Hindawi Publishing Corporation
Case Reports in Pediatrics
Volume 2016, Article ID 5437971, 3 pages
http://dx.doi.org/10.1155/2016/5437971

Case Report

A Physician's Nightmare: Fever of Unknown Origin

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Fever of Unknown Origin

Ghady Haidar, M.D., and Nina Singh, M.D.

PERSISTENT FEVER WITH AN ELUSIVE CAUSE HAS BEEN RECOGNIZED FOR more than a century. In 1907, Cabot, a cofounder of the Clinicopathological Conferences at Massachusetts General Hospital, characterized fever lasting for 2 weeks or longer as "long fever."[1] Over the ensuing decades, many studies of unexplained fever have been conducted with the use of various diagnostic criteria. In 1961, Petersdorf and Beeson defined fever of unknown origin (FUO) as a temperature of 38.3°C or higher for at least 3 weeks without a diagnosis, despite 1 week of inpatient investigations.[2] With the evolution of health care delivery in the am-

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N Engl J Med 2022;386:463-77.
DOI: 10.1056/NEJMra2111003

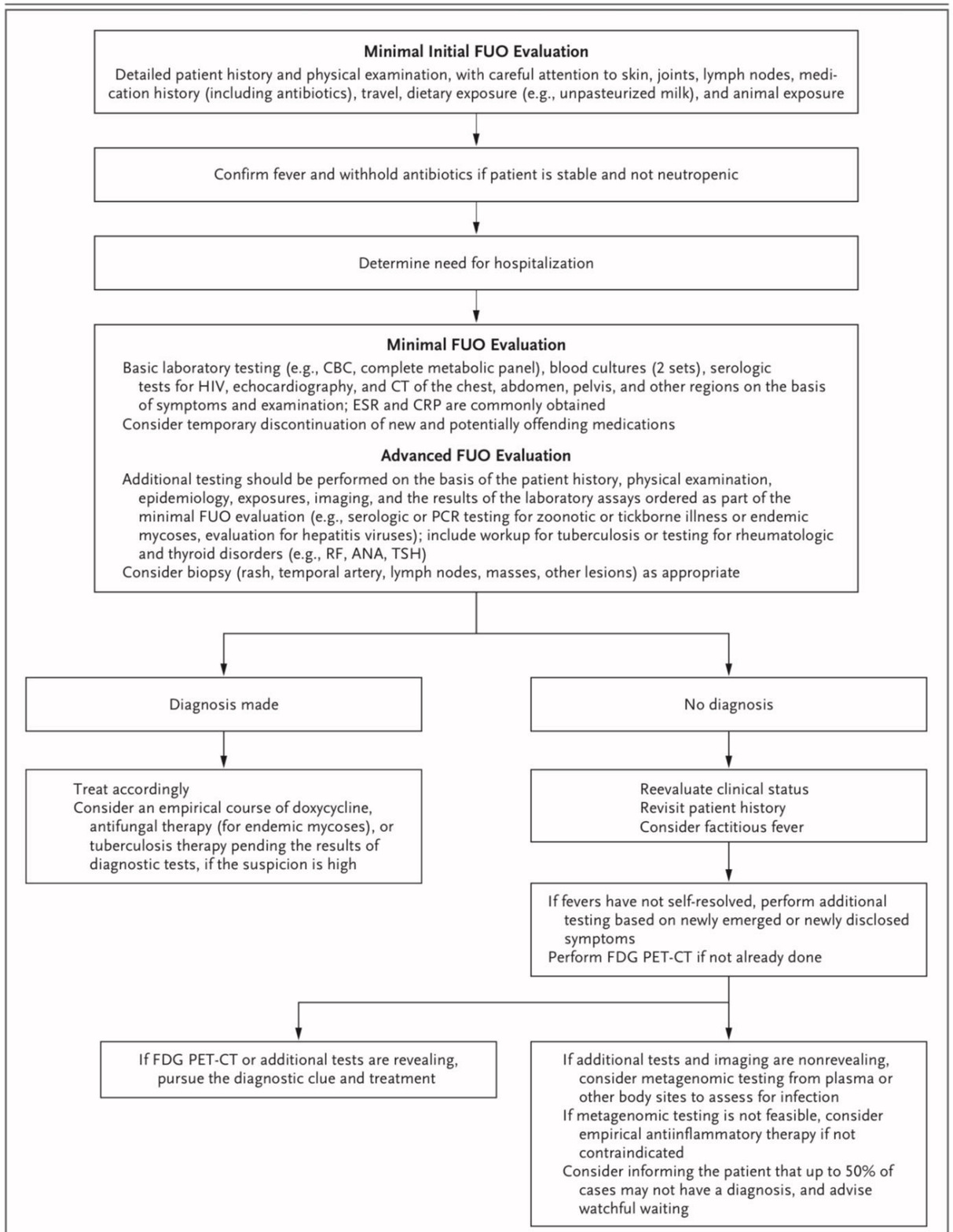
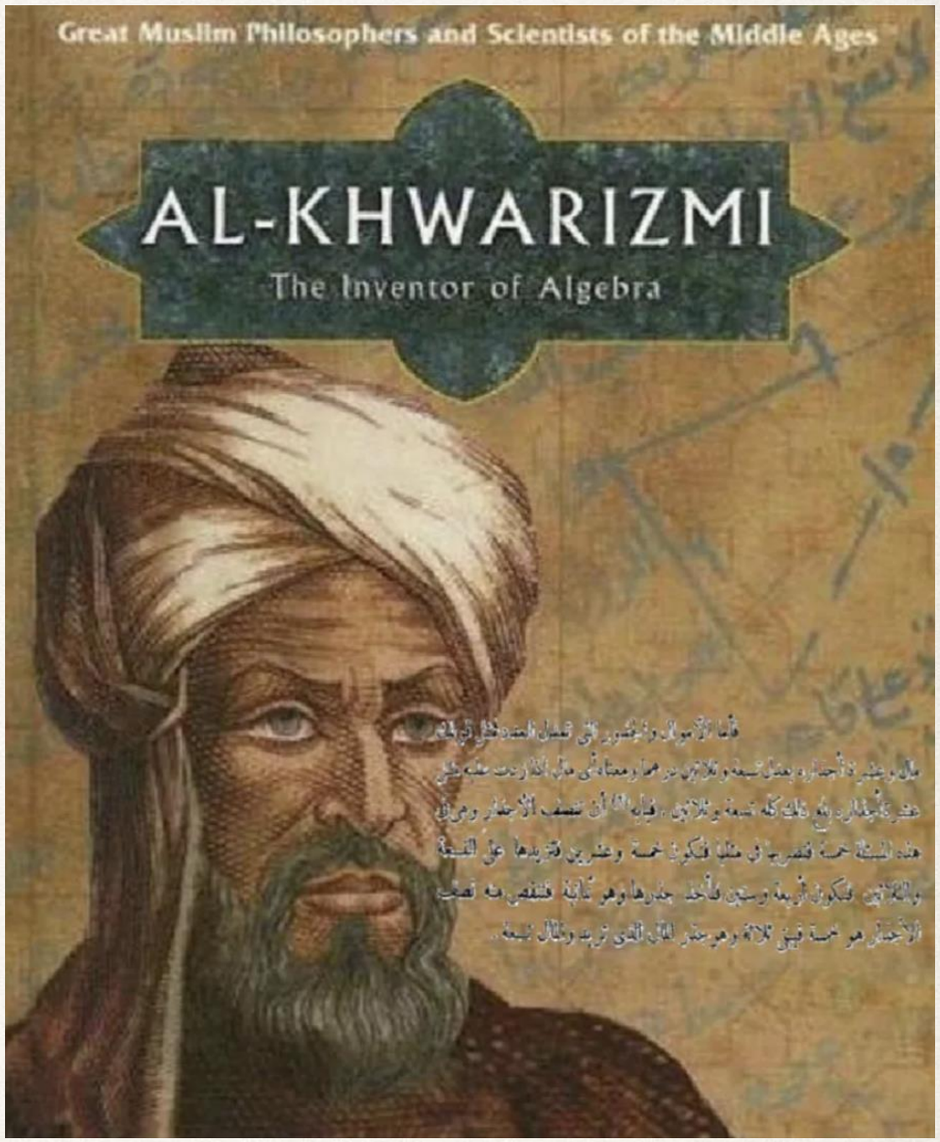


Figure 1. Suggested Diagnostic and Management Algorithm for Fever of Unknown Origin (FUO).

The approach should be individualized on the basis of the specific clinical scenario. ANA denotes antinuclear antibodies, CBC complete blood count, CRP C-reactive protein, CT computed tomography, ESR erythrocyte sedimentation rate, FDG PET-CT ^{18}F-fluorodeoxyglucose positron-emission tomography with CT, HIV human immunodeficiency virus, PCR polymerase chain reaction, RF rheumatoid factor, and TSH thyrotropin.



Minimal FUO Evaluation

Basic laboratory testing (e.g., CBC, complete metabolic panel), blood cultures (2 sets), serologic tests for HIV, echocardiography, and CT of the chest, abdomen, pelvis, and other regions on the basis of symptoms and examination; ESR and CRP are commonly obtained

Consider temporary discontinuation of new and potentially offending medications

Advanced FUO Evaluation

Additional testing should be performed on the basis of the patient history, physical examination, epidemiology, exposures, imaging, and the results of the laboratory assays ordered as part of the minimal FUO evaluation (e.g., serologic or PCR testing for zoonotic or tickborne illness or endemic mycoses, evaluation for hepatitis viruses); include workup for tuberculosis or testing for rheumatologic and thyroid disorders (e.g., RF, ANA, TSH)

Consider biopsy (rash, temporal artery, lymph nodes, masses, other lesions) as appropriate

If fevers have not self-resolved, perform additional testing based on newly emerged or newly disclosed symptoms

Perform FDG PET-CT if not already done

PET TAC CON FDG

Open Forum Infectious Diseases

REVIEW ARTICLE

Fever and Fever of Unknown Origin: Review, Recent Advances, and Lingering Dogma

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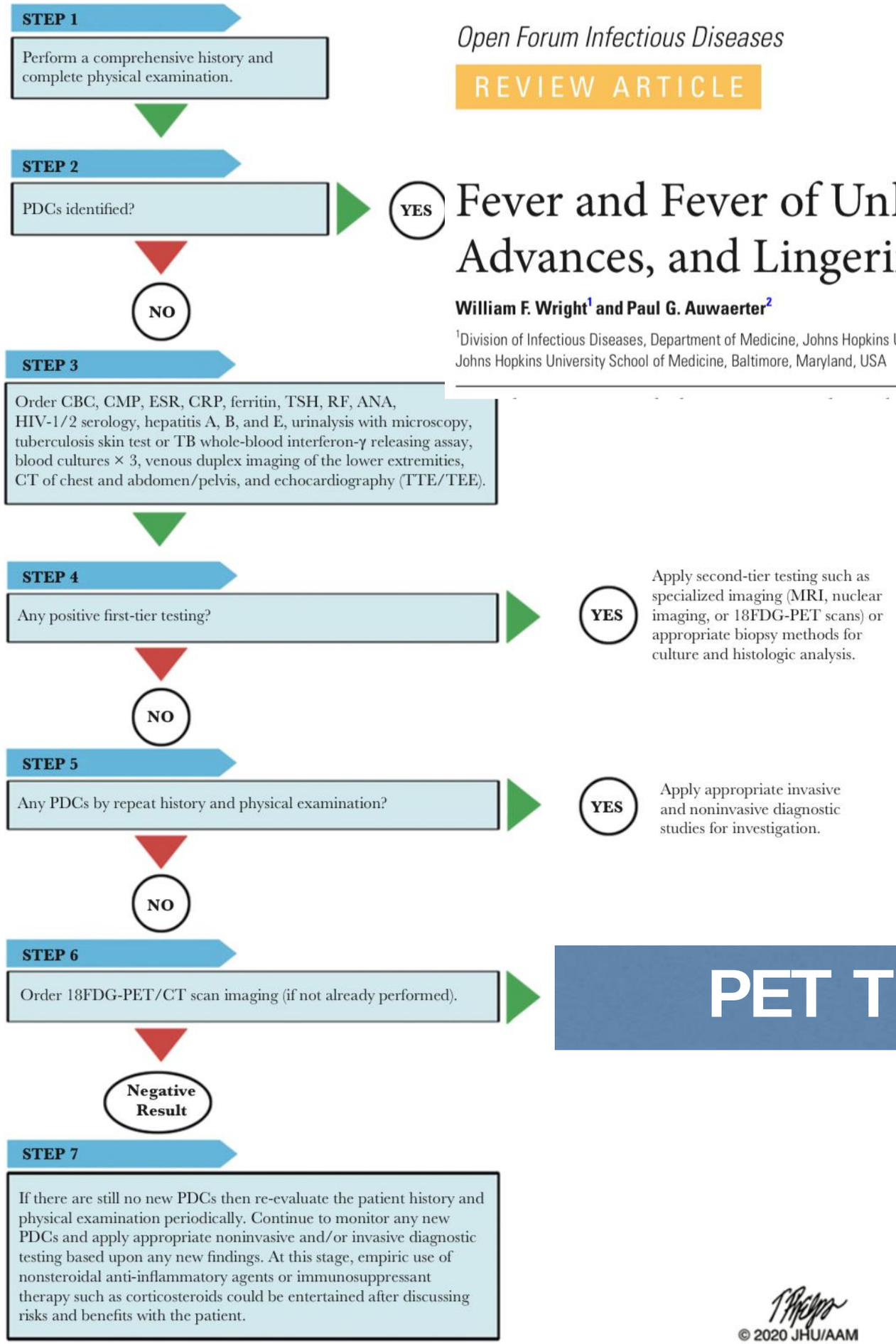


PET TAC CON FDG

<u>Gammagrafía con Galio:</u>
captación en fundus gástrico.

<u>Ecografía Arterias temporales</u>:
engrosamietos parcheados bilaterales , sugestivos de inflamación de la pared

<u>TAC TÓRAX-ABDOMEN PELVIS:</u> sin hallazgos

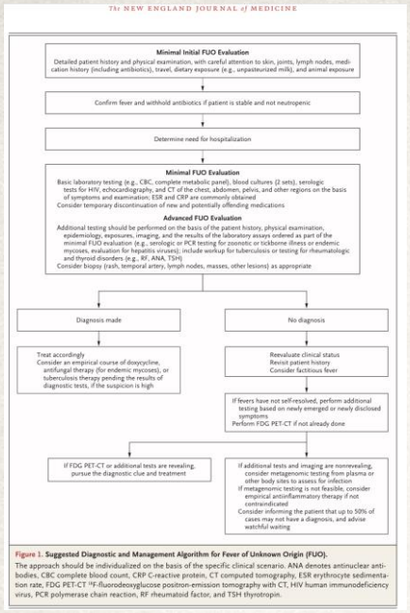
<u>EVOLUCIÓN</u>: (vista eco A. temporal) persiste Tª 38,5º (ingresada)

Además se agudiza anemia, hasta 7 gr Hb /dL, con VCM 72.

Se realiza transfusión y se inicia tratamiento esteroideo (1 mg/kg/d)

La fiebre desaparece (no lo hizo con Indometacina) y la paciente se encuentra asintomática

Faltan resultados…



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Minimal Initial FUO Evaluation
Detailed patient history and physical examination, with careful attention to skin, joints, lymph nodes, medication history (including antibiotics), travel, dietary exposure (e.g., unpasteurized milk), and animal exposure

Confirm fever and withhold antibiotics if patient is stable and not neutropenic

Determine need for hospitalization

Minimal FUO Evaluation
Basic laboratory testing (e.g., CBC, complete metabolic panel), blood cultures (2 sets), serologic tests for HIV, echocardiography, and CT of the chest, abdomen, pelvis, and other regions on the basis of symptoms and examination; ESR and CRP are commonly obtained
Consider temporary discontinuation of new and potentially offending medications

Advanced FUO Evaluation
Additional testing should be performed on the basis of the patient history, physical examination, epidemiology, exposures, imaging, and the results of the laboratory assays ordered as part of the minimal FUO evaluation (e.g., serologic or PCR testing for zoonotic or tickborne illness or endemic mycoses, evaluation for hepatitis viruses); include workup for tuberculosis or testing for rheumatologic and thyroid disorders (e.g., RF, ANA, TSH)
Consider biopsy (rash, temporal artery, lymph nodes, masses, other lesions) as appropriate

Diagnosis made

Treat accordingly
Consider an empirical course of doxycycline, antifungal therapy (for endemic mycoses), or tuberculosis therapy pending the results of diagnostic tests, if the suspicion is high

If FDG PET-CT or additional tests are revealing, pursue the diagnostic clue and treatment

No diagnosis

Reevaluate clinical status
Revisit patient history
Consider factitious fever

If fevers have not self-resolved, perform additional testing based on newly emerged or newly disclosed symptoms
Perform FDG PET-CT if not already done

If additional tests and imaging are nonrevealing, consider metagenomic testing from plasma or other body sites to assess for infection
If metagenomic testing is not feasible, consider empirical antiinflammatory therapy if not contraindicated
Consider informing the patient that up to 50% of cases may not have a diagnosis, and advise watchful waiting

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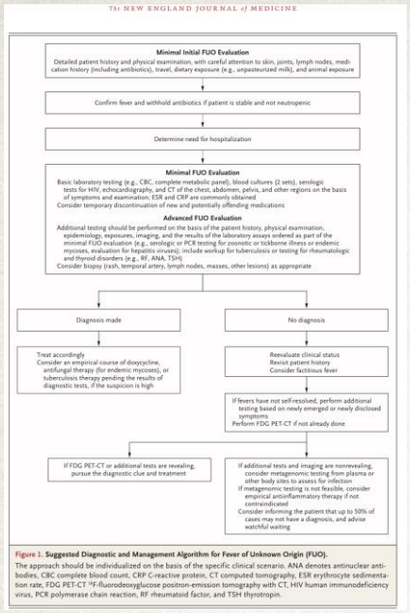
Y AHORA?

INTERFERÓN TB: positivo

GASTROSCOPIA Y COLONOSCOPIA:
sin hallazgos

BIOPSIA ARTERIA TEMPORAL: Negativa



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Y LUEGO…?

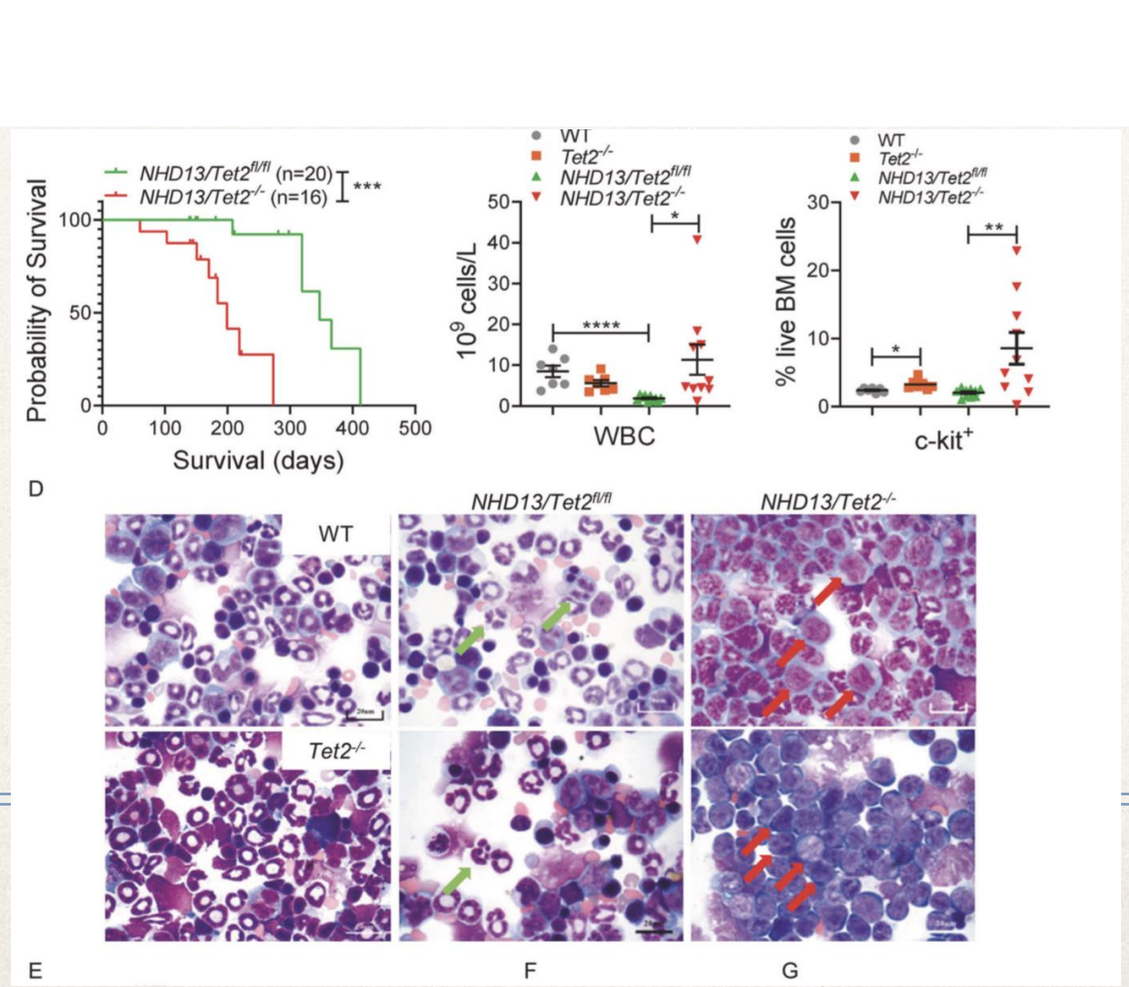
BIOPSIA MÉDULA ÓSEA: LEUCEMIA MIELOMONOCÍTICA CRÓNICA

Blood Cancer Journal www.nature.com/bcj

CORRESPONDENCE OPEN

Check for updates

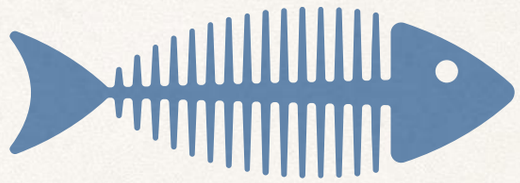
TET2 deficiency promotes MDS-associated leukemogenesis



Subtipos de la LMMC:

1) mielodisplásico (LMMC-MD) con recuento de leucocitos <13 000/µl

2) mieloproliferativo (LMMC-MP) con recuento de leucocitos ≥13 000/µl



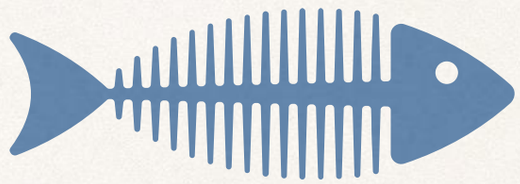
LMMC-0: blastosis en sangre periférica <2 % (blastos,

LMMC-1: blastosis en sangre periférica de un 2-4 % (blastos, promonocitos) y en médula ósea de un 5-9 %

LMMC-2: blastosis en sangre periférica de un 5-19 % (blastos, promonocitos) y en médula ósea de un 10-19 % (blastos, promonocitos, bastones de Auer).

La incidencia anual es de 0,4/100 000.

La edad promedio en el momento del diagnóstico es de 65-75 años, el doble de frecuente en hombres



Signos y síntomas generales

1) astenia asociada con anemia

2) pérdida de masa corporal

3) <u>febrícula, fiebre</u> y sudoración nocturna, en relación a la liberación de pirógenos en el contexto de la apoptosis de las células en proliferación.

DIAGNÓSTICO

LEUCEMIA MIELOMONOCÍTICA CRÓNICA (tipo 2 de la OMS)

INFECCIÓN TUBERCULOSA LATENTE