Diagnosed with CMV and macrophage activation syndrome (MAS) and started on GCV steroids and anakinra with improvement.

Hemophagocytic lymphohistiocytosis (HLH) / Macrophage activation syndrome (MAS)

- Uncontrolled immune activation, impaired NK and cytotoxic lymphocytes fail to suppress activated macrophages, leading to excessive macrophage activity and high levels of cytokines
- Sporadic or following a trigger
- Familial
- Infection, malignancy, CTD, immunodeficiencies
- Clinical
  - Fever, organomegaly, LAP, organ failure, hypotension, CNS

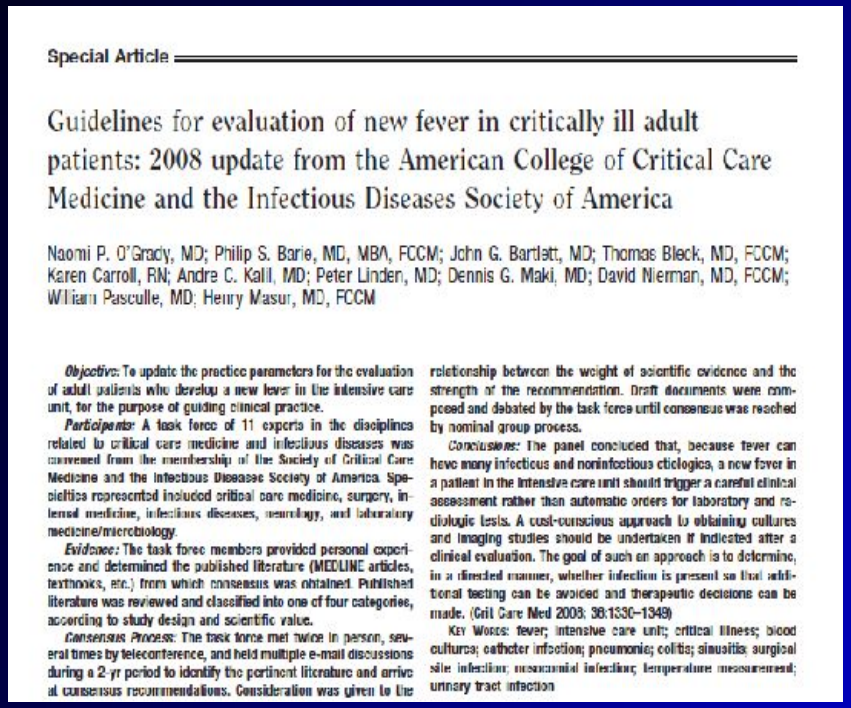
Hemophagocytic lymphohistiocytosis (HLH) / Macrophage activation syndrome (MAS)

- Labs
  - Cytopenias, high LDH, coagulopathies, elevated LFTs
  - High TG
  - Low fibrinogen
  - High ferritin (MAS ferritin)
  - Evidence of hemophagocytosis
  - Low or absent NK cell activity
  - Elevation of soluble CD25 (soluble IL-2 receptor)
- Treatment
  - Supportive
  - Underlying etiology
  - Steroids
  - IL-1, IL-6 blockers
  - Etoposide, cyclosporine, chemo
  - BMT

Case

- 72 yo lady, h/o asthma, admitted with cough, dyspnea and fever up to 102 for 3 weeks. Received levofloxacin without improvement, admitted. Chest imaging showed mosaic attenuation, pancytopenia, some atypical mononuclear cells, high ferritin and LDH
- No response to antibiotics, bone marrow normal, then dx with MAS, AKI, multiorgan failure, intubated, febrile, encephalopathic
- Repeated CT scan showed 2 hypodense splenic lesions and worsening lung infiltrates / ARDS
- Multiple HAI treated
- 3 months into her stay flow sent, concerning for intravascular lymphoma, skin biopsy non diagnostic, lung biopsy confirmed dx

Fever in the ICU



Special Article

Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America

Naomi P. O'Grady, MD; Philip S. Barie, MD, MBA, FCCM; John G. Bartlett, MD; Thomas Bleck, MD, FCCM; Karen Carroll, RN; Andre C. Kalil, MD; Peter Linden, MD; Dennis G. Maki, MD; David Nierman, MD, FCCM; William Pasculle, MD; Henry Masur, MD, FCCM

Objective: To update the practice parameters for the evaluation of adult patients who develop a new fever in the intensive care unit, for the purpose of guiding clinical practice.

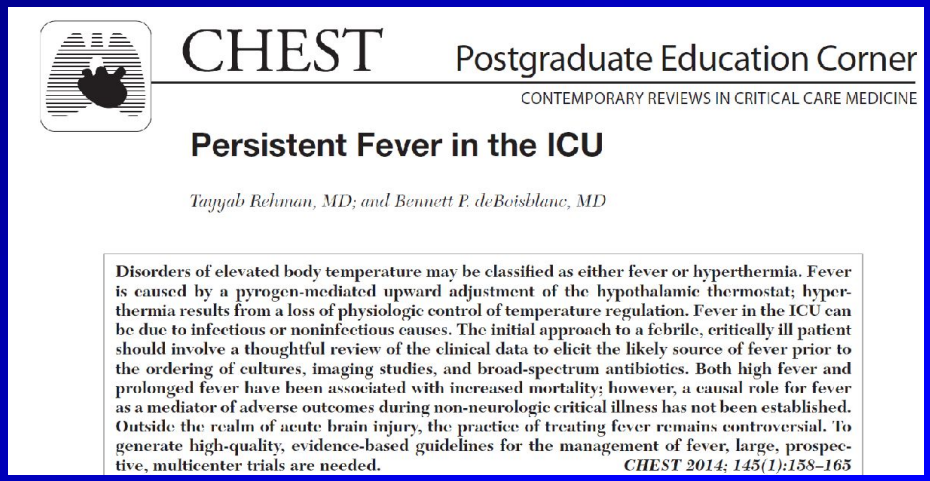
Participants: A task force of 11 experts in the disciplines related to critical care medicine and infectious diseases was convened from the membership of the Society of Critical Care Medicine and the Infectious Disease Society of America. Specialties represented included critical care medicine, surgery, internal medicine, infectious diseases, neurology, and laboratory medicine/microbiology.

Evidence: The task force members provided personal experience and determined the published literature (MEDLINE articles, textbooks, etc.) from which consensus was obtained. Published literature was reviewed and classified into one of four categories, according to study design and scientific value.

Consensus Process: The task force met twice in person, several times by teleconference, and held multiple e-mail discussions during a 2-yr period to identify the pertinent literature and arrive at consensus recommendations. Consideration was given to the relationship between the weight of scientific evidence and the strength of the recommendation. Draft documents were composed and debated by the task force until consensus was reached by nominal group process.

Conclusions: The panel concluded that, because fever can have many infectious and noninfectious etiologies, a new fever in a patient in the intensive care unit should trigger a careful clinical assessment rather than automatic orders for laboratory and radiologic tests. A cost-conscious approach to obtaining cultures and imaging studies should be undertaken if indicated after a clinical evaluation. The goal of such an approach is to determine, in a directed manner, whether infection is present so that additional testing can be avoided and therapeutic decisions can be made. (Crit Care Med 2008; 36:1330–1349)

Key Words: fever; intensive care unit; critical illness; blood cultures; catheter infection; pneumonia; colitis; sinusitis; surgical site infection; nosocomial infection; temperature measurement; urinary tract infection



CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Persistent Fever in the ICU

Tayyab Rehman, MD; and Bennett P. deBoisblanc, MD

Disorders of elevated body temperature may be classified as either fever or hyperthermia. Fever is caused by a pyrogen-mediated upward adjustment of the hypothalamic thermostat; hyperthermia results from a loss of physiologic control of temperature regulation. Fever in the ICU can be due to infectious or noninfectious causes. The initial approach to a febrile, critically ill patient should involve a thoughtful review of the clinical data to elicit the likely source of fever prior to the ordering of cultures, imaging studies, and broad-spectrum antibiotics. Both high fever and prolonged fever have been associated with increased mortality; however, a causal role for fever as a mediator of adverse outcomes during non-neurologic critical illness has not been established. Outside the realm of acute brain injury, the practice of treating fever remains controversial. To generate high-quality, evidence-based guidelines for the management of fever, large, prospective, multicenter trials are needed.

CHEST 2014; 145(1):158–165

Lymphoma

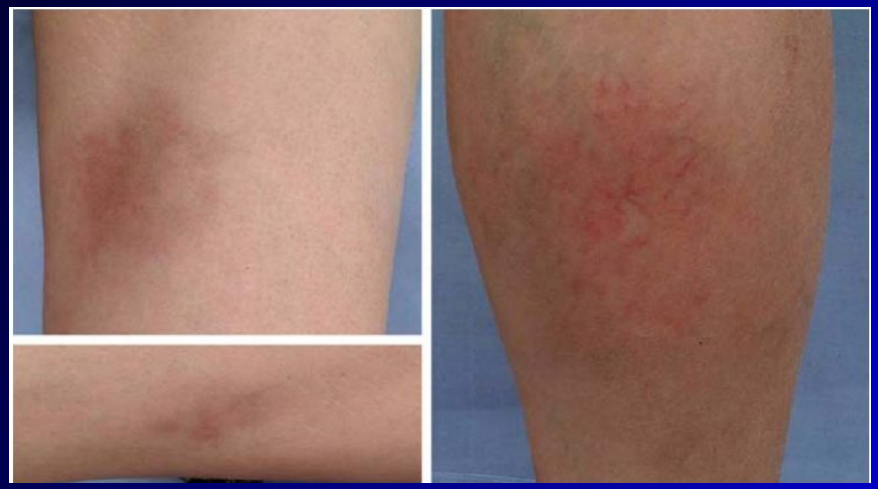
- Different kinds, some with big lymph nodes, some not
- Some with HSM some not
- Some with BM abnormalities some not
- Some with easy diagnosis from tissue some not
- Some with rapid course, some not

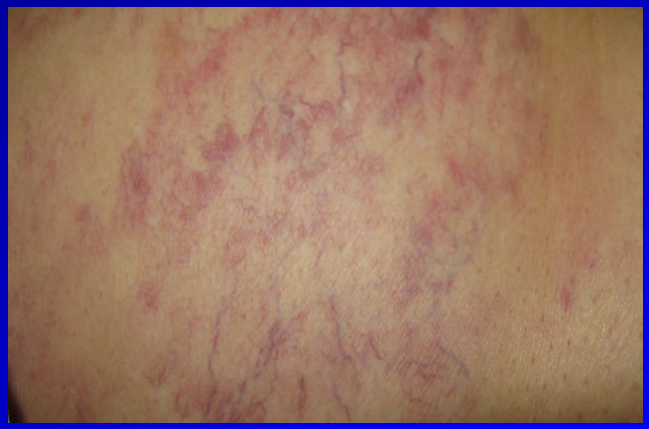
- Some misdiagnosed as sarcoidosis
- Some misdiagnosed as EBV infection or other viral infection
- Some require 2-3 biopsies or more before a diagnosis is made
- PET may help target tissue for diagnosis

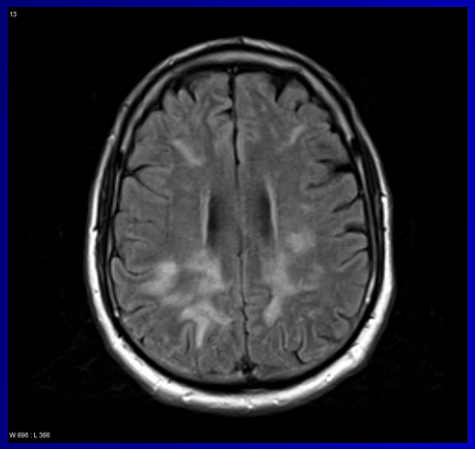
Intravascular lymphoma

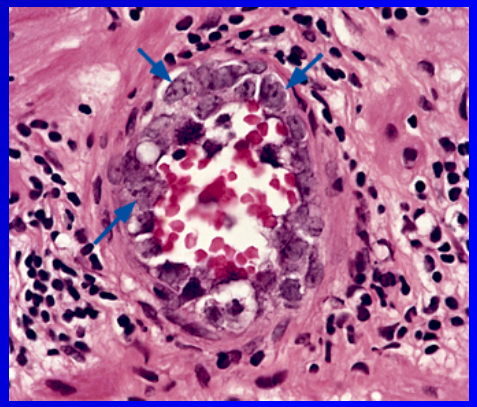
- Lymphomatous process in wall of small blood vessels, many times without lymph nodes, masses or circulating lymphoma cells in peripheral blood
- Very difficult to diagnose, many times at autopsy
- Fever present in over half, including MAS/HLH
- Consider it in patients with lung, brain and skin manifestations
- Bone marrow involvement in 1/3
- PET may show diffuse uptake in organs
- May have positive ANCA masking diagnosis
- Deep skin biopsy (including normal looking skin, 3 samples), lung biopsy, other tissue

Intravascular lymphoma





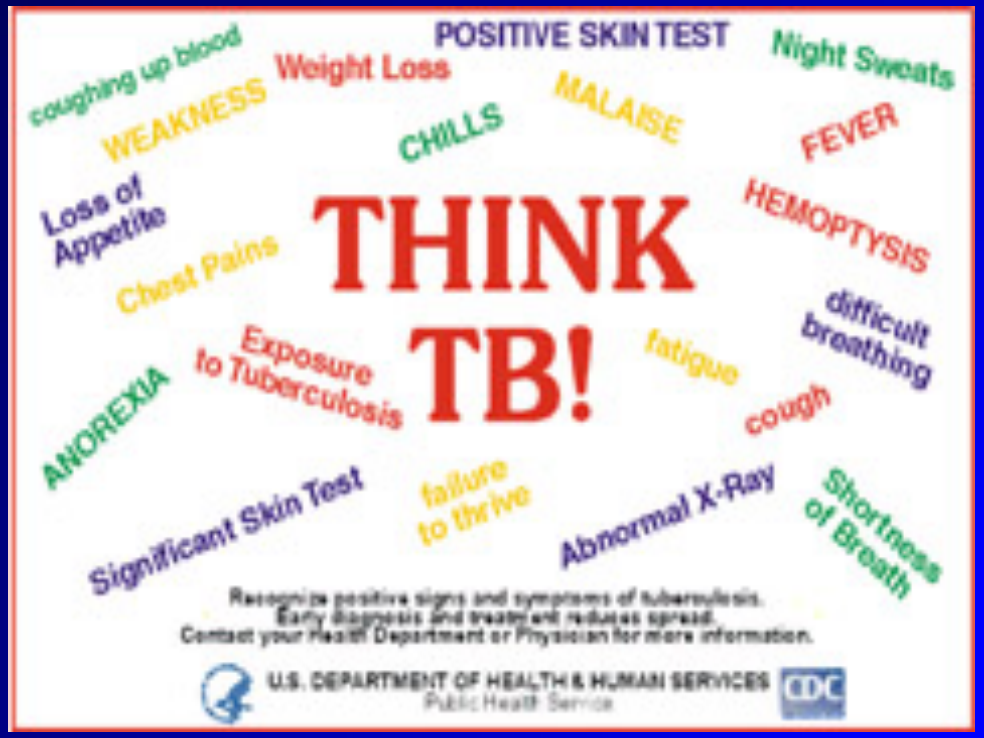




Int J Hematol 2010; 91:146. Dermetnz.org

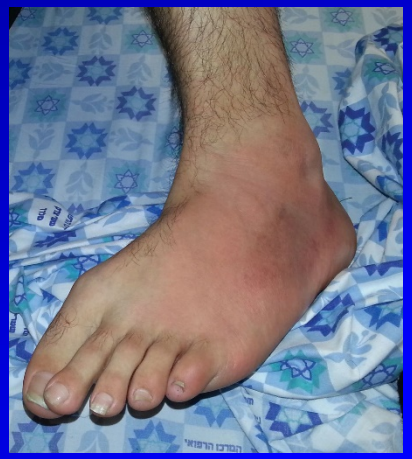
Case

- 85 yo man with metastatic lung SCC to bone, liver and abdomen, admitted with 1 week of fever difficulty walking and encephalopathy. On chemo, pancytopenic, exam non revealing. MRI consistent with small R basal ganglia infarct
- Managed as neutropenic fever, no response
- LP: WBC 65, 89% LMN, prot 255, glucose 46 (106 in blood)
- Treated as meningitis, PCCU, died
- Cerebrospinal fluid grew Mycobacterium tuberculosis 3 weeks later


POSITIVE SKIN TEST
coughing up blood
Weight Loss
Night Sweats
WEAKNESS
MALAISE
CHILLS
FEVER
Loss of Appetite
HEMOPTYSIS
Chest Pains
THINK
TB!
difficult breathing
Exposure to Tuberculosis
fatigue
ANOREXIA
cough
Significant Skin Test
failure to thrive
Abnormal X-Ray
Shortness of Breath
Recognize positive signs and symptoms of tuberculosis.
Early diagnosis and treatment reduces spread.
Contact your Health Department or Physician for more information.
U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
CDC

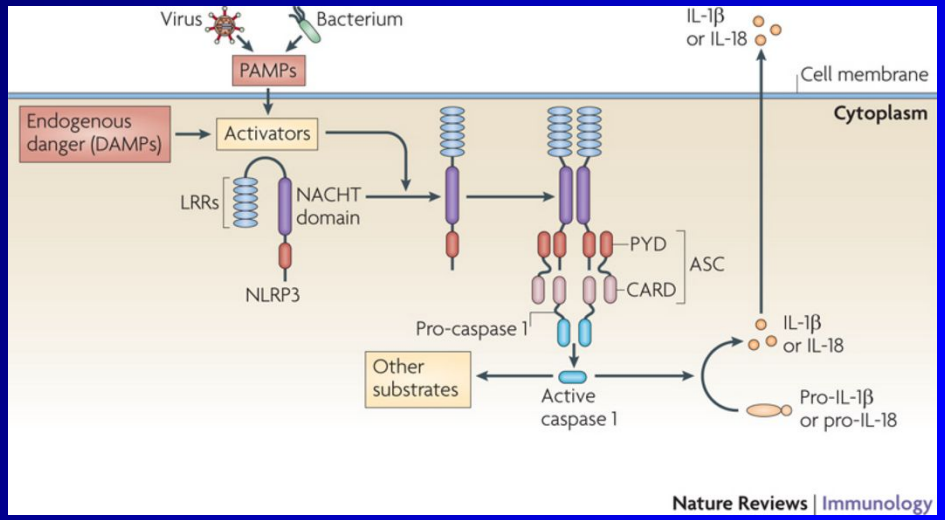
Case

- 20 yo man with multiple episodes of fever, abdominal pain, and cellulitis, for the last 5-6 years
- Has had 2 exploratory laparotomies with normal findings
- No symptoms in between episodes
- Periodic fever genetic panel showed mutation in MEFV gene
- Diagnosed with familial Mediterranean fever



Autoinflammatory syndromes

- Dysregulations of the innate immune system, inflammasomes, IL-1β pathway, protein folding, NF-kβ, cytokines, interferonopathies
- Most are monogenic autoinflammatory diseases causing periodic fever syndromes
- Other not familial or only weak familial component



Acta Paediatrica 2016; (105): 1140. Nature Immunol. 2017;18:832

Monogenic autoinflammatory syndromes

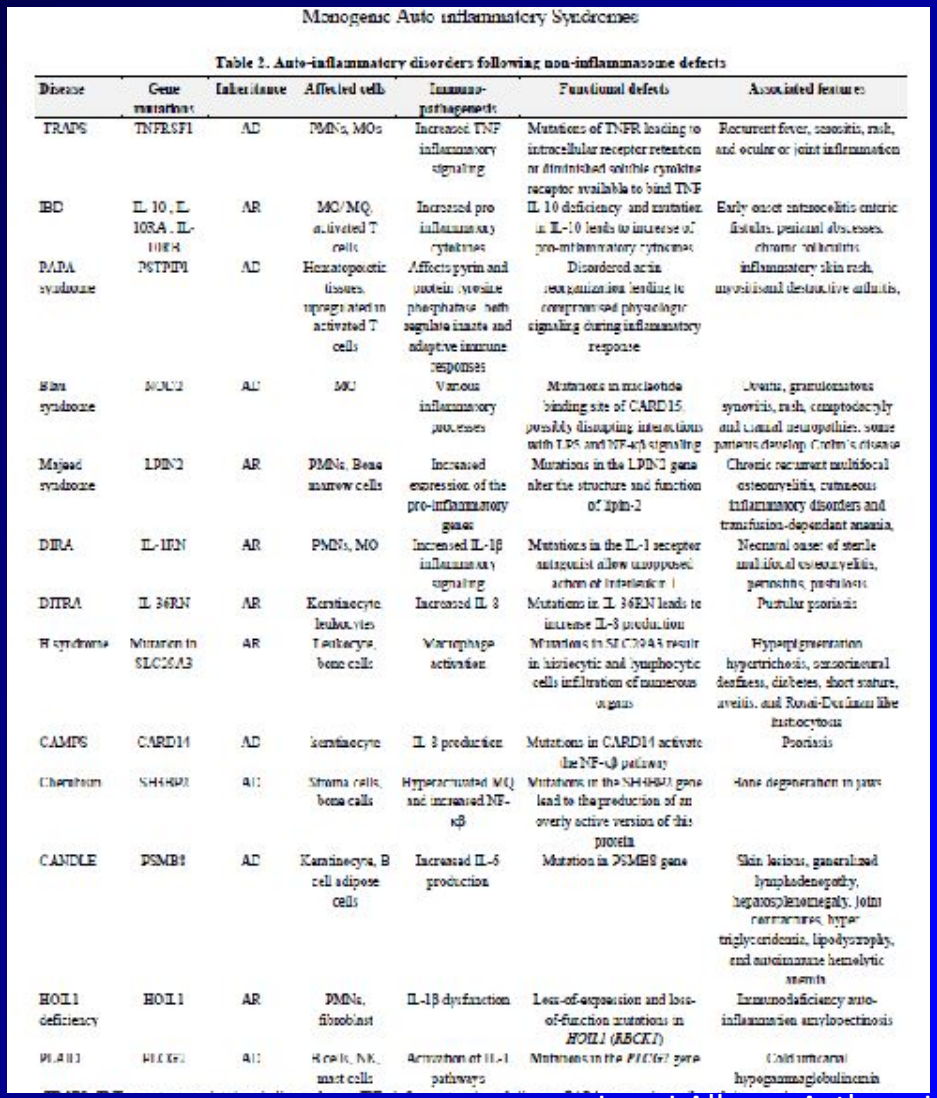
Table 1. Auto-inflammatory disorders following inflammasome defects

Disease	Gene Mutations	Inheritance	Affected cells	Immuno-pathogenesis	Functional defects	Associated features
FMF	MEFV	AR	PMNs, cytokine-activated MOs	Gain of pyrin function, resulting in inappropriate IL-1β release	Defects in pyrin production leads to ASC-induced IL-1 processing and inflammation following subclinical serosal injury; macrophage apoptosis decreased	Recurrent fever, serositis, and inflammation responsive to colchicine, susceptibility to vasculitis and IBD
MKD (HIDS)	MVK	AR	B cells, PBMCs	Mevalonate pathway blockage	Affecting cholesterol synthesis; IL-1β mediated inflammation	Periodic fever and leukocytosis along with high IgD serum levels
MWS	CIAS1	AD	PMNs, MOs	Activation of NLRP3 inflammasome	Defect in cryopyrin, involved in leukocyte apoptosis, NF-κβ signaling and processing of IL-1	Urticaria, amyloidosis, sensorineural hearing loss
FCAS	CIAS1, NLRP12	AD	PMNs, MOs	Activation of NLRP3 inflammasome	Defect in cryopyrin, involved in leukocyte apoptosis, NF-κβ signaling and processing of IL-1	Chills, fever, on-pruritic urticaria, arthritis, leukocytosis after cold exposure
NOMID	CIAS1	AD	PMNs, chondrocytes	Activation of NLRP3 inflammasome	Defect in cryopyrin, involved in leukocyte apoptosis, NF-κβ signaling and processing of IL-1	Neonatal onset rash, chronic meningitis, and arthropathy with fever and inflammation

FMF, familial Mediterranean fever; MKD, mevalonate kinase deficiency; HIDS, hyper IgD syndrome; MWS, Muckle-Wells syndrome; FCAS, familial cold auto-inflammatory syndrome, NOMID, neonatal onset multisystem inflammatory disease; IBD, inflammatory bowel disease; AR, autosomal recessive; AD, autosomal dominant; ASC, apoptosis-associated speck-like protein with a caspase recruitment domain; CIAS1, cold-

Iran J Allergy Asthma Immunol, Autumn 2016/ 434

Monogenic autoinflammatory syndromes



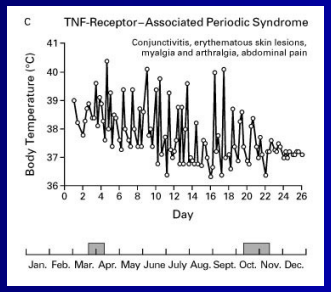
Monogenic Auto inflammatory Syndromes

Table 2. Auto-inflammatory disorders following non-inflammasome defects

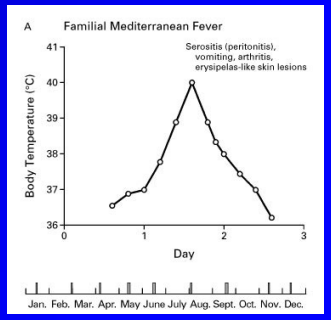
Disease	Gene mutations	Inheritance	Affected cells	Immuno-pathogenesis	Functional defects	Associated features
TRAPS	TNFRSF1	AD	PMNs, MOs	Increased TNF inflammatory signaling	Mutations of TNFR leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF	Recurrent fever, serositis, rash, and ocular or joint inflammation
IBD	IL 10 , IL 10RA , IL-10RB	AR	MO/MQ, activated T cells	Increased pro inflammatory cytokines	IL 10 deficiency and mutation in IL-10 leads to increase of pro-inflammatory cytocines	Early onset enterocolitis enteric fistulas, perianal abscesses, chronic colitis/itis
PAPA syndrome	PSTPIP1	AD	Hematopoietic tissues, upregulated in activated T cells	Affects pyrin and protein tyrosine phosphatase, both regulate innate and adaptive immune responses	Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response	Inflammatory skin rash, myositis and destructive arthritis,
Blau syndrome	NOD2	AD	MO	Various inflammatory processes	Mutations in nucleotide binding site of CARD15 possibly disrupting interactions with LPS and NF-κβ signaling	Uveitis, granulomatous synovitis, rash, camptodactyly and cranial neuropathies, some patients develop Crohn's disease
Majeed syndrome	LPIN2	AR	PMNs, Bone marrow cells	Increased expression of the pro-inflammatory genes	Mutations in the LPIN2 gene alter the structure and function of lipin-2	Chronic recurrent multifocal osteomyelitis, cutaneous inflammatory disorders and transfusion-dependant anaemia,
DIRA	IL-1RN	AR	PMNs, MO	Increased IL-1β inflammatory signaling	Mutations in the IL-1 receptor antagonist allow unopposed action of interleukin-1	Neonatal onset of sterile multifocal osteomyelitis, periostitis, pustulosis
DITRA	IL 36RN	AR	Keratinocyte leukocytes	Increased IL 8	Mutations in IL 36RN leads to increase IL-8 production	Pustular psoriasis
H syndrome	Mutation in SLC29A3	AR	Leukocyte, bone cells	Macrophage activation	Mutations in SLC29A3 result in histiocytic and lymphocytic cells infiltration of numerous organs	Hyperpigmentation hypertrichosis, sensorineural deafness, diabetes, short stature, uveitis, and Rosai-Dorfman like histiocytosis
CAMPS	CARD14	AD	keratinocyte	IL 8 production	Mutations in CARD14 activate the NF-κβ pathway	Psoriasis
Chronium	SH3BP2	AD	Stroma cells, bone cells	Hyperactivated MQ and increased NF-κβ	Mutations in the SH3BP2 gene lead to the production of an overly active version of this protein	Bone degeneration in jaw
CANDLE	PSMB8	AD	Keratinocyte, B cell adipose cells	Increased IL-6 production	Mutation in PSMB8 gene	Skin lesions, generalized lymphadenopathy, hepatosplenomegaly, joint contractures, hypertriglyceridemia, lipodystrophy, and autoimmune hemolytic anemia
HOIL1 deficiency	HOIL1	AR	PMNs, fibroblast	IL-1β dysfunction	Loss-of-expression and loss-of-function mutations in *HOIL1 (RBCK1)*	Immunodeficiency auto-inflammation amylopectinosis
PLAID	PLCG2	AD	B cells, NK, mast cells	Activation of IL-1 pathways	Mutations in the *PLCG2* gene	Cold urticaria/ hypogammaglobulinemia

Monogenic periodic fevers in adults

- TNF-receptor associated periodic fever (TRAPS)
  - Mutations in type 1 TNF receptor gene, AD
  - Scottish, Irish, other, usually onset <20 y
  - Attacks usually last several days
  - Fever, conjunctivitis, localized myalgias and rash



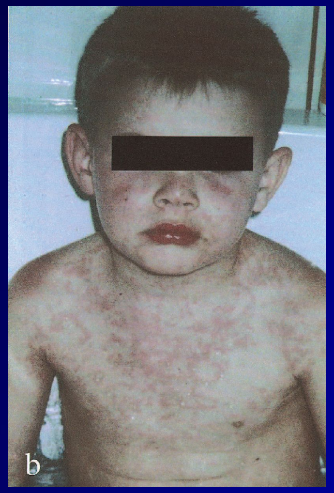
- Familial Mediterranean Fever (FMF)
  - Mutations in Mevalonate kinase gene (MEFV), AR
  - Jewish, Turkish, Armenian, Arab, usually onset <20 y
  - Attacks usually < 3-4 days
  - Fever, serositis, scrotal involvement, erysipelas-like erythema

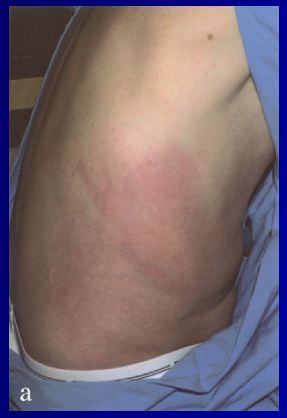


Drenth JPH. N Engl J Med 2001; 345:1748. Medicine 2002; 81: 349

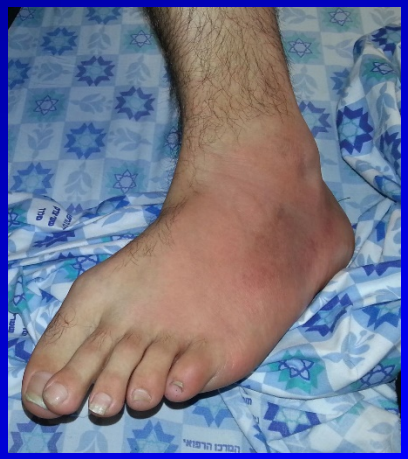
TRAPS and FMF

- TRAPS





- FMF



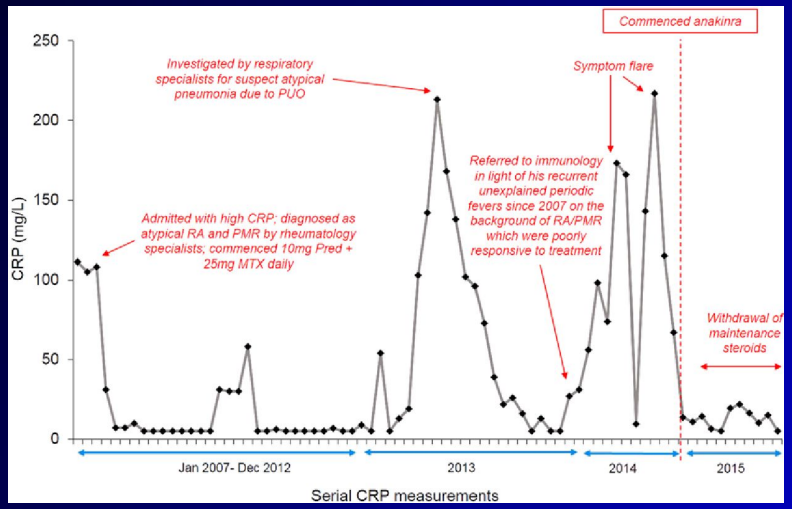
Medicine 2002; 81: 349. J Rheumatol 2014; 41:2271

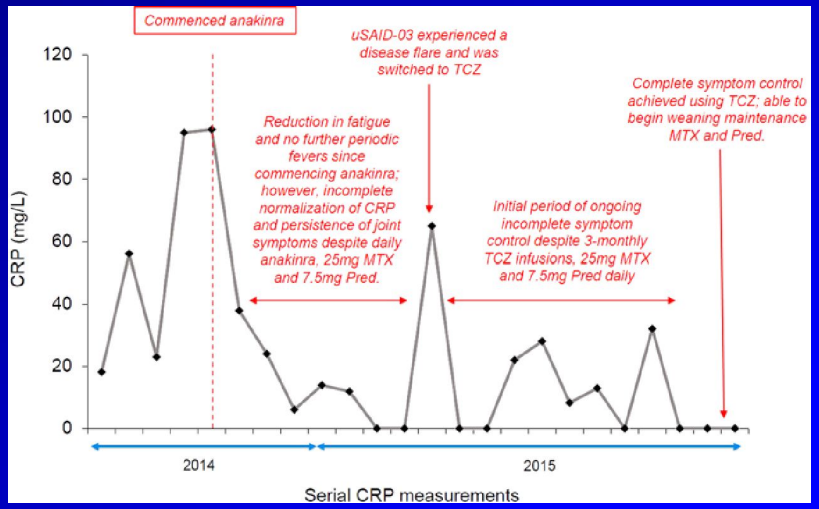
Undifferentiated autoinflammatory syndromes

- uSAID: undifferentiated systemic autoinflammatory syndrome
- No mutations found, no family history, any age
- Periodic fevers, myalgias, arthralgias or arthritis, rashes, headaches, aphthous ulcers, LAP, fatigue, malaise, serositis, GI, headaches
- Response to colchicine, anakinra, tocilizumab, steroids
- Diagnosis of exclusion and over time may evolve to a specific diagnosis

Harrison SR, et al. JCI Insight 2016; 1:e86336

Undifferentiated autoinflammatory syndromes





Harrison SR, et al. JCI Insight 2016; 1:e86336

Conclusions

- History, history, history
- Exam
- Repeat the above periodically, follow up is very important
- Stepwise approach to evaluation
- Beware of sending tests without thinking about pre-test probability and possibility of false positives
- The longer it lasts the less likely it is malignancy or infection (TB, Whipple's)
- Role for PET
- After very extensive work up may be reasonable to try empiric anti-inflammatory treatments in consultation with experts