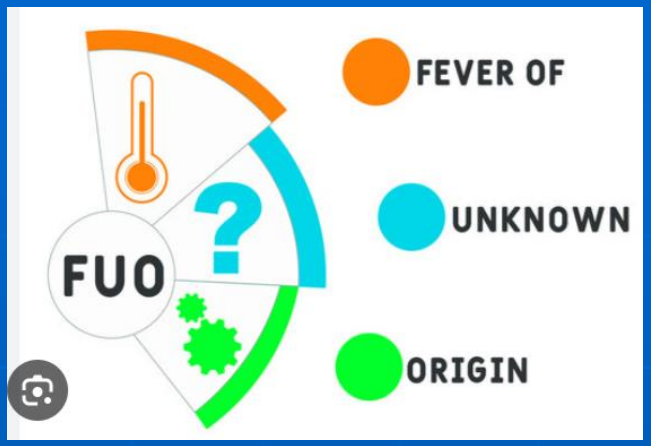


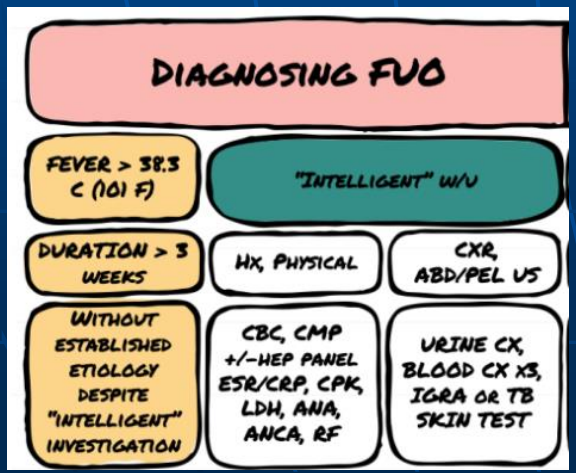
1. Classical FUO
2. Nosocomial FUO
3. Neutropenic FUO
4. HIV-Associated

New addition
Transplant FUO

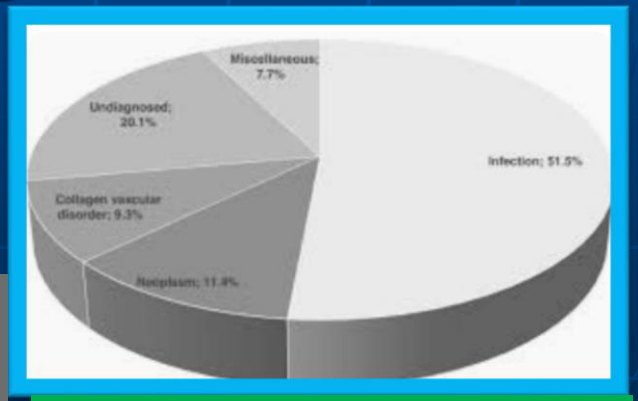
FUO
causes and management

Cheng-Yi Wang

2024.02.23



Erdem, H., Baymakova, M., Alkan, S. *et al.* Classical fever of unknown origin in 21 countries with different economic development: an international ID-IRI study. *Eur J Clin Microbiol Infect Dis* **42**, 387–398 (2023).



依據2016-2021, 世界21國案例的案例的分析感染還是最多的原因

Objectives:

- Describe the workup of a patient with a fever of unknown origin.
- Outline the causes for fever of unknown origin.
- Summarize the treatment of patients with fever of unknown origin.
- Review the importance of improving care coordination among interprofessional team members to improve outcomes for patients affected by fever of unknown origin.

1.病史上的特性,常可以指向特殊的疾病.
2,特殊的身體的徵象指向特殊的疾病
3.應用臨床推理的原則將可能之疾病減為3個
4.在個別應用特別的檢驗或醫學影像做鑒別診斷的依據
5.敘述特殊疾病的診斷依據-→很可能得到最可能的疾病
6.組織學檢查常常是最終診斷的最重要的依據
7.改善發燒原因不明之醫療照顧品質有賴組成多專科專家的團隊,及早確立診斷,可以改善預後
8.學習每一個案例找出診斷的關鍵點是學習的重點,務必寫成疾病劇本.作為往後處理病人的參考.

Definition

- *Fever of unknown origin (FUO) was defined by* ***Petersdorf and Beeson in 1961*** as
- (1) temperatures of >38.3°C (>101°F) on several occasions;
- (2) a duration of fever of >3 weeks; and
- (3) failure to reach a diagnosis despite 1 week of inpatient investigation.

In 1961, Petersdorf and Beeson defined fever of un known origin(FUO) as a stateof febrile illness for more than three weeks, with a body temperature greater than 38.3 ˚C on several occasions and uncertain diagnosis after one week of study in hospital.

Petersdorf and Beeson, Medicine 1961;40:1

- **Durack and Street** have proposed a new system for classification of FUO:

(1) Classic FUO;
(2) Nosocomial FUO;
(3) Neutropenic FUO; and
(4) FUO associated with HIV infection.

New definition of "classic FUO"

- The newer definition is broader, **stipulating three outpatient visits or 3 days in the hospital without elucidation of a cause or 1 week of "intelligent and invasive" ambulatory investigation.**

1991年，Durack和Street修訂了先前的FUO定義，並建議隨著醫院診斷能力的提高，診斷時間應縮短至三天[5]。

Durack DT, Street AC.Fever of unknown origin–reexamined and redefined. Curr Clin Top Infect Dis. 1991;11:35–51.

Causes of fever of unknown origin

Table 1 Causes of classic fever of unknown origin

[1]NIID, Non-infectious inflammatory disease

Author (pub. year)	Infection (%)	Neoplasm (%)	NIID[1] (%)	Misc. (%)	Undiagnosed (%)
Petersdorf (1961) [1]	36	19	19	19	7
Larson (1982) [7]	30	31	16	11	12
Knockaert (1992) [6]	22.5	7	23	21.5	26
De Kleijn (1997) [9]	26	12	25	8	30
Bleeker-Rovers (2007) [10]	16	7	22	4	51

發燒與感染有關是一個合理的推理想法. 應該是佔最多的原因. 事實不然. 依據個別的報告感染的原因已經降低了

定義改變, FOU的原因也改變 Infection減少了, NIID增加了 不明原因的案例更增加

Wien Klin Wochenschr (2016) 128:796–801
DOI 10.1007/s00508-016-1083-9

Wiener klinische Wochenschrift
The Central European Journal of Medicine

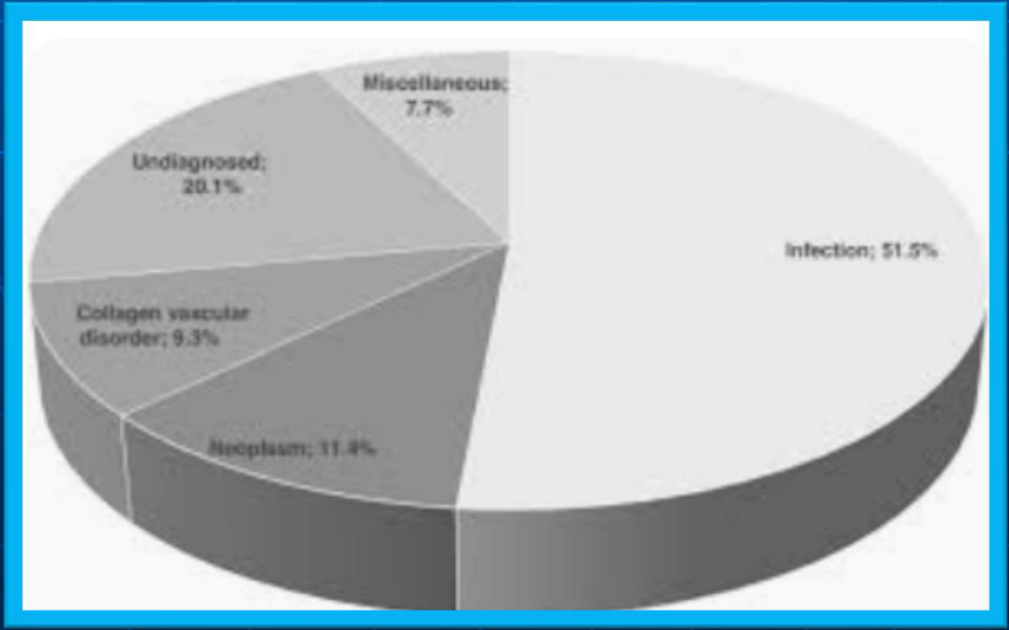
CrossMark

Fever of unknown origin (FUO) revised

Manuel Unger · Georgios Karanikas · Andreas Kerschbaumer · Stefan Winkler · Daniel Aletaha

感染引起的 FUO 最有可能與資源有限的國家有關

- 人們普遍認為，感染引起的 FUO 最有可能與資源有限的國家有關，而已開發國家或較富裕的國家偏好 FUO 診斷的非感染性子集，如腫瘤或膠原血管疾病 [2 , 24]。然而，除了膠原蛋白血管疾病之外，我們無法發現整個 FUO 群體的這種關係，這些疾病在富裕國家更常見。儘管世界範圍內知識的傳播和衛生基礎設施的改善似乎有使感染和腫瘤的診斷趨於統一的趨勢，但膠原血管疾病並未得到同等的識別，並且在經濟收入較低的國家群體中較少被發現。



依據2016-2021, 世界21國案例的案例的分析感染還是最多的原因

Erdem, H., Baymakova, M., Alkan, S. *et al.* Classical fever of unknown origin in 21 countries with different economic development: an international ID-IRI study. *Eur J Clin Microbiol Infect Dis* **42**, 387–398 (2023). (L1361)

另有一個特別的狀況是器官移植後發燒之原因

- 最近有幾個相關的報告值得注意：

1. Comparison of two different anti-infectious approaches after high-dose chemotherapy and autologous stem cell **transplantation** for hematologic malignancies in a 12-year period in British Hospital, Uruguay.Oliver AC, Riva E, Mosquera R, Galeano S, Pierri S, Bello L, Caneiro A, Gai R, Miller A, Muxi P.Ann Hematol. 2020 Apr;99(4):877-884. doi: 10.1007/s00277-020-03947-1. Epub 2020 Feb 15.
2. Prospective evaluation of procalcitonin in adults with non-neutropenic **fever** after allogeneic hematopoietic stem cell **transplantation**.Ortega M, Rovira M, Filella X, Martínez JA, Almela M, Puig J, Carreras E, Mensa J.Bone Marrow Transplant. 2006 Mar;37(5):499-502. doi: 10.1038/sj.bmt.1705262.
3. Tumor necrosis factor-alpha inhibitor-induced lupus-like syndrome presenting as **fever** of **unknown origin** in a liver **transplant** recipient: case report and concise review of the literature.
Page AV, Liles WC.Transplant Proc. 2008 Jun;40(5):1768-70. doi: 10.1016/j.transproceed
4. Clinical significance of pre-**transplant** circulating $CD3^+$ $CD4^+$ $CD161^+$ cell frequency on the occurrence of neutropenic infections after allogeneic stem cell **transplantation**.Kim TW, Lee SE, Lim JY, Ryu DB, Jeon YW, Yoon JH, Cho BS, Eom KS, Kim YJ, Kim HJ, Lee S, Cho SG, Kim DW, Lee JW, Min WS, Min CK.Transpl Infect Dis. 2017 Feb;19(1). doi: 10.1111/tid.12643. Epub 2017 Jan 10.
5. Adenovirus Infection as a Cause of **Fever** of **Unknown Origin** and Allograft Dysfunction in a Kidney **Transplant** Recipient.
Saliba M, Kfoury Assouf H, Abbas S, Abi Hanna P, Kamel G, Barbari A
6. Efficacy of continuous infusion of ceftazidime for patients with neutropenic **fever** after high-dose chemotherapy and peripheral blood stem cell **transplantation**.Egerer G, Goldschmidt H, Salwender H, Hegenbart U, Ehrhard I, Haas R, Ho AD.Int J Antimicrob Agents. 2000 Jul;15(2):119-23. doi: 10.1016/s0924-8579(00)00155-2.
7. @@@Acute graft-versus-host disease **associated** cerebellitis as the cause of pyrexia of **unknown origin** detected with ^{18}F-FDG-PET/CT.Jewell KE, Kuzich JA, Lee ST, Trethowan R, Macdonell R, Schwarer AP.Cancer Treat Res Commun. 2021;27:100341. doi: 10.1016/j.ctarc.2021.100341. Epub 2021 Feb 16.
8. Antimicrobial de-escalation in adult hematopoietic cell **transplantation** recipients with febrile neutropenia of **unknown origin**.Petteys MM, Kachur E, Pillinger KE, He J, Copelan EA, Shahid Z.J Oncol Pharm Pract. 2020 Apr;26(3):632-640. doi: 10.1177/1078155219865303. Epub 2019 Aug 18.
9. @@@c Jorgenson MR, Parajuli S, Kleiboeker HL, Felix DC, Astor BC, Saddler CM, Smith JA, Mandelbrot DA.Clin Transplant. 2024 Jan;38(1):e15217. doi: 10.1111/ctr.15217. Epub 2023 Dec 11
10. Unexplained **fever** after pancreas **transplantation**.Klasek R, Kuten SA, Patel SJ, Graviss EA, Nguyen DT, Hobeika MJ, Gaber OA, Podder H, Knight RJ.Clin Transplant. 2018 Sep;32(9):e13351. doi: 10.1111/ctr.13351. Epub 2018 Aug 11.

另有一個特別的狀況是器官移植後發燒
1.Stem cell transplantation

- Antimicrobial de-escalation in adult hematopoietic cell transplantation recipients with febrile neutropenia of unknown origin.Petteys MM, Kachur E, Pillinger KE, He J, Copelan EA, Shahid Z.J Oncol Pharm Pract. 2020 Apr;26(3):632-640. doi: 10.1177/1078155219865303. Epub 2019 Aug 18.
- Comparison of two different anti-infectious approaches after high-dose chemotherapy and autologous stem cell transplantation for hematologic malignancies in a 12-year period in British Hospital, Uruguay.Oliver AC, Riva E, Mosquera R, Galeano S, Pierri S, Bello L, Caneiro A, Gai R, Miller A, Muxi P.Ann Hematol. 2020 Apr;99(4):877-884. doi: 10.1007/s00277-020-03947-1. Epub 2020 Feb 15
- 266例ASCT手術。2006-2013年期間納入的患者稱為第 1 組（環丙沙星預防和頭孢他啶-阿米卡星作為經驗性抗生素），2013-2017 年期間的患者稱為第 2 組（左氧氟沙星預防和美羅培南作為經驗性抗生素）
- 發熱性中性粒細胞減少症在第 1 組為 72%，在第 2 組為 86.2%（p = 0.004）。大多數感染發作與不明原因的發熱有關：第 1 組為 55%，第 2 組為 59%。不明原因的發熱發作在第 1 組中為 82.6%，在第 2 組中為 80%。
- （第 1 組的 Gram+ 為 66.6%，第 2 組為 69%（p = 0.68））。
- **不明原因的發熱是最常見的感染併發症，革蘭+bacilli.**
- 移植后 100 天內的死亡率較低，為 1.87%。
- ASCT是一種安全的手術，左氧氟沙星(levoflaxacin)與環丙沙星(ciprofloxacin)預防相比沒有明顯的益處。兩種抗感染方法都是可以接受的，產生相似的結果。

2. Kidney transplantation

SOT:shower over tub 在浴盆裡沖澡.

- **Incidence and outcomes of fever of unknown origin after kidney transplant in the modern era.** Margaret R Jorgenson[1] et al Clin Transplant 2024 Jan;38(1):e15217.
- (Department of Pharmacy, University of Wisconsin Hospital and Clinics, Madison, Wisconsin, USA.
- [2]Department of Medicine, University of Wisconsin-Madison School of Medicine and Public Health, University of Wisconsin Hospital and Clinics, Madison, Wisconsin, USA.

Patients transplanted from January 1, 1995 to December 31, 2005 were included in the "early era"; patients transplanted from January 1, 2006 to December 31, 2018 were included in the "modern era".

5590 kidney transplants at our center during the study window. FUO was identified in 323 patients with an overall incidence rate of .8/100 person-years. Considering only the first 3 years after transplant, the incidence of FUO was significantly lower in the modern era than in the early era, with an Incidence Rate Ratio (IRR) per 100 person-years of .48; 95%.

A total of 102 (31.9%) of 323 patients had an etiology determined within 90 days after FUO diagnosis: 100 were infectious, and two were malignancies. In the modern era, FUO remained significantly associated with rejection (HR = 44.1; 95% CI: 16.6-102; $p < .001$) but not graft failure (HR = 1.21; 95% CI: .68-2.18; $p = .52$) total graft loss (HR = 1.17; 95% CI: .85-1.62; $p = .34$), or death (HR = 1.17; 95% CI: .79-1.76; $p = .43$.

Conclusions: FUO is less common in KTRs during the modern era. Our study suggests infection remains the most common etiology. FUO remains associated with significant increases in risk of rejection, warranting further inquiry into the management of immunosuppressive medications in SOT recipients in the setting of FUO.

3. CNS-GVHD

- Highlights
- • Graft versus host disease of the central nervous system (CNS-GVHD) is a controversial entity, and its diagnosis is often hampered by the absence of a histological specimen.
- • The structural and functional imaging characteristics of CNS-GVHD are poorly described.
- • We present the first description of acute CNS-GVHD manifesting as cerebellitis, associated with marked cerebellar hypermetabolism on ^{18}F-fluorodeoxyglucose PET/CT (FDG-PET).
- • FDG-PET may have a role in investigating pyrexia of unknown origin following allogeneic stem cell transplant.

@@@ Jewell KE, Kuzich JA, Lee ST, et al. Acute graft-versus-host disease associated cerebellitis as the cause of pyrexia of unknown origin detected with ^{18}F-FDG-PET/CT. Cancer Treat Res Commun. 2021;27:100341. (Department of Molecular Imaging and Therapy, Austin Health, Heidelberg, Australia.)

FUO-→sarcoidosis

- A 46-year-old man with a classic case of fever of unknown origin (FUO), who visited the outpatient department of the division of Infectious Diseases and Tropical Medicine in December 2015. His main complaint was a sustaining fever up to 39.2 ˚C, which was not subsiding since three weeks despite two different antibiotics prescribed by the general practitioner. He reported distinctive symptoms with night sweats and incipient weight loss, as well as emerging dyspnoea. Routine blood tests showed no significant ab normalities, whereas a chest radiograph indicated **bihiliary lymphadenopathy**, leading to the differential diagnoses of tuberculosis, lymphoma, or possibly sarcoidosis. Therefore, a computed tomography was per formed, which on the one hand confirmed the finding of the enlarged lymph nodes, and on the other hand showed no sign of tuberculous cavity. Interferon gamma-release assay (IGRA) testing for tuberculosis was also negative. Furthermore, angiotensin-con verting enzyme determined in the serum was highly elevated, making the diagnosis of sarcoidosis much more likely than lymphoma. In parallel, fever disappeared immediately under treatment with naproxen, which was another indication for a nonmalignant cause of fever. Already on the third day after admission, mediastinoscopy and a consecutive lymph node biopsy were performed. Histologic examination confirmed the diagnosis of sarcoidosis.

依賴一連串的影像檢查以及內視鏡切片方才得到正確的診斷

有幾項轉折-臨床推理的原則下

- 1.標準的FOU,抗生素治療也無效
- 2.night sweat+ weight loss, as well as emerging dyspnoea →TB?-
- →Chest X-Ray
- 3.Chest x-ray: Bilateral hilar L-N adenopathy-→
- **TB, Lymphoma, sarcoidosis**
- 4. Chest CT---confirmed LN(++)+ NO TB cavity
- 5. **Interferon gamma-release assay** (IGRA) testing for
- tuberculosis was also negative.-→Excluded TB
- 6 Angiotensin-converting enzyme determined in the serum was
- highly elevated, making the diagnosis of sarcoidosis much more
- likely than lymphoma.
- 7. Fever disappeared immediately under treatment with naproxen,
- which was another indication for a nonmalignant cause of fever.
- 8. On the third day after admission, mediastinoscopy and a
- consecutive lymph node biopsy were performed. Histologic
- examination confirmed the diagnosis of sarcoidosis.

詳細問history方能縮小診斷的可能性

- 詳細問history-→得到重點
- FOU + night sweat+ weight loss, as well as emerging dyspnoea →TB?
- TB 是FOU最常見的原因
- TB 最普通的檢查/也最重要-→Chest X-ray-→hilar L-N enlargement-→得出3個最重要的診斷:
- **TB, Lymphoma, sarcoidosis**
- 然後再一一排除

思考診斷或排除診斷之特殊檢驗

- 1. **Interferon gamma-release assay** (IGRA) testing for
- tuberculosis一定要知道的檢驗

- The Interferon Gamma Release Assay (IGRA) is a blood test used to see whether a person has been infected with Mycobacterium tuberculosis (the bacteria causing TB). The IGRA test works by measuring the body ‘s immune response to the TB bacteria.相當specific and相當specific.
- Latent TB infection causes no symptoms and cannot be passed on to other people.
- There is a small risk that latent TB infection can progress to TB disease. The risk is increased in young children and old people, as well as people with weak immune systems.

IGRA tests 可以判斷出Latent and active TB.

- 2. Angiotensin converting enzyme Test、ACE

參考值 :<22.5 IU/L

血管收縮素轉換? (Angiotensin converting enzyme，ACE)其主要生理功能為將血管收縮素I催化為血管收縮素II，促進血管收縮，使血壓升高。正常情況下，ACE低量存在於周邊組織中，**當罹患肉芽腫性疾病時，ACE會從肉芽腫內的類上皮細胞(epithelioid cells)中大量釋放出來，使得血液中濃度增加**。目前認為類肉瘤的產生疑似因為免疫系統的失調 (可能是過度的免疫反應)有關

類肉瘤(sarcoidosis)是一種慢性、全身性之疾病，平均每10 萬人之中約有 40 人可能罹患。 它可發 生在所有年齡層，但以年輕成人最為常見。 全身所有器官皆可能受影響，但以肺臟最常受侵 犯。 臨床症狀包括可能有發燒、厭食、倦怠、體重減輕、咳嗽、呼吸困難、結節狀紅診、視 力模糊、淋巴結腫大及多發性關節炎等，其中以咳嗽最為常見。

3. NSAID for FOU/Naprosyn test (therapeutic trial)

❑ **Naprosyn test –**

- A common clinical problem is to differentiate infectious from malignant/neoplastic fevers of unknown origin.
- While the work-up is in progress, the Naprosyn test may be done early to differentiate infectious from malignant fever of unknown origin.
- During the 3-day Naprosyn test, if temperatures decrease markedly, then a malignant/ neoplastic disorder is likely (positive Naprosyn test).
- However, if fevers remain elevated/only slightly decrease, an infectious etiology is likely (negative Naprosyn test).

Fever disappeared immediately under treatment with naproxen, which was another indication for a nonmalignant cause of fever

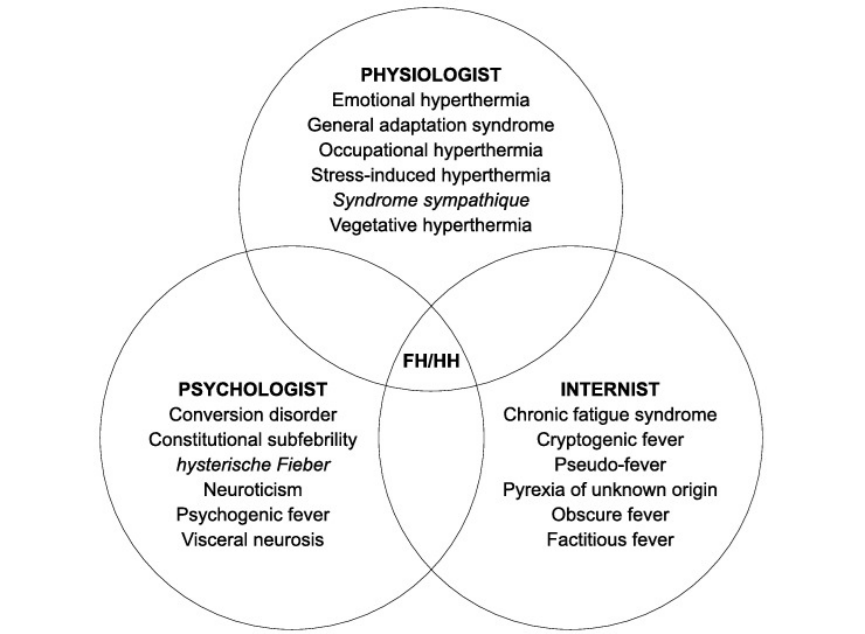
- Positive naproxen test in psychogenic fever. *Prim Care Companion CNS Disord*. 2021;23(3):20l02630. (L1223)
- Moideen S, Anver PC, Uvais NA, et al. (India)

一名 57 歲男性因發熱伴寒戰、寒戰和輕度頭痛約12 天，打嗝 3 天到急診科就診。他沒有其他重要病史。他是一名吸煙者，一級親屬有血液系統惡性腫瘤病史。體格檢查發現患者發熱（39.9°C/103.8°F）。其他體格檢查結果均正常。他被送進醫院，在住院期間，他持續發燒，在接受對乙醯氨基酚治療后沒有消退。考慮到血液系統惡性腫瘤的家族史，入院一周后，開始了芐普生 500 mg 的試驗，導致單次給葯后發熱完全溶解（芐普生試驗陽性）。患者仍無發熱，在給予芐普生后 3 天出院。廣泛的調查檢查顯示沒有PUO的潛在病因

在住院期間，他報告經歷了嚴重的情緒障礙，並被轉診進行精神病評估。精神病學評估顯示，他情緒低落、快感缺乏、絕望、哭泣、睡眠和食慾受損約一個月。這些癥狀對他的日常功能產生了重大影響。這些癥狀開始一個多星期後，他出現發燒伴寒戰和寒戰，芐普生緩解，但情緒癥狀持續存在。這些癥狀是在7周前兩名近親因傳染性腦病死亡後開始的。根據 *ICD-10* 標準，他被診斷為中度抑鬱發作，並在重大壓力性生活事件的背景下出現心因性發熱。在精神病學評估后，他被開了阿戈美拉汀每天 25 毫克作為抗抑鬱葯。在2周後的隨訪中，他的睡眠、食慾和情緒都有所改善。出院後沒有進一步發燒

Functional hyperthermia
Psychogenic fever

- **重點**：心理壓力源，核心體溫升高。[6]大多數心因性發熱患者使用精神藥物（如苯巴比妥）和抗抑鬱药（如選擇性 5-羥色胺再攝取抑製劑和三環類抗抑鬱药）后發熱消退，但使用標準退熱藥則不然.



FH/HH 處於醫學、心理學和生理學三大學科的十字路口

Mathieu Ginier-Gillet [1](France)
'Functional hyperthermia': a historical overview
Biopsychosoc Med. 2023 Nov 13;17(1):38.

Conclusion 'Habitual hyperthermia' is not an obsolete entity and forces the clinician to explore nonstandard possibilities. However, differential diagnoses, such as circadian temperature rhythm, iatrogenesis, malingering, and above all, incomplete history-taking, must not be neglected. Thus, in the absence of clear signs, tests should be performed with tact, and measurement and medical reassessment should be the primary focus to avoid misdiagnosis. Finally, yet importantly, Canguilhem's theories on nor mality should continue to be a guide for patient-centred care

G. Canguilhem(1904-1995)

- 10. Spicker SF: 喬治·坎吉勒姆（Georges Canguilhem）的醫學認識論簡介：超越蜜雪兒·福柯（Michel Foucault）。*J Med Philos*。1987;**12**：397-411。doi： 10.1093/jmp/12.4.397.

- 11. Debru C、Dupont JC、Fagot-Largeault A、Lambert J、Schmidgen H，編輯。喬治·坎吉萊姆（Georges Canguilhem）。OEuvres complètes tome II.Écrits de médecine et de philosophie ： Les thèses [喬治·坎吉萊姆論文集第二卷。醫學和哲學著作：博士論文]。巴黎：Librairie philosophique J. Vrin;2021. 法語

Vitamin ABCDEFG：病因及鑒別診斷

在教醫學生如何進行鑑別診斷，我常會說可以用 VITAMIN ABCDEFG 的暴力解開法，比較不會有所缺漏：

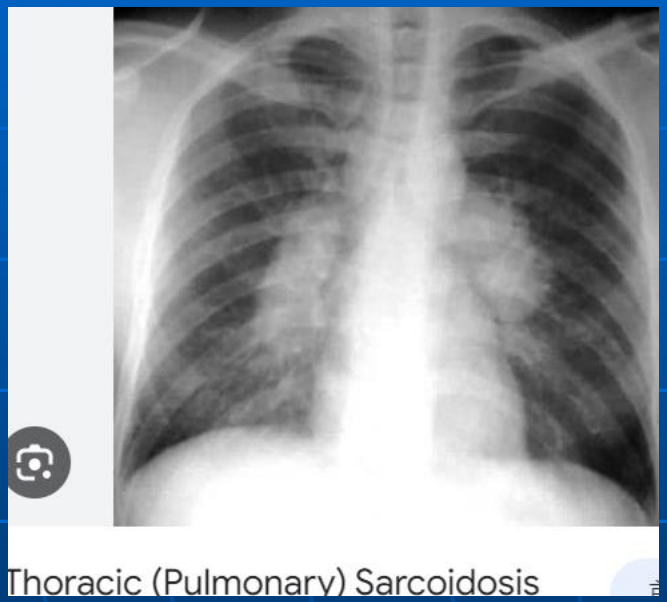
- “V” 代表 “vascular” 血管問題，包括動脈粥狀硬化與血栓。
- “I” 則是 “infective” or “post infective” 感染或感染後。
- “T” 為 “trauma” 創傷或任何物理性傷害與阻塞情況。
- “A” 是 “autoimmune”-related illnesses or “allergy” 自體免疫問題。
- “M” 為 “metabolic” 代謝問題，包括脂肪、蛋白、醣類與營養素。
- “I” 則是醫師們最不喜歡的 “idiopathic” 原發性或 “iatrogenic” 醫源性問題。
- “N” 為 “neoplasia” 腫瘤等惡性疾病。
- “A” 是 “alcohol & substance abuse” 酒精與物質濫用
- “B” 作為 “behavioral” 行為與精神問題。
- “C” 則在小兒科較為常見， “congenital” 先天性問題。
- “D” 是 “drug” 藥物副作用。
- “E” 則提醒我們 “environmental problems” 環境與 “occupational hazards” 職業災害。
- “F” 和生活型態有關 “Food” ，吃太多、太少、吃到不該吃的，沒吃該吃的。
- “G” 是老年科的 “Geriatrics” 等退化性問題。

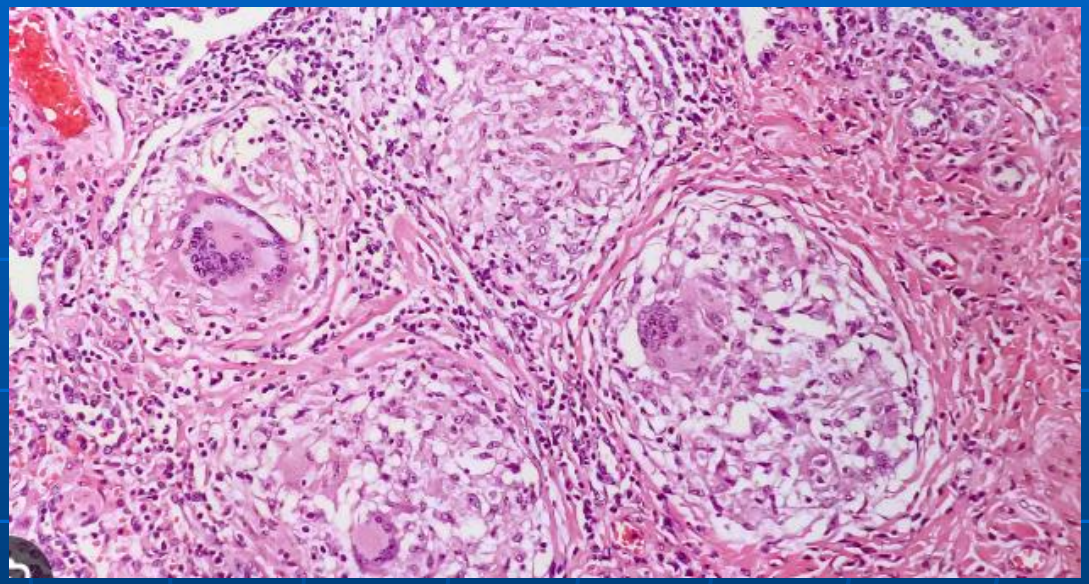
Diagnostic Value of Naproxen

- 77 patients presenting with FUO were treated with naproxen. Overall temperature decreased from 39.1°C to 37.4°C. The sensitivity of the naproxen test for neoplastive fever was 55% and the specificity was 62%.

Vanderschueren, et al. Am J Med 2003;115:572

4. Final diagnosis can be confirmed by histological examination





Sarcoidosis類肉瘤

Sarcoidosios 案例很少但臺灣也有報告

圖一：胸部 X 光顯示有左肺門腫瘤。

圖二：胸部電腦斷層掃描顯示除了左肺門腫瘤，還有多個縱隔腔淋巴結腫大的現象。

小算盤

- 一名患有糖尿病及高血壓的 58 歲女性，因持續一週不定時地嘔吐而求診，病人合併 有輕微流鼻水、吞嚥困難及胸悶，無發燒、咳嗽、頭痛或腹痛等症狀。病人曾至嘉義二林醫 院求診症狀並未改善。但在胸部 X 光片上發現有肺腫瘤，故轉介至本院作進一步檢查。病人 的血液學檢查、肝功能及腎功能檢查均為正常，僅有輕微血糖偏高。胃鏡檢查有輕度食道炎 及胃炎，腹部超音波僅顯示有輕微脂肪肝。但在胸部 X 光顯示有左肺門腫瘤(圖一)，胸部電 腦斷層掃描更進一步顯示除了左肺門腫瘤外，還有多個縱隔腔淋巴結腫大的現象(圖二)。經 內視鏡超音波引導作細針抽吸切片，發現有多紡綞狀的類上皮細胞，疑似類肉瘤。經照會胸 腔外科以胸腔鏡取出腫瘤後，證實病人罹患類肉瘤。病人於開刀後症狀完全改善

張廷仰.張維興 :綜合醫院消化系中心
臨床論壇 Vol 4, No 2. Apr, 2003

在現代醫學中，FUO仍然是最具挑戰性的診斷之一。

- 全面的病史和體格檢查有助於診斷和直接診斷性檢查。推薦的病情檢查包括全血細胞計數（CBC）和分類計數、三組血培養（從不同部位進行，間隔數小時，如果有指徵，在開始抗生素治療之前）、胸片、完整的代謝檢查（如果肝功能檢查異常，則包括肝炎血清學檢查）、尿液顯微鏡檢查和尿培養、紅細胞沉降率（ESR）、C 反應蛋白（CRP）、抗核抗體（ANA）、類風濕因數（RA）、巨細胞病毒 IgM 抗體或血液病毒檢測、嗜異性抗體檢測、結核菌素皮膚試驗、HIV 檢測和腹部計算機斷層掃描（CT）掃描。
- **超過 200 種惡性/腫瘤性、感染性、風濕性/炎症性和其他疾病可引起 FUO**。[4] 醫務人員通常會在 FUO 病情檢查的早期安排非基於線索的影像學檢查和特異性檢查，這可能會產生誤導，而且肯定不經濟. 儘管病情檢查和診斷取得了廣泛進展，**但仍有高達 51% 的 FUO 病例未被診斷**。 在現代醫學中，FUO仍然是最具挑戰性的診斷之一。

處理FOU的步驟

- 1.可能的原因超過200種,
- 2.好好問病史知道病人問題的特性 Problems
- 3.特別是要了解發燒的模式fever patterns
- 4.從病史上約略區分為 A.感染疾病 B感染性疾病 C.惡性
- 腫瘤或血液疾病 D.HIV或免疫力降低之疾病.
- 5.然後從身體之檢查確認疾病之徵象Physical signs,進行
- 一般抽血檢驗.選擇不同之影像檢查-→盡可能將診斷縮小為
- 三項以內
- 6. 再考慮做特殊檢查檢驗來區分可能之疾病並正確找出發燒
- 的原因
- 7.病因涉及各個領域常見和少見的疾病. 因此必須組成多領
- 域專家的團隊.從臨床推理的觀點上逐步趨向正確的診斷
- 8.累積臨床經驗增加疾病之認識方能及早找到發燒的原因.

- 四大類別原因之中有一些比較多見的,一定優先思考可能性,要熟悉診斷/排除診斷之主要檢查方法.步步逼近真正的原因.
- 詢問病史注意身體之各項特殊徵象(皮膚疹子rashes) –可以指出特殊的病因
- 免疫功能低下和 HIV 患者可能需要完全不同的方法來診斷和治療復發性發熱。

發燒的常見原因

- **經典型 FUO**：每類 FUO 的發生率因時間和地點而異，但心內膜炎、複雜性尿路感染、膿腫和結核病（TB）在經典 FUO 患者中屢見不鮮。在65歲以上的患者中，結締組織病被確定為更頻繁的發熱原因。[7] 旅行者的發燒更可能繼發於瘧疾、傷寒和急性 HIV 等感染。[8]
- **院內病人 FUO**：醫療保健相關發熱可能是由於藥物發熱、術后併發症、靜脈血栓栓塞性疾病、惡性腫瘤、輸血相關反應或*艱難梭菌*感染所致。[7] 外科手術、器械、血管內裝置、制動和藥物等危險因素有助於確定獲得診斷所需的診斷性檢查。
- **中性粒細胞減少性 FUO**：發熱在該亞類中很常見，通常是由於**感染**引起的。
- **HIV 相關 FUO**：發熱可出現在急性疾病期間，但在未經治療的感染中也很常見，這意味著**機會性病原體的額外感染。**

❖ *Nosocomial FUO*

- *A temperature of ≥38.3°C* (≥101°F) develops 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 investigation, including at least 2 days' incubation of cultures, is the minimum requirement for this diagnosis.**

❖ *Neutropenic FUO*

- *Defined as a temperature of* ≥38.3°C (≥101°F) on several occasions in a patient whose **neutrophil count is <500/µL or is expected to fall to that level in 1–2 days.**
- The diagnosis of neutropenic FUO is invoked if a specific cause is not identified **after 3 days of investigation, including at least 2 days' incubation of cultures.**

❖ *HIV-associated FUO*

- *Defined by a temperature* of ≥38.3°C (≥101°F) on several occasions **over a period of >4 weeks for outpatients or >3 days for hospitalized patients with HIV infection.**
- This diagnosis is invoked if appropriate investigation over 3 days, including 2 days' incubation of cultures, reveals no source.

Nosocomial FUO

- The primary considerations in diagnosing nosocomial FUO are the underlying susceptibility of the patient coupled with the potential complications of hospitalization.
- The original surgical or procedural field is the place to begin a directed physical and laboratory examination for abscesses, hematomas, or infected foreign bodies.
- More than 50% of patients with nosocomial FUO are infected.
- Intravascular lines, septic phlebitis, and prostheses are all suspect.
- In this setting, the best approach is to focus on sites where occult infections may be sequestered, such as the sinuses of intubated patients or a prostatic abscess in a man with a urinary catheter.
- *Clostridium difficile colitis may be associated with fever* and leukocytosis before the onset of diarrhea.

Nosocomial FUO

- In ~25% of patients with nosocomial FUO, the fever has a **noninfectious cause**. Among these causes are
- **acalculous cholecystitis,**
- **deep-vein thrombophlebitis, and**
- **pulmonary embolism.**
- **Drug fever,**
- **transfusion reactions,**
- **alcohol/drug withdrawal,**
- **adrenal insufficiency,**
- **thyroiditis,**
- **pancreatitis,**
- **gout, and**
- **pseudogout** are among the many possible causes to consider.

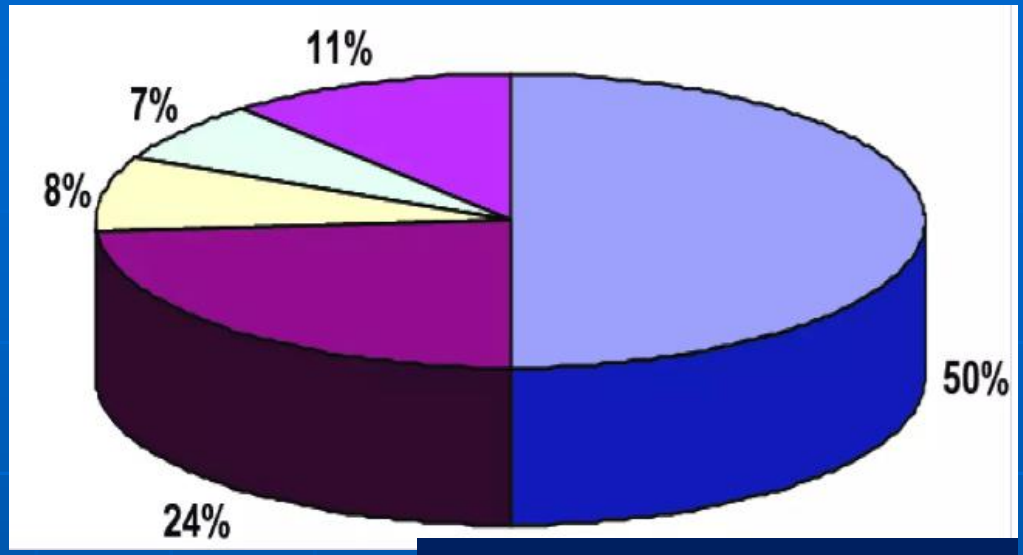
Neutropenic FUO

- Neutropenic patients are susceptible to focal bacterial and fungal infections, to bacteremic infections, to infections involving catheters (including septic thrombophlebitis), and to perianal infections.
- ***Candida* and *Aspergillus*** *infections are common.*
- *Infections due to* herpes simplex virus or CMV are sometimes causes of FUO in this group.
- Although the duration of illness may be short in these patients, the consequences of untreated infection may be catastrophic;
- 50–60% of febrile neutropenic patients are infected, and 20% are bacteremic.

HIV-Associated FUO

- HIV infection alone may be a cause of fever. Infection due to
  - ***Mycobacterium avium or***
  - ***Mycobacterium intracellulare,***
  - **tuberculosis,**
  - **toxoplasmosis,**
  - **CMV infection,**
  - ***Pneumocystis* infection,**
  - **salmonellosis,**
  - **cryptococcosis,**
  - **histoplasmosis,**
  - **non-Hodgkin's lymphoma, and (of particular importance)**
  - **drug fever** are all possible causes of FUO.

1960-1980



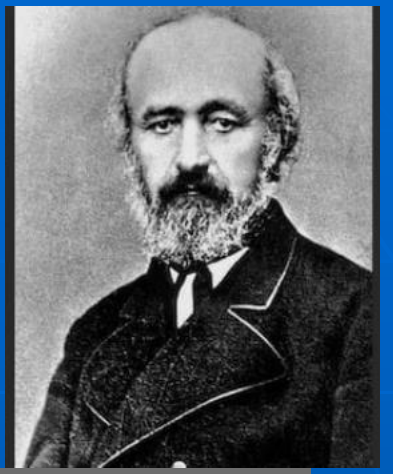
Infection—----------50 %
Connective tissue disorders
--24 %
Others----------8 %]
Neoplastic ----------7 %
Unidentified,----------11 %

- **Etiology**
- • Infections (25 to 50%)
- • Connective tissue disorders (10 to 20%) • Neoplasms (5 to 35%)
- • Miscellaneous (15 to 25%)

Mechanism of fever

- Fever: resetting of the thermostatic set-point in the anterior hypothalamus and the resultant initiation of heat-conserving mechanisms until the internal temperature reaches the new level. Hyperthermia: an elevation in body temperature that occurs in the absence of resetting of the hypothalamic thermoregulatory center.
- 發燒：重置下視丘前部的恆溫設定點，並由此啟動保溫機制，直到內部溫度達到新水準。體溫過高：在下視丘溫度調節中樞未重置的情況下發生的體溫升高

Wunderlich's Maxim
正常的體溫



- After analyzing >1 million axillary temperatures from ~25,000 patients, Wunderlich identified 37.0° C ( ) as the mean temperature in healthy adults. Temperature readings >38.0° C were deemed as "suspicious/probably febrile."

1Wunderlich C. Das Verhalten der Eiaenwarme in Krankenheiten.Leipzig, Germany: Otto Wigard;1868.

Carl Reinhold August Wunderlich (1815 – 1877) was a German physician, pioneer, and clinical academic, who is generally regarded as the father of clinical thermometry.

2Mackowiak, et al., JAMA 1992;268:1578

Normal Body Temperature

- For healthy individuals 18 to 40 years of age, the mean oral temperature is 36.8° ± 0.4°C (98.2° ± 0.7°F). Low levels occur at 6 A.M. and higher levels at 4 to 6 P.M. **The maximum normal oral temperature is 37.2°C (98.9°F) at 6 A.M. and 37.7°C (99.9°F) at 4 P.M.** These values define the 99th percentile for healthy individuals.

R: Mackowiak, et al., JAMA 1992;268:1578

Normal Body Temperature Caveats

- Rectal temperatures are generally 0.4°C (0.7°F) higher than oral readings. Tympanic membrane (TM) values are 0.8°C (1.6°F) lower than rectal temperatures when thermometer is in the unadjusted-mode.
  身體不同部位的溫度也不相同

Mechanisms of Hyperthermia and Associated Conditions:

- 1. Excessive heat production: exertional hyperthermia,
- thyrotoxicosis, pheochromocytoma, cocaine, delerium
- tremens, malignant hyperthermia
- 2. Disorders of heat dissipation: heat stroke, autonomic
- dysfunction
- 3. Disorders of hypothalamic function: neuroleptic malignant
- syndrome(nms), CVA, trauma For DTs, GABA (inhibitory
- neurotransmitter) receptors are down regulated and its
- neuronal activity decreased in alcohol withdrawal. In addition,
- norepinephrine is increased do to decreased alpha-2 inhibition
- of its release. Both contribute to hyperarousal. NMS is believed to
- result from central nervous system dopamine receptor blockade.
- Hyperthermia results from increased myocyte metabolic activity
- and altered hypothalamic thermoregulation.

Historical Causes of FUO
古代的想法

- Hippocrates: excess of yellow bile
- Middle Ages: demonic possession (encephalitis?)
- 18th Century: Friction associated with the flow of blood through the vascular system and from fermentation and putrefaction occurring in the blood and intestines

Fever 現代的想法

- **高熱和相關病症的機制**
  1.產熱過多：勞力性高熱、甲狀腺毒症、嗜鉻細胞瘤、古柯鹼、震顫性震顫、惡性高熱
- 2.散熱障礙：中暑、植物神經功能失調3. 下視丘功能障礙：抗精神病藥物惡性症候群、CVA、創傷對於 DT，GABA（抑制性神經傳導物質）受體在酒精戒斷過程中下調，其神經元活性降低。
- 此外，去甲腎上腺素增加會減少α-2對其釋放的抑制。兩者都會導致過度興奮。NMS 被認為是中樞神經系統多巴胺受體阻斷所致。體溫過高是由於心肌細胞代謝活動增加和下視丘溫度調節改變所引起的。

Objectives:

- Describe the workup of a patient with a fever of unknown origin.
- Outline the causes for fever of unknown origin.
- Summarize the treatment of patients with fever of unknown origin.
- Review the importance of improving care coordination among interprofessional team members to improve outcomes for patients affected by fever of unknown origin.

Over 200 malignant/neoplastic, infectious, rheumatic/inflammatory, and miscellaneous disorders can cause FUO.[4] Providers often order non-clue-based imaging and specific testing early in the FUO workup, which may be misleading and is certainly not economical.[4] Despite extensive workup and diagnostic advances, up to 51% of FUO cases remain undiagnosed.[5][6] In modern medicine, FUO remains one of the most challenging diagnoses.

It is important to note that immunocompromised and HIV patients may require an entirely different approach in diagnosing and treatment of recurrent fevers.

Infections associated with FUO

Bacterial Infections

Localized pyogenic infections			Intravascular infections	
Appendicitis	Perinephric/intrarenal abscess		Bacterial aortitis	
Cat-scratch disease	Prostatic abscess		Bacterial endocarditis	
Cholangitis	Subphrenic abscess		Vascular catheter infection	
Cholecystitis	Tuboovarian abscess		Bartonellosis	
Diverticulitis	Suppurative thrombophlebitis		Brucellosis	
Liver abscess			Gonococcemia	
Mesenteric lymphadenitis			Legionnaires' disease	
Osteomyelitis			Leptospirosis	
Pancreatic abscess			Listeriosis	
Pelvic inflammatory disease			Lyme disease	

Intravascular infections	Q fever
Melioidosis	Rickettsialpox
Meningococcemia	Rocky Mountain spotted fever
Rat-bite fever	**Mycoplasmal infections**
Relapsing fever	**Chlamydial infections**
Salmonellosis	Lymphogranuloma venereum
Syphilis	Psittacosis
Tularemia	**Mycobacterial infections**

Yersinia infection	*M. avium/M. intracellulare*
Rickettsial infections	Tuberculosis
Anaplasmosis	
Ehrlichiosis	
Murine typhus	

學會FUO的診斷內科學大概學會了70%. 常見疾病必須熟悉

- **Infections** :
- The most common cause of FUO. In patients with HIV infection,
- a. opportunistic infections : eg, TB
- b. Infection by atypical mycobacteria
- c. disseminated fungi
- d. cytomegalovirus

- Infections were the leading cause for classical FUO in most published studies, accounting for approximately one third of all cases: abscesses, endocarditis, tuberculosis, and complicated urinary tract infections dominate the group of infection-related FUO, regardless of the age of the patient.

Infectious Causes of FUO

- @@Tuberculosis (TB)
- Q fever
- @@Brucellosis
- HIV infection
- Abdominopelvic abscesses
- @@Cat scratch disease (CSD)
- Epstein-Barr virus (EBV) infection
- @@Cytomegalovirus (CMV) infection
- **@@Enteric (typhoid) fever**
- Toxoplasmosis
- Extrapulmonary TB
- Organ-based infectious causes of FUO
- @@ Subacute bacterial endocarditis (SBE)
- Chronic sinusitis/mastoiditis
- Chronic prostatitis
- @@Leptospirosis

- @@常見原因必須熟悉
- Nosocomial FUO: Healthcare-associated fevers can be due to drug fever, complications post-operatively, venous thromboembolic disease, malignancy, transfusion-related reactions, or *Clostridium difficile* infection.
- Risk factors such as surgical procedures, instrumentation, intravascular devices, immobilization, and medications can help determine the diagnostic testing necessary to obtain a diagnosis.

Noninfectious Inflammatory Causes of FUO

- Giant cell (temporal) arteritis
- Adult Still disease (juvenile rheumatoid arthritis)
- Systemic lupus erythematosus (SLE)
- Periarteritis nodosa/microscopic polyangiitis (PAN/MPA)
- **Rheumatoid arthritis (RA)**
- **Antiphospholipid syndrome (APS)**
- **Gout**
- Pseudogout
- Behçet disease
- Sarcoidosis
- Felty syndrome
- Takayasu arteritis
- Kikuchi disease
- Periodic fever adenitis pharyngitis aphthous ulcer (PFAPA) syndrome

Collagen Vascular Diseases
Adult Still's disease, SLE,
Giant cell arteritis/polymyalgia rheumatica, ankylosing spondylitis
Wegener's granulomatosis
Rheumatic fever
Polymyositis,
rheumatoid arthritis
Felty's syndrome,
eosinophilic fasciitis
Felty's syndrome (FS) is an uncommon but severe subset of seropositive rheumatoid arthritis (RA) complicated by granulocytopenia and splenomegaly (90%).

- **Connective tissue disorders** :
- SLE ,
- RA ,
- giant cell arteritis vasculitis juvenile
- RA of adults (adult Still disease)

NIID: Non-infectious inflammatory diseases

- In the group of NIID, mostly rare diseases are represented, such as Still's disease and systemic lupus erythematosus as the most frequent causes seen in younger patients, and temporal arteritis and polymyalgia rheumatica in the elderly. In this older age group, NIID, even though rare them selves, are even more frequent causes of FUO than infections

@@Malignant and Neoplastic Causes of FUO

- Lymphoma
- Renal cell carcinoma
- Myeloproliferative disorder
- Acute myelogenous leukemia
- Multiple myeloma
- Breast/liver/pancreatic/colon cancer
- Atrial myxoma
- Metastases to brain/liver
- Malignant histiocytosis

Neoplastic fever.

- **The most common neoplastic causes the incidence of neoplastic** causes has been decreasing, probably because they are being detected by ultrasonography and CT, which are now widely used during initial evaluation L

- **lymphoma:約占這一群1/3**
- **leukemia**
- **renal cell carcinoma**
- **hepatocellular carcinoma**
- **metastatic carcinomas**

Miscellaneous Causes of FUO

- @@Cirrhosis (due to portal endotoxins)
- @@Drug fever
- @@Thyroiditis
- @@Crohn disease
- @@Pulmonary emboli
- Hypothalamic syndrome
- Familial periodic fever syndromes
- Cyclic neutropenia
- @@Factitious fever

Miscellaneouscauses

drug reactions

deep venous thrombosis

recurrent pulmonary emboli

sarcoidosis

inflammatory bowel disease

factitious fever

No cause of FUO is identified in about 10% of adults.

Prognosis of FUO

- In terms of prognosis, overall, 12–35% of patients were reported to die from diseases underlying classical FUO [7, 14]. Mortality depends on the nature of the underlying disease, and prognosis is worse if diagnostic delay occurs [4]. Especially patients with **undiagnosed FUO (unresolved cause) have overall a good prognosis, usually with resolution of their fever in four or more weeks; the 5-year mortality rate lies around 3.2 %, and** between 51 and 100% of these patients are reported to have spontaneous recovery

2023年21個國家的綜合報告(1916-2021)死亡率是6.3%

Erdem, H., Baymakova, M., Alkan, S. *et al.* Classical fever of unknown origin in 21 countries with different economic development: an international ID-IRI study. *Eur J Clin Microbiol Infect Dis* **42**, 387–398 (2023). (L1361)

Drug fever

- Episodes in Dallas (n=51)

  Drug Fever : No characteristic fever pattern was observed.
- Maximum temperatures ranged from 38°C to 43°C
- The mean lag time between initiation of a drug and the onset of fever was 21
- days, but lag times varied considerably.
- **Alpha methyldopa and quinidine** were the two drugs most
- commonly implicated, but antimicrobials (as a group) were responsible for the
- largest number of episodes.
- Episodes in Dallas (n=51)
- Episodes in Lit. (n=97) ------Total Episodes (n=148)
- **an infrequent association with either rash or eosinophilia; and**
- **no apparent association of drug fever with systemic lupus**
- **erythematosus, atopy, female sex, or advanced age.**

- Mackowiak and LeMaistre Ann Intern Med 1987;106:728

FUO的原因也有改變:
非感染性疾病多於感症

- 1990 年至 1999 年間對 290 名受試者進行的 FUO 前瞻性回顧發現，非感染性發炎性疾病佔 35.2%，感染佔 29.7%，其他原因佔 19.8%，惡性腫瘤佔 15.1%。大多數在 3 次就診或 3 住院天內確診。
- 這與先前的估計不同，先前的估計主要是感染，其次是惡性腫瘤、膠原血管疾病和許多其他疾病。
- 隨著越來越多地使用免疫調節劑來治療越來越多的疾病，感染可能重新成為 FUO 的主要原因。有趣的是，本報告中不明原因的比例高於先前的估計，33.8% 的患者在 7 天後仍未被診斷。較短的時間範圍可能會高估未確診病例的數量。過去的評估可能沒有那麼快，而且即使是現在，較新的檢測也可能需要運送到專業實驗室，診斷可能仍需要 7 天以上的時間。[15]

Steven Vanderschueren, MD, PhD; Daniël Knockaert, MD, PhD; Tom Adriaenssens, et al : **From Prolonged Febrile Illness to Fever of Unknown Origin**The Challenge Continues
Arch Intern Med. 2003;163(9):1033-1041.

- **Some Causes of FUO**
- Abscesses (abdominal, pelvic, dental) • Suggestive Findings Abdominal or pelvic discomfort, usually tenderness
- Sometimes history of surgery, trauma, diverticulosis, peritonitis, or gynecologic procedure •
- Diagnostic Approach CT or MRI

- **Cause** Cat-scratch disease •
- Suggestive Findings
- History of being scratched or licked by a cat
- Regional adenopathy,
- Parinaudoculoglandular syndrome,
- headache •
- **Diagnostic Approach**
- Culture (sometimes of lymph node aspirate), antibody titers,
- PCR test.

貓抓病臺灣也有報告，
愛貓愛狗者可要小心

- 貓抓病 （CSD） 由漢塞巴爾通體引起，是一種人畜共患病，以自限性淋巴結腫大為特徵。它通常通過貓或小貓的抓撓或咬傷傳播。
- Cat scratch disease (CSD), first described by Debre et al in 1950, is usually characterized by self-limited regional lymphadenopathy, cutaneous papule, or pustule at the site of inoculation, low grade fever, malaise, headache, and sore throat.2,3 This disease is caused by Bartonella henselae or possibly by other Bartonella species, which is transmitted to humans through a scratch or bite by a kitten that was infested from cat flea. Domestic cats serve as a major persistent
- reser voir for B. henselae. Dogs or puppies are rarely the reservoir of B. henselae.

Tun-Chieh Chen [1], Wei-Ru Lin, Po-Liang Lu, Chun-Yu Lin, Yen-Hsu Chen

- [1]Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital,
- Kaohsiung Medical University, Kaohsiung, Taiwan. **Cat scratch disease from a domestic dog** J Formos Med Assoc. 2007 Feb;106(2 Suppl):S65-68.

- **Cause** CMV infection •
- Suggestive Findings
- History of blood transfusion from CMV-positive donor Syndrome that resembles mononucleosis (fatigue, mild hepatitis, splenomegaly, adenopathy), chorioretinitis) •
- Diagnostic Approach:
- CMV IgM antibody titers
- Possibly PCR testing

Cause EBV infection •

Suggestive Findings Sore throat, adenopathy, right upper quadrant tenderness, splenomegaly, fatigue Usually occurring in adolescents and young adults

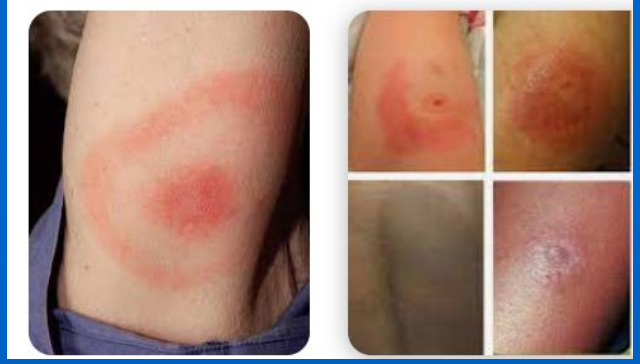
In older patients, typical findings possibly absent • Diagnostic Approach : Serologic testing

- **Cause** HIV infection •
- Suggestive Findings : History of high-risk behaviors (eg, unprotected sex, sharing needles)
- Weight loss, night sweats, fatigue, adenopathy, opportunistic infections •
- Diagnostic Approach: Testing for HIV antibodies (ie, ELISA, Western blot)
- Sometimes testing for HIV RNA (for acute HIV infection)

SBE

- **Cause** Infective endocarditis •
- Suggestive Findings Often history of risk factors (eg, structural heart disease, prosthetic heart valve, periodonta disease, IV catheter, injection drug use)
- Usually a heart murmur, sometimes extracardiac manifestations (eg, splinter hemorrhages, petechiae, Roth spots, Oslernodes, Janeway lesions, joint pain or effusion, splenomegaly)
- **Diagnostic Approach** : Serial blood cultures,
- echocardiography

Tick bite



- **Cause** Lyme disease •
- Suggestive Findings Visiting or living in an endemic area
- Erythemamigrans rash, headache, fatigue, Bell palsy, meningitis, radiculopathy, heart block, joint pain and swelling
- • Diagnostic Approach Serologic testing
- 萊姆病是由伯氏疏螺旋體（Borrelia burgdorferi）細菌引起的，很少由馬約氏疏螺旋體（Borrelia mayonii）引起。它透過受感染的黑腿蜱蟲叮咬傳播給人類。典型症狀包括發燒、頭痛、疲勞和稱為遊走性紅斑的特徵性皮疹。
- **ENDEMICITY**
- North America, in the Northeast, mid-Atlantic, and upper Midwest of the United States
- Northern Asia (temperate forest regions)
- Europe

Osteomyelitis •

- **Cause** Osteomyelitis •
- Suggestive Findings Localized pain, swelling, erythema • Diagnostic Approach X-rays Sometimes MRI (most accurate test), radionuclide scanning with indium-111, bone scanning

@@@ TB

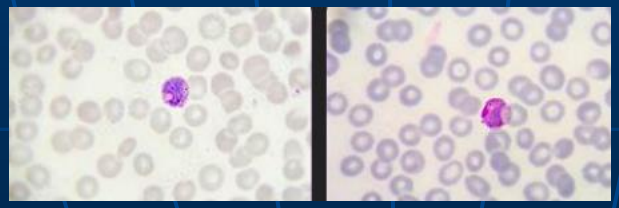
- **Cause** TB (pulmonary and disseminated) • Suggestive Findings :
- History of high-risk exposure ,
- Cough, weight loss, fatigue ,Use of immunosuppressants
- History of HIV infection •
- Diagnostic Approach Chest-x-ray, PPD,
- interferon-gamma release assay(IGRA)
- Sputum smear for acid-fast bacilli,
- nucleicacid amplification testing (NAAT),
- culture of body fluids (eg, gastric aspirates, sputum, CSF)

Sinusitis

- **Cause** Sinusitis • Suggestive Findings Prolonged congestion, headache, facial pain • Diagnostic Approach Prolonged congestion, headache, facial pain

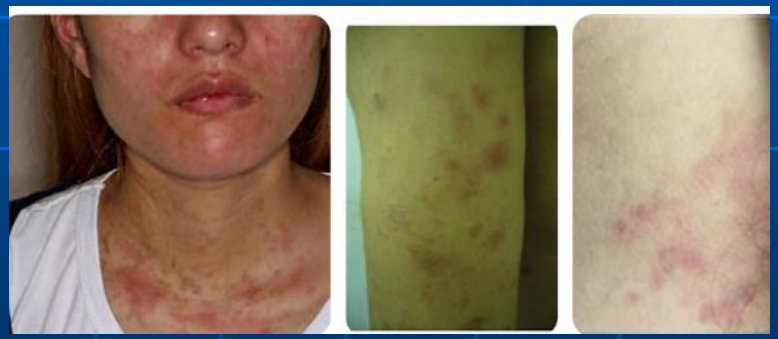
Uncommon infections

- **Cause** Uncommon infections (eg, brucellosis, **malaria,** Q fever, toxoplasmosis, trichinosis, **typhoid fever)** •
- Suggestive Findings.
- History of travel to endemic areas
- Exposure to or ingestion of certain animal products • Diagnostic Approach :
- Serologic testing for individual causes
- **Peripheral blood smear for malaria**



Connective tissue • Cause (Collagen diseases)

- **Connective tissue** •
- **Cause Adult Still disease :** **Adult-onset Still disease (AOSD) is a rare autoinflammatory condition. The presence of an evanescent, salmon-pink, nonpruritic rash is one of the major diagnostic criteria for the disease. The rash occurs with fever and subsides with defervescence.**
- Suggestive Findings
- Evanescent salmon-pink rash,
- arthralgias, arthritis,
- myalgias, cervical adenopathy,
- sore throat, cough, chest pain •
- Diagnostic Approach ANA, RF, serum ferritin concentration, x-rays of affected joints



Diagnostic Approach to Classic Fever of Unknown Origin

- **First**, verify the prolonged fever meets the fever-of unknown- origin definition.
  - The fever-of-unknown origin work-up should be **symptom (history) and sign (physical examination) driven.**

- **Second**, based on history and physical clues, **try to determine the appropriate category for the fever**.
  - Each fever of unknown origin category has clinical hallmarks, for example, usually, malignant/neoplastic disorders are associated with early anorexia and significant weight loss.
  - With infectious fevers of unknown origin, chills are common, but weight loss less pronounced and anorexia late. Excluding vasculitis, synovitis is the rheumatic/ inflammatory hallmark.

- **Third**, within the fever-of-unknown-origin category, **try to determine the pattern of organ involvement.**
  - Each disorder has a characteristic pattern of organ involvement that suggests/limits diagnostic possibilities.

Diagnostic Approach to Classic Fever of Unknown Origin

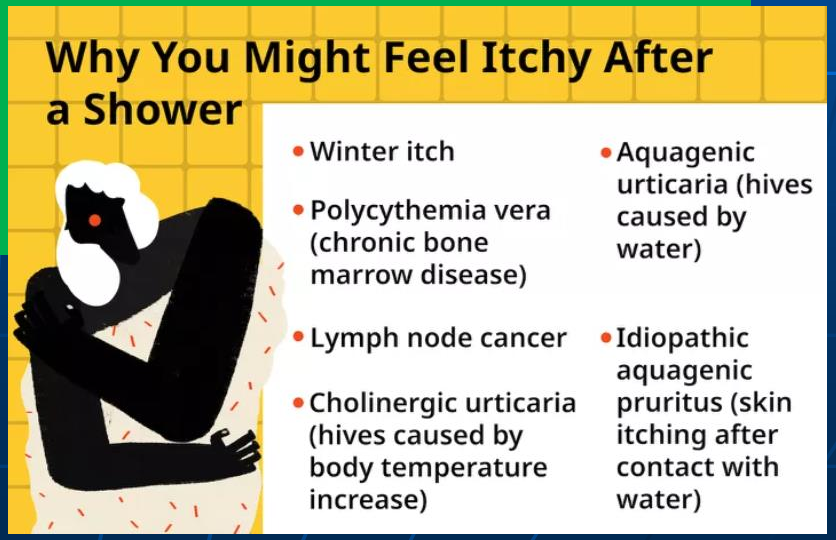
- For example, pattern of organ involvement of **systemic lupus erythematosus** involves multiple organs but **importantly, spares the liver.**
- Similarly, while **splenomegaly** is a cardinal subacute bacterial endocarditis finding,
- **hepatomegaly** essentially **rules out subacute bacterial endocarditis** on the basis of pattern of organ involvement alone.
- The most diagnostically difficult fevers of unknown origin have no localizing signs.
- In the fever of unknown origin focused physical examination, special attention should be given to the eyes, skin, nodes, liver, and spleen.
- Testing should be selective and based on diagnostic probabilities, not possibilities, for example, routine blood cultures.

不可能所有的檢驗都做,
好好的問history及Physical examination
才能及早發現診斷的線索

- It is obviously impossible to perform all tests on all patients. There is also common agreement that a detailed patient history and physical examination is crucial in patients
- presenting with an unclear febrile illness.

仔細詢問病史
I.可能是惡性疾病

- 1.注意有無體重減輕之現象(只一個星期減
- 少1公斤以上)同時詢問有無胃口變差
- (anorexia)
- 2. 熱水浴以後出現皮癢症狀pruritus 可能是惡性疾病引起的FUO
- 3.注意有無淋巴腺腫脹



6 Reasons Why You Might Itch After Taking a Shower By Daniel More, MD Updated on November 04, 2022.
Verywell Health https://www.verywellhealth.com/reasons-why-you-itch-after-taking-a-shower-83217
(accessed on 2024.02.16)

History-1

❑ Malignant/Neoplastic Disorders-

- Significant weight loss (>2 lbs/week), particularly if accompanied by
- early anorexia, is a hallmark of malignant/neoplastic fevers of unknown origin.
- Post-hot bath pruritus suggests a malignant/neoplastic disorder. A malignant/neoplastic fever of unknown origin should be considered in those with
- a history of adenopathy or malignancy.

❑ Infectious Diseases.

- The history should include
- prior/ invasive procedures or surgeries (abscesses),
- dentition (apical abscesses, subacute bacterial endocarditis),
- antecedent/ concomitant infections, and tuberculosis.

仔細詢問病史
II.可能是感染

- 1.之前的手術病史如果侵襲性之處置---
- abscess
- 2.之前只牙科疾病,有無牙周病等-→可能造
- 成endocarditis SBE
- 3.最近發生的感染症
- 4有無肺結核

仔細詢問病史
III.可能與小動物接觸或蚊蟲叮咬

❑ **Animal or pet contact suggests**

- Q fever,
- brucellosis,
- toxoplasmosis,
- cat scratch disease, or
- trichinosis.

❑ **Mosquito or tick exposure suggests**

- ehrlichiosis/anaplasmosis,
- babesiosis, or
- malaria,

❑ **Rodent exposure suggests**

- rat bite fever,
- relapsing fever, or
- leptospirosis.

仔細詢問病史
Iv 輸血史 :CMV & HIV

- **Blood transfusions** may be an important clue to
  - **ehrlichiosis/anaplasmosis,**
  - **babesiosis,**
  - **cytomegalovirus, or**
  - **human immunodeficiency virus. In normal hosts, the only clue to cytomegalovirus may be secretion exposure.**

艾利希氏體症（Ehrlichiosis）是蜱蟲媒介的人畜共通傳染疾病，台灣過去有關艾利希氏體症的研究較多著重在動物，但近年來人類感染病例逐漸浮現，患者常出現不明原因發燒，白血球及血小板低下，肝功能異常等症狀

潛伏的人畜共通傳染病：艾利希氏體症

陳冠宇(Kuan-Yu Chen) ； 詹明錦(Ming-Chin Chan) ； 張峰義(Feng-Yi Chang)

《感染控制雜誌》 29卷6期 (2019 / 12) Pp. 301-306

Babesiosis is caused by microscopic parasites that infect red blood cells and are spread by certain ticks. 巴貝斯蟲症

Anaplasmosis 無形體

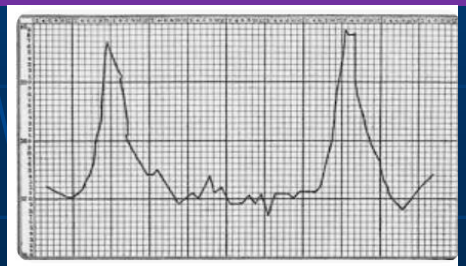
- 根據患者的癥狀，全面瞭解病史，重點關注最可能的病因，是確定 FUO 起源的關鍵。
- 不應忽視有關既往疾病、局部癥狀、酒精攝入量、家庭用藥、職業暴露、寵物、旅行和家庭性疾病的資訊。
- 患者報告的一系列癥狀應有助於醫務人員縮小發熱病因類別的病因範圍，因為每種癥狀都有臨床特徵。例如，如果患者出現 B 癥狀、早飽和體重明顯減輕，醫務人員應進行惡性腫瘤檢查。另一方面，
- 如果患者出現**寒戰，應考慮感染性病因**，
- 而關節受累是風濕性疾病的標誌。[4]

仔細詢問:發熱模式

- 重要的是，應在臨床環境中驗證發熱，並分析發熱模式。發熱模式分析可以為特定的感染罪魁禍首提供額外的線索。

- **1.長期瘧疾中的**Tertian or quartan fever（每三天或第四天發生一次）
- **2. 布魯氏菌病的起伏性發熱** (Undulant fever, 傍晚發熱和出汗，早晨消退）
- **3. Tick-borne relapsing fever in borrelios**is回歸熱（持續一周的發熱，持續一周的緩解）:萊姆病,伯氏疏螺旋體
- **4. 霍奇金病中的 Pel-Ebstein 熱**（持續一周的高熱，持續一周緩解）
- **5. 週期性中性粒細胞減少症的週期性發熱** (Periodic fevers)
- **6. 成人斯蒂爾病、瘧疾和傷寒的雙重日常熱** Double quotidian fever （每天兩次發熱）

A double quotidian fever is one that is characterized by 2 fever spikes per day



History- 3

❑ **Immunosuppressive drugs** predispose to particular pathogens, for example,

- cytomegalovirus,
- **tuberculosis.**
- **Disparate multiple symptoms/signs suggest multisystem disease, for example, miliary tuberculosis or Whipple's disease**, rather than several different disorders.

❑ **Rheumatic/Inflammatory Disorders-**

- With prominent arthralgias/ myalgias, a rheumatic/ inflammatory fever of unknown origin is likely,
- but **chills argue against a rheumatic/inflammatory etiology.**

History -4

- .病史- 風濕性/發炎性疾病-
- 乾咳也可能是鉅細胞動脈炎/顳動脈炎的微妙線索。不明原因發燒，
- **口腔潰瘍**提示Bechet 症候群或系統性紅斑狼瘡。
- Ø 不明原因發燒的器官受累模式，伴隨關節症狀和全身淋巴結病史，提示**成人斯蒂爾病或系統性紅斑狼瘡**。
- Ø 不明原因發燒伴隨非**結石性膽囊炎病史是系統性紅斑狼瘡或結節性動脈周圍炎的一個容易被忽略的線索。**
- Ø 若考慮Bechet氏症，家族史很重要

病史-雜項疾病-5

- Ø如果病史沒有提示特定類別，則應考慮不明原因發燒的其
- 他原因。
- Ø 週期性發燒可能是週期性嗜中性白血球減少症的唯一線索Ø 淋巴結腫大病史可能提示羅薩伊-多夫曼病或菊池氏症。
- Ø 頸部/下顎疼痛很容易被誤認為是牙痛，但可能是亞急性
- 甲狀腺炎的線索。
- Ø 醫護人員應考慮人為發燒。具體來說，請詢問是否有發炎
- 性腸道疾病（區域性腸炎）、酗酒（肝硬化）和藥物（假
- 性淋巴瘤、藥物熱）。
- ❖ 一些不明原因的雜項**發燒是家族性的**，例如 Ø 家族性地
- 中海熱或 Ø 高 IgD 症候群

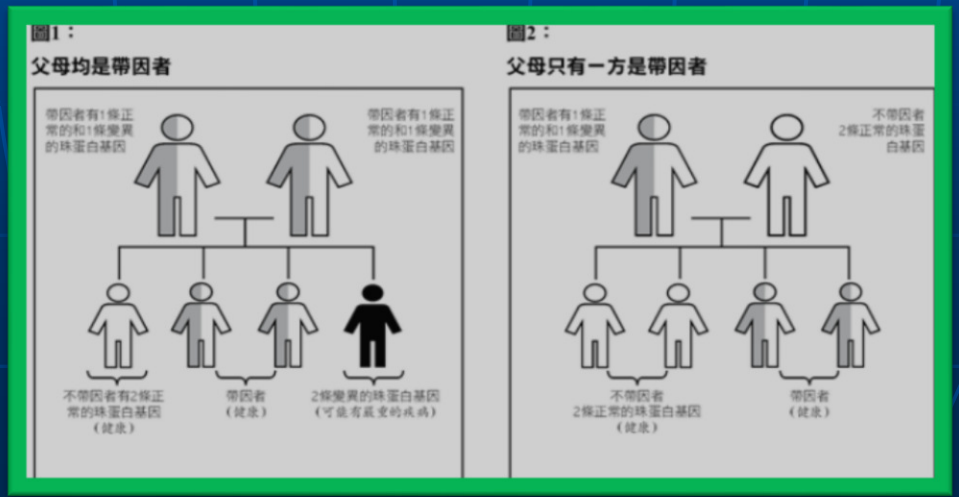
Ø 家族性地中海熱:隱性遺傳

家族性地中海熱（Familial Mediterranean fever，FMF）是一種遺傳性疾病，特徵是週期性高熱，伴有腹部、胸部疼痛和關節腫痛。該病通常見於地中海和中東，尤其是猶太人（特別是西班牙系猶太人）、土耳其人、阿拉伯人和亞美尼亞人.

家族性地中海熱常見嗎？

家族性地中海熱在高危人群中的患病率是1-3/1000，而在世界其它地方則較為罕見。然而，在發現相關致病基因後，即使在那些被認為家族性地中海熱罕見的人群中，如義大利人、希臘人和美國人，該病的診斷也多了起來。大約90%的FMF病人在20歲之前發病，其中一半的病人在10歲內發病。男孩的患病率比女孩稍高（13：10）

相關基因由地中海熱（Mediterranean fever）而得名被稱作MEFV基因,
該蛋白能夠抑制發炎反應。如果該基因發生突變，就不能調節，病人則表現為發熱



高 IgD 症候群
（Hyper IgD Syndrome：HIDS)

高IgD綜合症是一種少見的遺傳性疾病，表現為生后1年內反覆發作的寒戰、發熱，通常持續4~6天。 發作由疫苗接種或輕微外傷等軀體應激因素誘發，沒有確定的治療。 診斷以臨床為主，但包括血清IgD水準和可能的基因檢測。 可以用阿那白滯素(anakinra)或康納單抗(conakinuimab)進行預防。 可以使用NSAID藥、皮質類固醇和阿那白滯素治療癥狀。

高免疫球蛋白血症D型和週期性發熱綜合征（chronic fever syndrome， HIDS）是一種自身炎症性疾病，其特徵是反覆發作發熱、頸部淋巴結腫大、肝腫大、脾腫大、腹痛、皮疹、關節痛和其他炎症癥狀[1]，並伴有C反應蛋白（CRP）和血清澱粉樣蛋白A（SAA）等炎症標誌物增加。發熱發作可由兒童期疫苗接種或輕微感染引發，但大多數發作的誘因尚不清楚。HIDS這個名字來源於這樣一個事實，即在第一個病例系列中，在所有患有這種綜合征的患者中發現血清免疫球蛋白D（IgD）水準升高。現在已知了遺傳背景，目前更準確的疾病名稱是甲羥戊酸激酶缺乏症 （MKD）(mevalonate kinase gene deficiency)。

C M Mulders-Manders[1], A Simon

:Hyper-IgD syndrome/mevalonate kinase deficiency: what is new?

Semin Immunopathol. 2015 Jul;37(4):371-6. Epub 2015 May 20

Hyper-IgD syndrome

- *Hyper-IgD syndrome is a rare autosomal recessive disorder in which recurring attacks of chills and fever begin during the first year of life. Episodes usually last 4 to 6 days and may be triggered by physiologic stress, such as vaccination or minor trauma.*
- Hyper-IgD syndrome clusters in children of Dutch, French, and other Northern European ancestry and is caused by mutations in the gene coding mevalonate kinase, an enzyme important for cholesterol synthesis. Reduction in the synthesis of anti-inflammatory isoprenylated proteins may account for the clinical syndrome.

Keywords: higds, mevalonate kinase, IL1, inborn error of metebolism, recurrent fever

PE-1, Malignancy

Physical Examination

❑ **Malignant/Neoplastic Disorders.**

- **Hectic fevers** of lymphoma may resemble infection.
- **Relative bradycardia** may accompany lymphoma or central nervous system malignancy.

❖ **Eye examination** may be helpful, for example,

- **Roth spots (lymphoma, atrial myxoma),**
- **cytoid bodies (atrial myxoma), or**
- **retinal hemorrhages (preleukemia).**

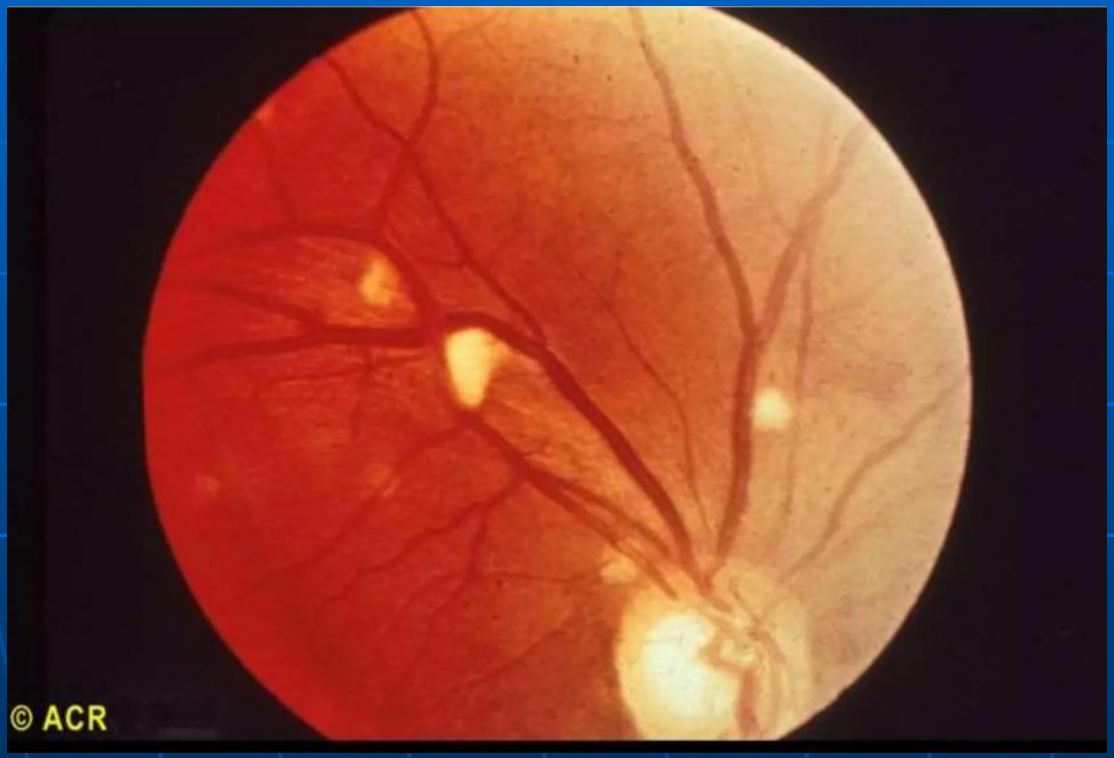
❖ **A murmur** is a key finding in

- **subacute bacterial endocarditis,**
- **noninfectious culture-negative endocarditis, for example,**
- **marantic endocarditis or**
- **atrial myxoma.**

Litten’s sign--=hemorrhage

A Roth spot is a hemorrhage, which is blood from ruptured blood vessels. It affects your retina — the part of your eye that senses light and sends signals to your brain that allow you to see. Roth spots are also called Litten's signs.

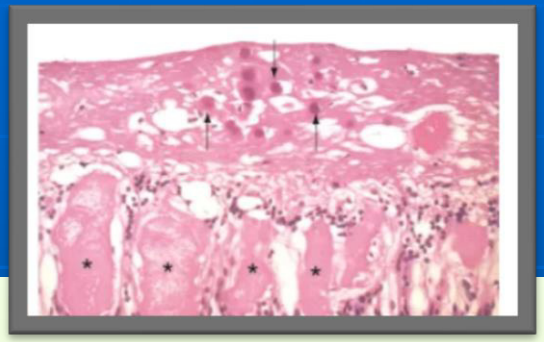
Eyeground :cytoid bodies



Systemic lupus erythematosus:
cytoid bodies

External eyes/fundus

細胞體



- **cytoid bodies**
  - **systemic lupus erythematosus,**
  - **giant cell arteritis/temporal arteritis,**
  - **periarteritis nodosa,**
  - **adult Still's disease),**

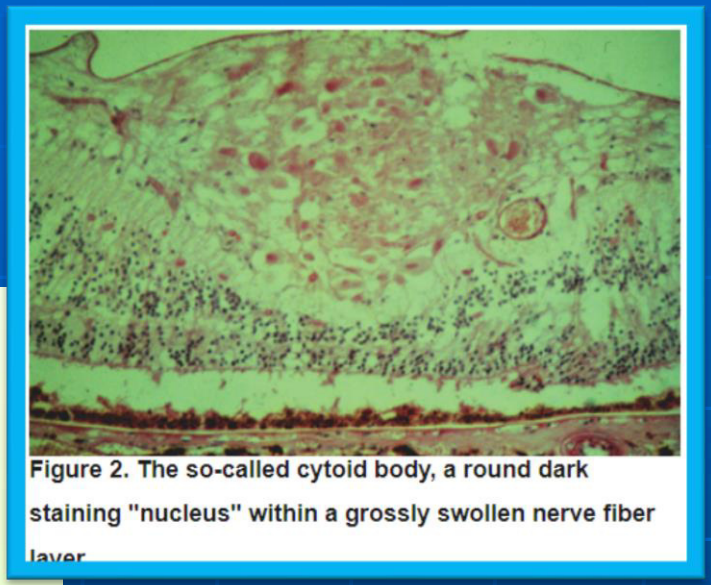


Figure 2. The so-called cytoid body, a round dark staining "nucleus" within a grossly swollen nerve fiber layer

Cytoid bodies (arrows) within the NFL. Cystoid spaces (asterisks) are filled with proteinaceous fluid (H&E stain).

Soon after the revolutionary invention of the direct ophthalmoscope by Hermann von Helmholtz in 1851, ophthalmologists began identifying small, whitish/grey, cloud-like, linear or serpentine, slightly elevated lesions with fimbriated edges that appeared to float within the substance of the inner retina. These lesions were initially given the misnomer "soft exudates" to differentiate them from the correctly termed "hard exudates" (deeper, yellowish, well-defined, crystalline granules commonly associated with retinal exudative and inflammatory processes). The name was later changed to the more descriptive term, "cotton-wool spots" *(See Figure 1).*

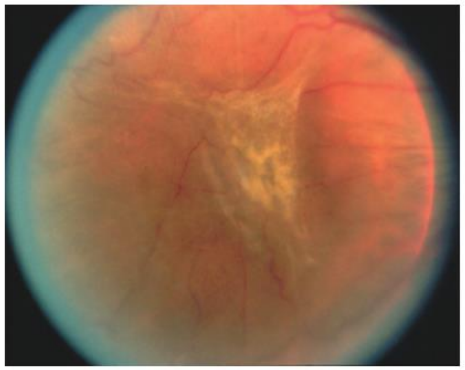


Figure 3. Retinal cotton-wool spots.

Mechanical Distortion

In contrast to a vascular occlusion of the precapillary arterial flow, mechanical distortion or traumatic laceration of the nerve fiber layer can also result in the interruption of axoplasmic flow and the development of a cotton-wool spot. Severe retinal distortion due to epiretinal membrane contraction (classically seen after cryoretinopexy or scleral-buckle placement) can result in retinal cotton-wool spots *(See Figure 3)*. These cotton-wool spots will disappear within one week (as opposed to the eight to 10 weeks for cotton-wool spots caused by diabetes or hypertension) after successful epiretinal membrane peeling.[2]

Diabetes mellitus and systemic hypertension are by far the most common cause of cotton-wool spots. In patients who have a cotton-wool spot and no known history of diabetes, an elevated blood sugar level is identified in 20 percent of patients and an elevated blood pressure (diastolic blood pressure of 90 mmHg or greater) in 50 percent of patients.[1] Patients with diabetes mellitus might also harbor other typical retinal findings such as macular edema, retinal exudate, flame or dot/blot hemorrhages, microaneurysms, venous beading or microvascular abnormalities or proliferations. Conversely, patients with systemic hypertension would be expected to demonstrate generalized arteriolar narrowing, arteriolar/venous nicking and, in extreme cases, optic-disk swelling.

In addition to systemic hypertension and diabetes mellitus, cotton-wool spots may be found in numerous other diseases. These

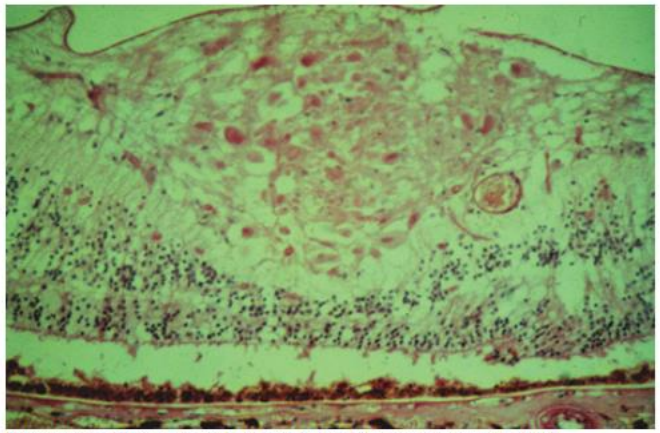


Figure 2. The so-called cytoid body, a round dark staining "nucleus" within a grossly swollen nerve fiber layer.

Ischemic,embolic, infectious, toxic, radiation induced, neoplastic, tractional, traumatic, immune-mediated and idiopathic

PE-1. malignancy

Physical Examination

❖ **Sternal tenderness**

- points to a bone marrow disorder (preleukemia, myeloproliferative disorders).

❖ **Isolated hepatomegaly**

- **hepatoma,**
- **renal cell carcinoma, or**
- **liver metastases.**

PE-2, Infectious diseases

❑ **Infectious Diseases.**

- The approach to infectious fevers of unknown origin begins with fever pattern analysis.

❖ **Morning temperature spikes** suggest

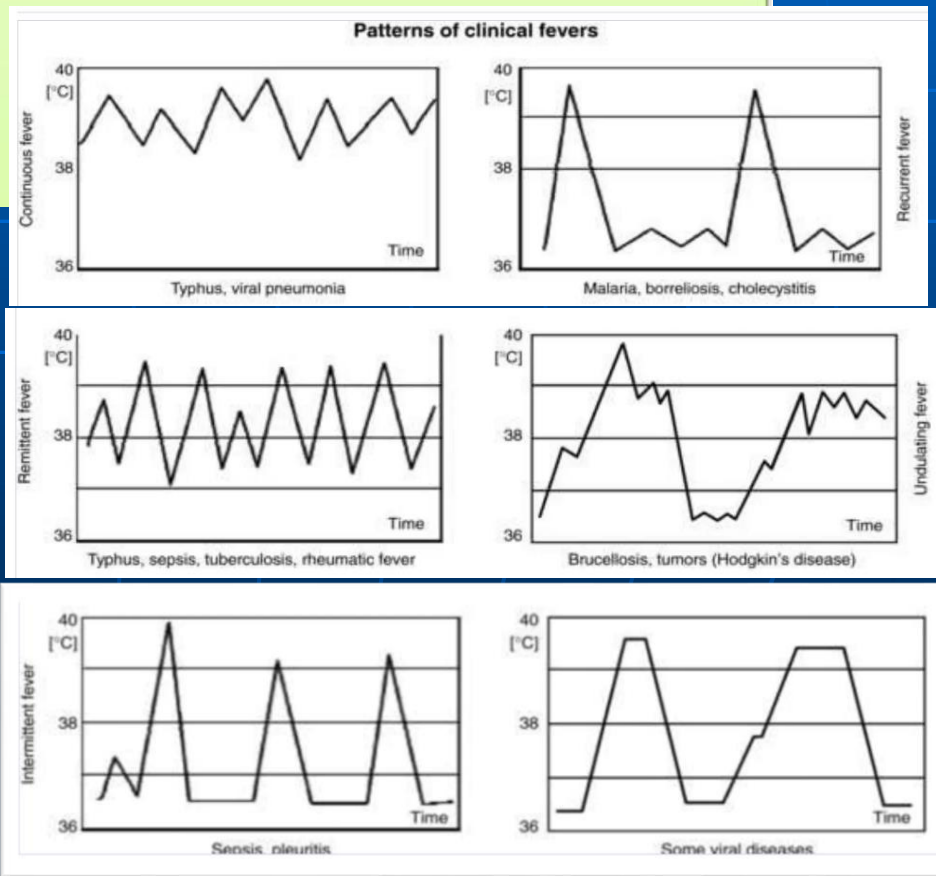
- **miliary tuberculosis,**
- **typhoid/enteric fever, or**
- **Whipple's disease.**

❖ **Relative bradycardia**

- **typhoid/enteric fever,**
- **malaria,**
- **babesiosis,**
- **ehrlichiosis/anaplasmosis,**
- **leptospirosis, and**
- **Q fever.**

PE-2, Infectious diseases

- ❖ **Twice daily fever spikes (double quotidian fevers)**
- ➢ **malaria,**
- ➢ **miliary tuberculosis, or**
- ➢ **visceral leishmaniasis.**
- ❖ **Two fever peaks per week (camel back fever curve)**
- ➢ **ehrlichiosis/ anaplasmosis,**
- ➢ **leptospirosis,**
- ➢ **brucellosis, or**
- ➢ **rat bite fever.**



Fever patterns

Camel back fever curve
Dengue fever.

Dengue fever: diagnostic importance of a camelback fever pattern
Kostas Sideridis DO [a], Daniel Canario MD [b], Burke A Cunha MD [c] Heart & Lung Volume 32, Issue 6, November–December 2003, Pages 414-418 (L1267)

Physical Examination

❖ **Fundoscopic findings** may be a clue to

- **toxoplasmosis,**
- **tuberculosis,**
- **histoplasmosis, or**
- **cat scratch disease. Spinal tenderness points to subacute vertebral osteomyelitis, typhoid/enteric fever, spinal tuberculosis, or brucellosis.**

❖ **Hepatomegaly alone** suggests

- **Q fever,**
- **typhoid/enteric fever,**
- **visceral leishmaniasis,**
- **brucellosis,**
- **rat bite fever, or**
- **relapsing fever.**

❖ **Epididymo-orchitis/epididymal nodule** is an easily overlooked sign of

- **Epstein-Barr virus,**
- **renal tuberculosis, or**
- **brucellosis.**

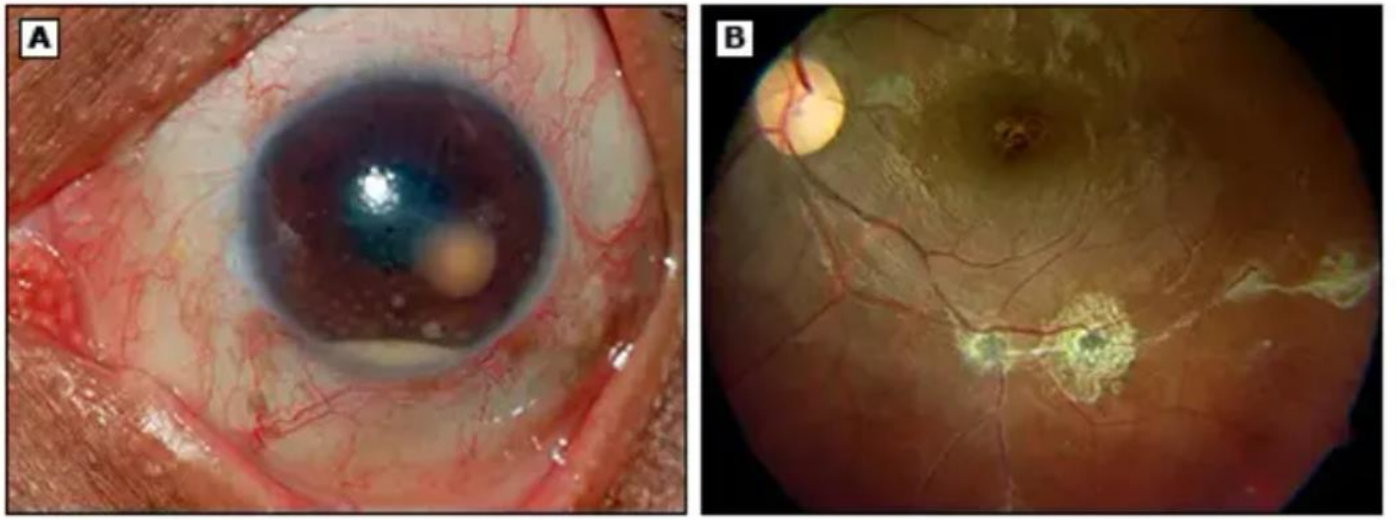


Figure2. Anterior chamber granuloma due to ocular TB. (Panel A) Anterior chamber granuloma with granulomatous keratic precipitates and **hypopyon**. Aspiration of the granuloma demonstrated acid fast bacilli in Ziehl-Neelsen stain. (Panel B) Following antituberculous treatment, the posterior segment demonstrates healed pigmented scars along the vasculature. (©2014 UpToDate®)

OCT 2014

Ocular Tuberculosis (TB) - Asia Pacific

Amer. Acad. Ophthamology.

https://www.aao.org › topic-detail › ocu...accessed on 2024.02.16

Splenomegaly

❖ **Splenomegaly** narrows diagnostic possibilities to

- **miliary tuberculosis,**
- **Epstein-Barr virus,**
- **cytomegalovirus,**
- **typhoid/enteric fever,**
- **brucellosis,**
- **histoplasmosis,**
- **ehrlichiosis/anaplasmosis,**
- **malaria,**
- **Q fever,**
- **subacute bacterial endocarditis,**
- **cat scratch disease, and**
- **rat bite fever.**

Physical examination reveals splenomegaly in 75% of patients. Nearly all exhibit a maculopapular skin rash (rose colored spots). Relative bradycardia in the presence of high fever is characteristic of the disease. Laboratory examination usually shows anemia and leukopenia

Typhoid Fever Robert S. Francis
• Robert N. Berk
Published Online: Sep 1 1974
https://doi.org/10.1148/112.3.583
Radiology, 1974, Vol: 112.

❑ Rheumatic/Inflammatory Disorders.

- **Morning temperature spikes** are an important clue to **periarteritis nodosa**
- **double quotidian fever** is a key finding in **adult Still disease.**

❖ In a fever of unknown origin, **rash**, if present, suggests

- ➢ **sarcoidosis,**
- ➢ **systemic lupus erythematosus, or**
- ➢ **adult Still's disease.**

- **Unequal pulse suggests Takayasu's arteritis.**

❖ **Lacrimal gland enlargement** is a clue to

- ➢ **late-onset rheumatoid arthritis,**
- ➢ **sarcoidosis, or**
- ➢ **systemic lupus erythematosus.**

Lacrimal gland enlargement in SLE

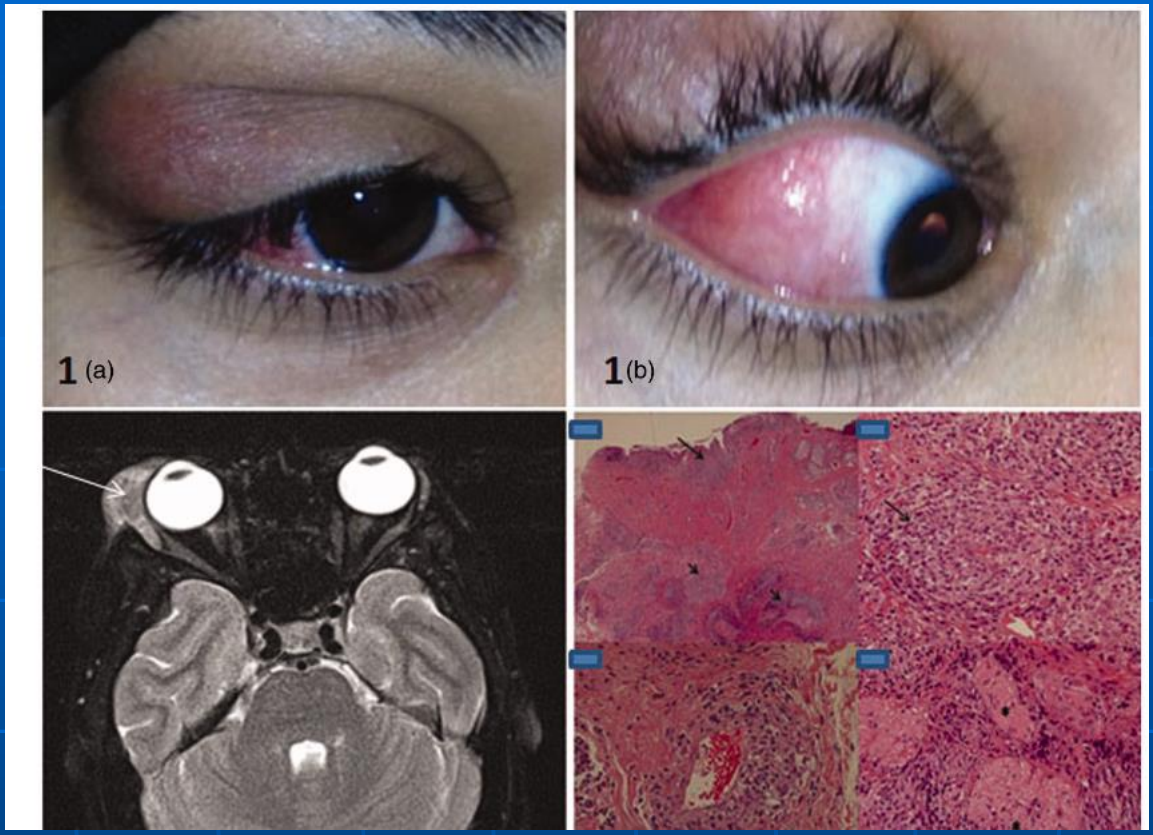
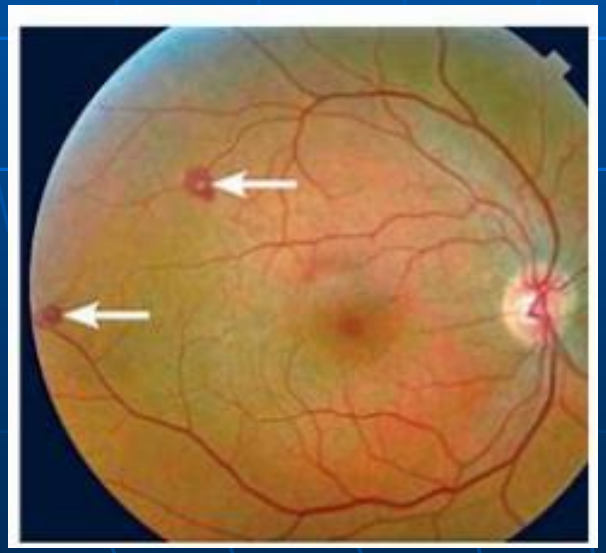


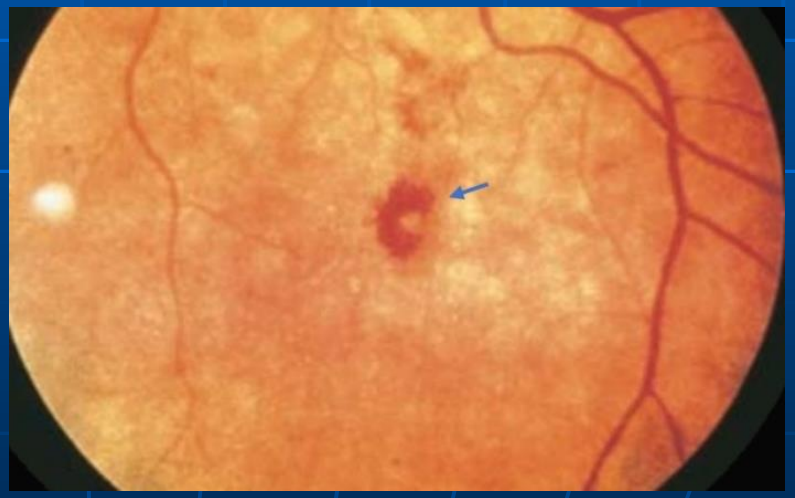
Figure 1(a): right upper lid swelling localized to lacrimal gland fossa. The swelling was painless. 1(b): salmon patch appearance of conjunctiva. 1(c): MRI image showing soft tissue mass originating from right lacrimal gland, extending around the lateral rectus muscle into extraconal space. 1(d): Histopathology (H&E stain). Low magnification: conjunctival infiltration with dense subepithelial inflammatory cell infiltrate (long arrow) and dense inflammatory aggregates in stroma (short arrows). High magnification revealing non-necrotizing granulomas composed of lymphocytes and histiocytes, surrounding blood vessels and nerves (asterisks).

Al-Busaidi T, Wali U, Al-Shirawi A, Al-Mujaini A. Dacryoadenitis as first presenting feature in systemic lupus erythematosus. *Lupus*. 2013;22(13):1431-1432. doi:10.1177/0961203313498804

External eyes/fundus

- **Roth spots**
  - **systemic lupus erythematosus,**
  - **periarteritis nodosa), or**
  - **retinal artery occlusion (Takayasu's arteritis, giant call arteritis/temporal arteritis, systemic lupus erythematosus).**



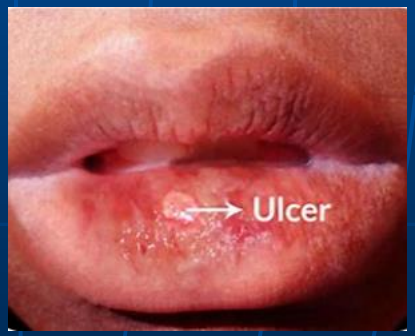


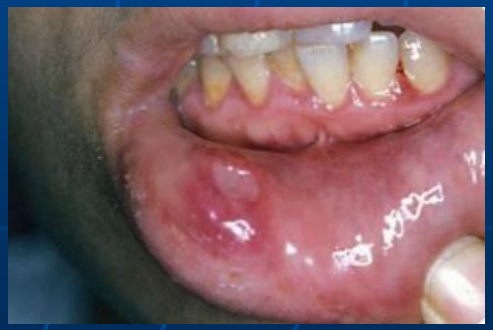
- Roth Spots are defined as a **white centered retinal hemorrhage and are associated with multiple systemic illnesses, most commonly bacterial endocarditis.** Originally described by Moritz Roth in 1872 while at the University of Basel, Roth spots were first seen in individuals with bacteremia secondary to subacute bacterial endocarditis.[1][2] The retinal findings Roth made in 1872 were described as round, oval or flame-shaped hemorrhages with a central white spot. Although originally described by Roth, Roth spots earned their name only later by the (biologist) Litten in 1878. Litten made more detailed observations of these entities and claimed they appeared in approximately 80% of cases of subacute bacterial endocarditis, thus cementing the hallmark association.[3][2] However they can be seen in a wide variety of conditions, and more recent research has found that only 2% of patients with endocarditis had Roth spots present on their retina.[4] Though Roth spots are usually thought of as pathognomonic for bacterial endocarditis, they can occur in a number of conditions (**Table 1**).

❖ **Oral ulcers suggest**

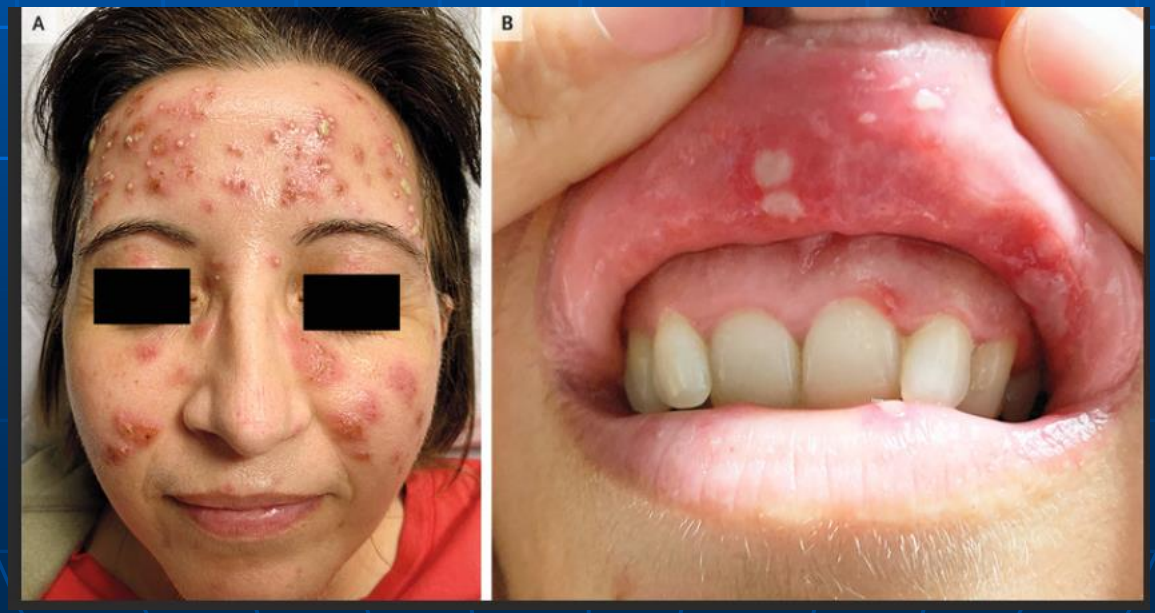
- **Behçet's disease or**
- **systemic lupus erythematosus.**

Painful mouth sores that look similar to canker sores are the most common sign of Behcet's disease. They begin as raised, round lesions in the mouth that quickly turn into painful ulcers. The sores usually heal in one to three weeks, though they do recur.





- Papulopustular Rash in Behçet’ s Disease
- Andrea Finazzi, M.D., and Roberto Cosentini, M.D.
- N Engl J Med 2023; 388:e30 (March 9,2023)



❖ **Lymphadenopathy suggests**

- **systemic lupus erythematosus,**
- **late-onset rheumatoid arthritis, or**
- **sarcoidosis.**

❑ In a fever of unknown origin with systemic lupus erythematosus, a murmur with negative blood cultures suggests possible

- Libman-Sacks endocarditis.

❑ **Hepatomegaly without splenomegaly argues against a rheumatic/inflammatory fever of unknown origin etiology.**

❖ **Epididymitis/epididymal nodules** are subtle clues to

- **periarteritis nodosa,**
- **systemic lupus erythematosus, or**
- **sarcoidosis**

[Epididymitis: Unusual presentation of periarteritis nodosa].
Coulomb MA , et al **Progres en Urologie** 05 Sep 2009, 20(4):311-313

Epididymotesticular manifestations are a very rare mode of revelation of periarteritis nodosa. We report a case of a patient where the diagnosis of periarteritis nodosa was made on the histological analysis of a part of epididymectomy. Through this observation, we will discuss the diagnostic difficulties of periarteritis nodosa.

突尼西亞裔50歲男子，因下肢結節性病變檢查住院，最初提示結節性紅斑。
這些病變在一般狀況惡化的情況下出現了兩個月，伴有振蕩性發熱、虛弱和盜汗。該患者除主動吸煙外無明顯病史。
臨床檢查顯示下肢疼痛性結節性皮膚病變，以及頸部淋巴結腫大。皮膚和全身性結核很快被排除。感染和免疫學檢測呈陰性（抗核抗體、ANCA、乙型肝炎、丙型肝炎、HIV血清學）。
住院48小時后，**右附睾硬化腫脹不是很痛。對側睾丸正常。**
陰囊超聲證實附睾尾部存在異質性腫塊，與鞘膜積液層有關。睾丸實質其他方面正常。睾丸腫瘤標誌物正常。在即興組織學分析后，決定採用附睾切除術.診斷出 PAN。

Minimal Initial Diagnostic Workup For FUO

- Comprehensive history/Physical examination
- CBC + differential
- Blood film reviewed by hematopathologist
- Routine blood chemistry: UA and microscopy
- Blood (x 3) and urine cultures
- Antinuclear antibodies, rheumatoid factor
- HIV antibody
- CMV IgM antibodies; heterophile antibody test (if c/w mono-like syndrome)
- Q-fever serology (if risk factors)
- Chest radiography
- Hepatitis serology (if abnormal LFTs)

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

Rapid ESR

Nonspecific Laboratory Tests

- In each fever of unknown origin category, nonspecific tests often provide useful diagnostic clues.
- Elevated erythrocyte sedimentation rate, serum ferritin, alkaline phosphatase, and rheumatoid factor titers are particularly useful in fever of unknown origin diagnosis.
- Diagnostic specificity of nonspecific laboratory abnormalities is increased when considered together.
- A highly elevated erythrocyte sedimentation rate (>100 mm/h) narrows diagnostic possibilities to very few entities.
- Similarly, 6% atypical lymphocytes (drug fever, toxoplasmosis) have a different differential than 36% atypical lymphocytes (Epstein-Barr virus, cytomegalovirus).
- Nonspecific findings may be exclusionary clues, for example, eosinophilia argues strongly against typhoid/enteric fever.

Eosinopenia and typhoid fever

- Uzma Ishaq,[1] Jahanzeb Malik, et al Eosinopenia in Patients With Typhoid Fever: A Case-Control Study (L1181)
- Cureus. 2020 Sep; 12(9): e10359. Published online 2020 Sep 10.

Out of 200 participants, 59 participants with diagnosed typhoid fever had eosinopenia. There were 29 participants who had been diagnosed with typhoid fever via culture or serology and had leukopenia. **Eosinopenia** and **leukopenia** were more likely to be present in patients with a diagnosis of typhoid (OR: 9.60, 20.00)

The presence of eosinopenia and features or serology suggestive of typhoid

- **Complete blood count** often contains easily overlooked clues, for example,
  - leukopenia,
  - monocytosis,
  - lymphocytosis-relative lymphopenia,
  - eosinophilia,
  - basophilia,
  - atypical/abnormal lymphocytes,
  - thrombocytosis, and
  - thrombocytopenia.
- In a fever of unknown origin, an **isolated alkaline phosphatase elevation suggests lymphoma.**

- Lymphopenia (also called lymphocytopenia) is a disorder in which your blood doesn't have enough lymphocytes. Lymphocytes play a protective role in your immune system.
- There are three types of lymphocytes. All lymphocytes help protect you from infection, but they have different functions.
- **B lymphocytes** are made in the bone marrow. These cells make antibodies
- **T lymphocytes** develop in the thymus gland. T cells can kill viruses -infected cells or cancer cells and signal other cells to help destroy viruses (cellular immunity).
- **Natural killer cells,** which develop in the bone marrow, thymus, and liver, are immune cells that contain enzymes to kill cancer cells or cells infected with a virus

Laboratory Clues in different FUOs Categories

WBC abnormalities	
Leukocytosis	Infectious: Most infections
	Rheumatic/inflammatory: Adult Still's disease (juvenile rheumatoid arthritis [JRA])
	Miscellaneous: Drug fever
Leukopenia	Malignant/neoplastic: Leukemias
	Infectious: Miliary TB, typhoid/enteric fever, malaria, brucellosis, visceral leishmaniasis (kala-azar), EBV, CMV, histoplasmosis, relapsing fever, ehrlichiosis/anaplasmosis
	Rheumatic/inflammatory: RA (Felty's syndrome), Gaucher's disease, SLE, sarcoidosis
	Miscellaneous: Cyclic neutropenia
Relative lymphocytosis	Malignant/neoplastic: ALL, lymphomas, carcinomas, multiple myeloma
	Infectious: Whipple's disease, miliary TB, brucellosis, histoplasmosis, EBV, CMV, visceral leishmaniasis (kala-azar), toxoplasmosis, typhoid/enteric fever
	Rheumatic/inflammatory: LORA
Basophilia	Malignant/neoplastic: Preleukemia (AML), acute leukemias, lym as, MPDs

Serum protein electrophoresis

❑ **Serum protein electrophoresis** also may provide diagnostic clues, for example,

❖ **elevated a1/a2 globulin elevations**

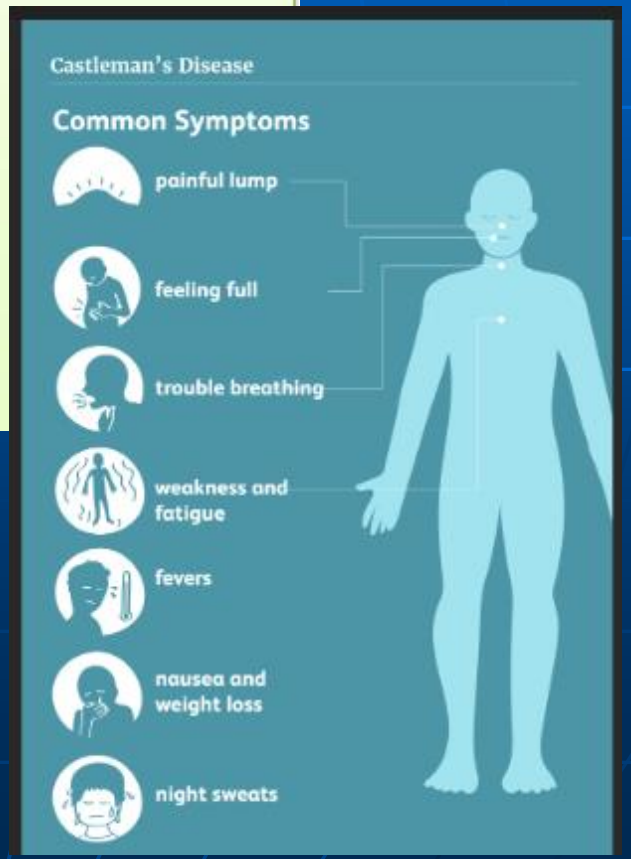
- **lymphoma,**
- **systemic lupus erythematosus);**

❖ **monoclonal gammopathy**

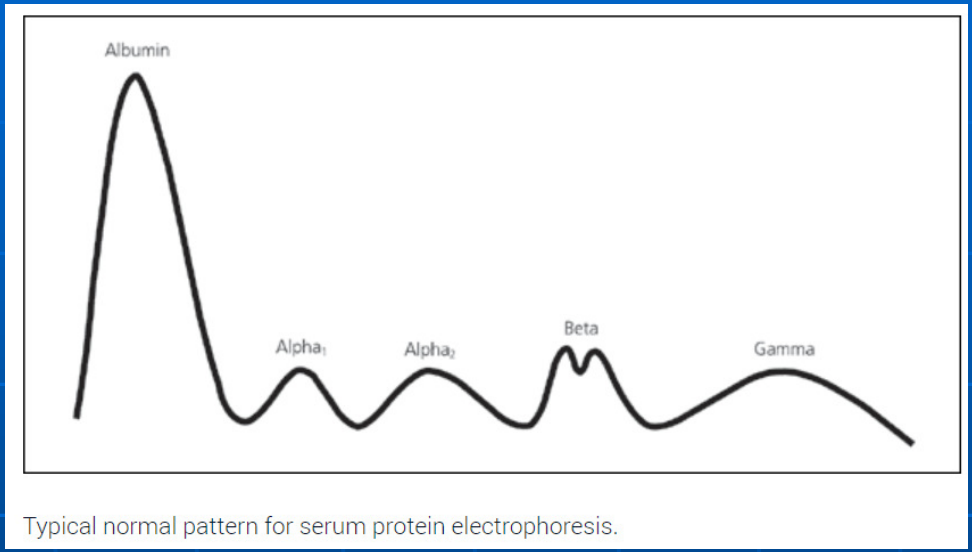
- **multiple myeloma,**
- **hyper-IgD syndrome,**
- **multicentric Castleman's disease**

❖ **polyclonal gammopathy**

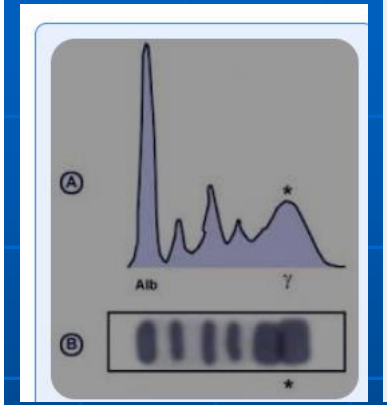
- **human immunodeficiency virus,**
- **cytomegalovirus,**
- **cirrhosis,**
- **sarcoidosis,**
- **malaria.**



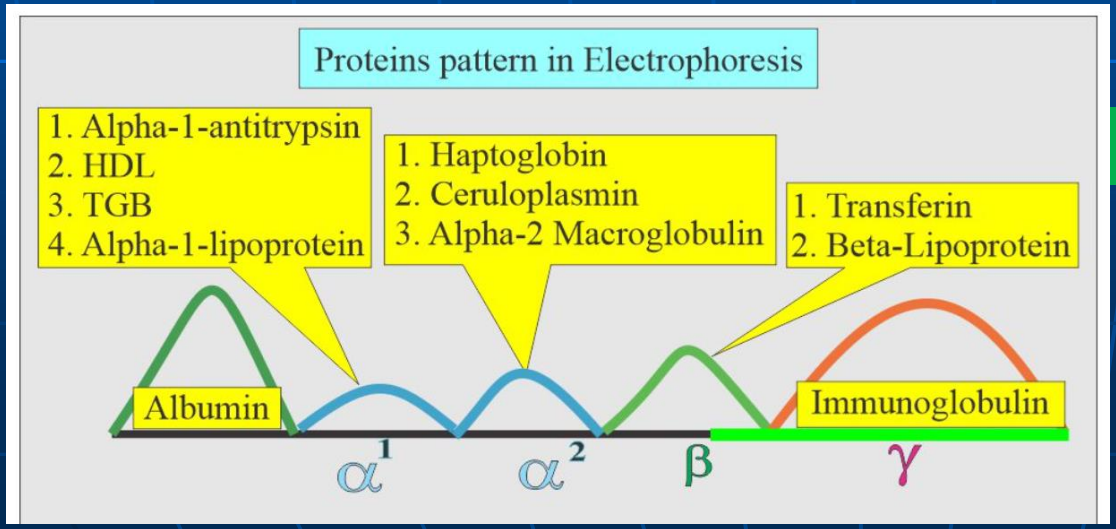
Protein electrophoresis



Typical normal pattern for serum protein electrophoresis.



項目	參考區間
Albumin	54.0-60.3%
Alpha 1	1.8-4.0%
Alpha 2	7.6-10.9%
Beta	11.4-16.1%
Gamma	13.4-20.7%

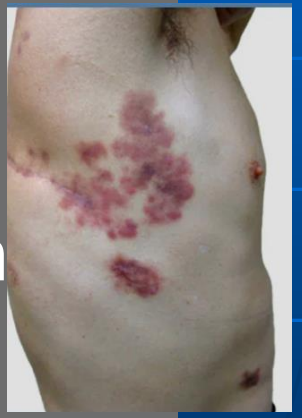


TGB: **thyroid-binding globulin,**

Castleman disease

卡斯爾曼病可以侵襲任何年齡的任何人。另一方面，患有單中心卡斯爾曼病的人通常年齡在 35 歲左右。大多數患有多中心病的人都在 50 多歲和 60 多歲。此外，多中心形式在男性中比在女性中更常見。

- 卡斯爾曼氏病（**Castleman disease**）是一類罕見的淋巴增生性疾患（英語：**lymphoproliferative disorder**），疾病特徵主要為淋巴結腫大。
- 卡斯爾曼氏病目前已知至少有三種亞型：
- 局灶性卡斯爾曼氏病（**Unicentric Castleman disease，UCD**）、
- 人類疱疹人類疱疹病毒第8型關聯性多發性卡斯爾曼氏病（HHV-8-associated MCD），以及特發性多發性卡斯爾曼氏病（idiopathic multicentric Castleman disease，iMCD）

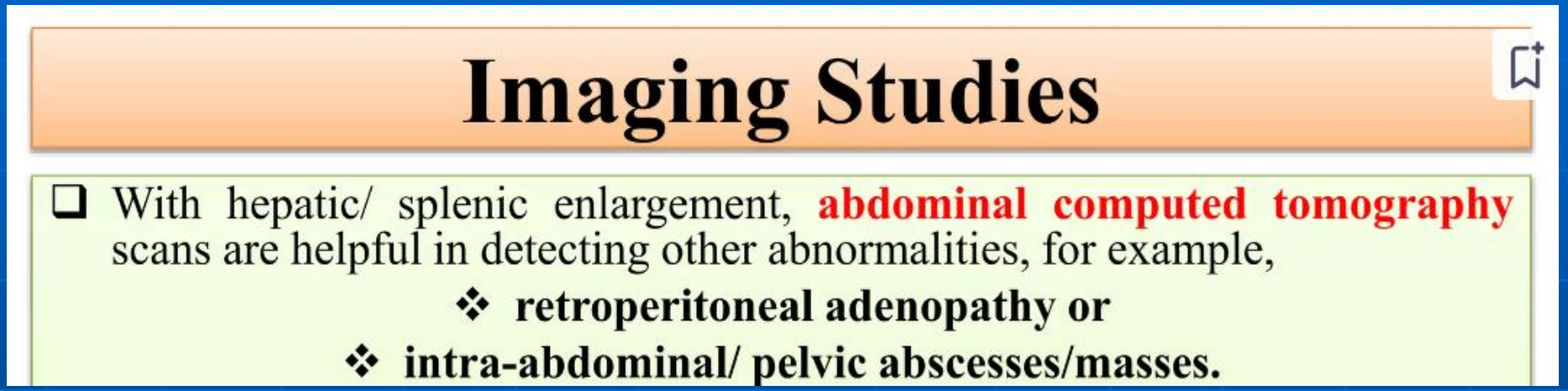


Nonspecific Laboratory Tests

❖ **Microscopic hematuria** may be the only clue to

- **subacute bacterial endocarditis,**
- **renal tuberculosis,**
- **brucellosis,**
- **periarteritis nodosa,**
- **lymphoma, or**
- **renal cell carcinoma.**

Medical images



Conventional diagnostic imaging is often ineffective in revealing the underlying cause in a considerable proportion of patients with fever of unknown origin (FUO).

- **Gallium/indium scans** are useful, but indium scans are relatively insensitive (false negative) with bone infections, for example,
  - **chronic osteomyelitis and**
  - **malignancies.**
- **Cardiac echocardiography** is important in
  - **culture negative endocarditis, and**
  - **atrial myxoma.**

- **Positron emission tomography-**computed tomography scans are most useful in detecting obscure infectious/ neoplastic fevers of unknown origin, for example,
  - **lymphomas,**
  - **Erdheim-Chester disease,**
  - **Q fever**
  - **endocarditis, or**
  - **aortic graft infection.**

PET scan (2000)

Table 1. Demographic and clinical characteristics of the study group.

Characteristic	*n* (%)	Median (IQR, Min–Max)
Number of patients	50	
Gender (male/female)	28/22 (56%/44%)	
Age (years)		59 (25, 17–85)
Concomitant Diseases/Conditions	50 (100%)	
Malignancies	8 (16%)	
Breast/ AML/H&N/URO/CR/WM	2/2/1/1/1/1	
Diabetes Mellitus	7 (14%)	
Chronic kidney desease	7 (14%)	
Cardiovascular devices	6 (12%)	
Vascular grafts/Prosthetic valves/CIED	4/1/1	
Bowel diversions	4 (8%)	
Thyroid diseases	3 (6%)	
Multinodular goiter, Hashimoto thyroiditis	2/1	
Prosthetic joints	3 (6%)	
Spinal surgery	2 (4%)	
Miscellaneous	3 (6%)	
SLE/AS/Meningioma	1/1/1	

Table 3. Final diagnoses of 50 patients with fever of unknown origin (FUO).

Diagnostic Categories	*n* (%)
Infections	20 (40%)
Abdominal abscesses	4
Infectious cyst in polycystic renal disease	3
Pneumonia/inflammation of bronchiectasis cysts	3
Vascular graft infection	3
Tuberculous spondylitis	1
Bacterial spondylodiscitis	1
Pulmonary tuberculosis	1
CIED-associated infection	1
Infectious lymphadenopathy	1
Cryptococcosis	1
Leishmaniasis	1
Malignancy	8 (16%)
Non-Hodgkin's lymphoma	5
Hodgkin's disease	1
Lung cancer	1
Relapse of urinary tract carcinoma	1
Non-infectious Inflammatory diseases (NIID)	11 (22%)
Large vessel vasculitis/Takayasu's arteritis	3
Adult-onset Still's disease	2
Sarcoidosis	1
Polymyalgia rheumatica	1
Inflammatory bowel disease	1
Familial Mediterranean fever	1
Neo-esophagus inflammation from gastroesophageal reflux	1
Subacute thyroiditis	1
Undiagnosed fever	11 (22%)
Spontaneous recovery of fever	7
Recovery of fever with corticosteroids or NSAIDs	3
Recurrent fever until death	1

PET scan is sensitive

- ^{18}F-FDG-PET/CT scan substantially contributed to the diagnosis in 70% of the patients, either by identifying the underlying cause of FUO or by directing to the most appropriate site for biopsy.
- Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of ^{18}F-FDG-PET/CT for active disease detection in patients with FUO were 94.7%, 50.0%, 84.0%, 85.7%, and 75.0%, respectively.

  In conclusion, whole-body ^{18}F-FDG-PET/CT is a highly sensitive method for detection of the underlining cause of FUO or for correctly targeting suspicious lesions for further evaluation.
- Sensitivity, ----------94.7 %
- specificity, ----------50.0 %
- accuracy, ----------84 %
- positive predictive value (PPV) ----------85.7 %
- negative predictive value (NPV)----------75 %

FDG-PET/CT in FUO

Table. Review of the Literature on FDG-PET/CT in Patients With FUO

Reference	Study Design (No. of Patients)	FUO Definition	Helpfulness FDG-PET/CT
Keidar 2008[24]	Prospective (48)	Fever > 38.3°C > 3 wk; no diagnosis after 1 wk of inpatient investigations	46%
Singh 2015[37]	Retrospective (47)	Fever > 38.3°C > 3 wk; no diagnosis after > 1 wk of inpatient investigations	38%
Gafter-Gvili 2015[38]	Retrospective (112)	Fever > 38.3°C > 3 wk; no diagnosis after > 1 wk of inpatient or outpatient investigations	46%
Pereira 2016[39]	Retrospective (76)	Fever > 38.3°C > 3 wk	60%
Hung 2017[40]	Retrospective (58)	Fever > 38.3°C > 3 wk; no diagnosis after > 1 wk of inpatient investigations	57%

Ilse J.E. Kouijzer et al : Fever of Unknown Origin: the Value of FDG-PET/CT

Seminars in Nuclear Medicine Volume 48, Issue 2, March 2018, Pages 100-107

PET/MR in FUO(2024)

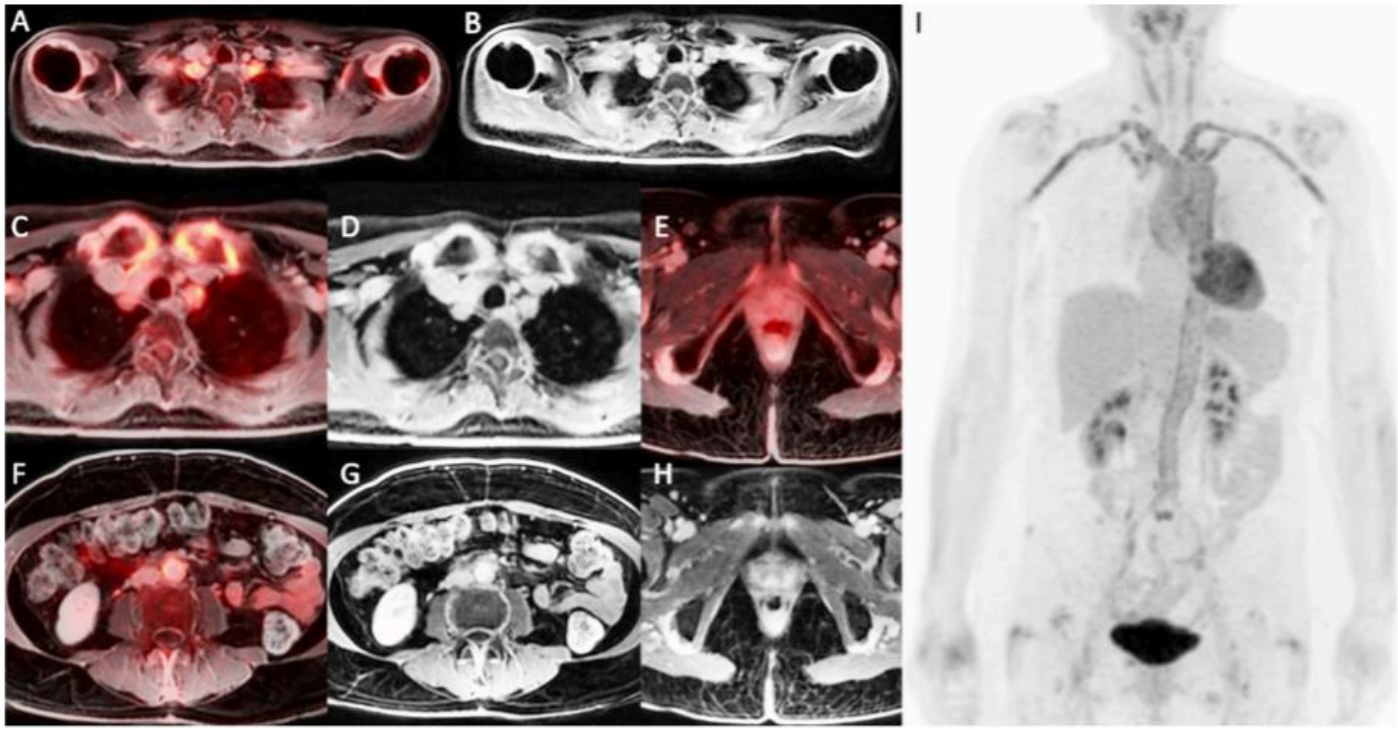


Fig. 1. Example of patient classified as Likert 5. The F-18 FDG PET/MRI fusion images (A, C, E, H) and PET 3D image (I) show increased FDG uptake in the soft tissues around the shoulder joints (A), sternoclavicular joints (C), tubera ischiadica (E) and between the spinal processes of lumbar spine (F) with visible enhancement on LAVA WATER sequence (B, D, F, H). F-18 FDG PET/MRI fusion images additionally demonstrate an increased activity in the wall of aorta (F), subclavian (A) and axillary (C) arteries. Findings were typical for the diagnosis of polymyalgia rheumatica associated with giant cell vasculitis.

Tomáš Rohan [1et al "Eur J Radiol. 2024 Feb:171:111281.Epub 2024 Jan 3.
Significance of F-18 FDG PET/MRI in the search for the etiology of inflammation of unclear origin and fever of unknown origin

L.1190, L1267, L1268

PET/MR in FUO (2024)

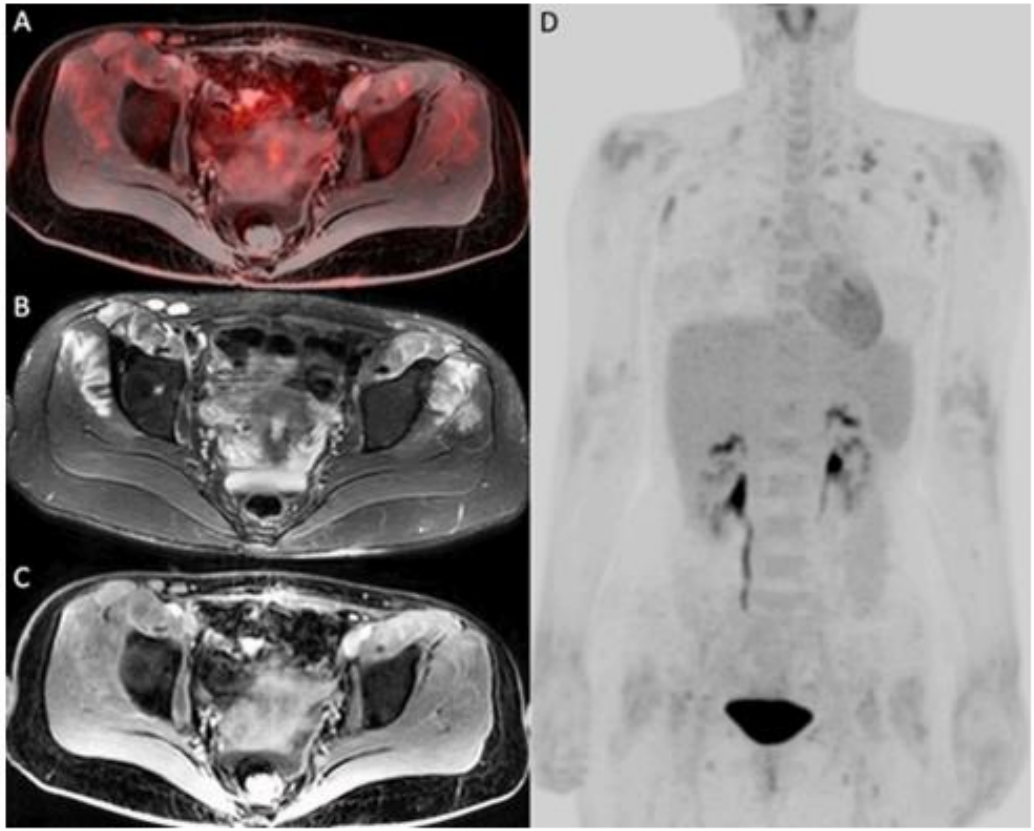


Fig. 2. Example of patient classified as Likert 4. The F-18 FDG PET/MRI fusion image (A) and PET 3D image (D) show a moderately increased FDG uptake in muscles around hip joints. T2 IDEAL WATER image (B) show increased T2 signal, LAVA WATER (C) image show mild enhancement in these muscles. Findings were suspicious of myositis, which was histopathologically confirmed.

Myositis,(L1890)

PET/MR, FUO-2024

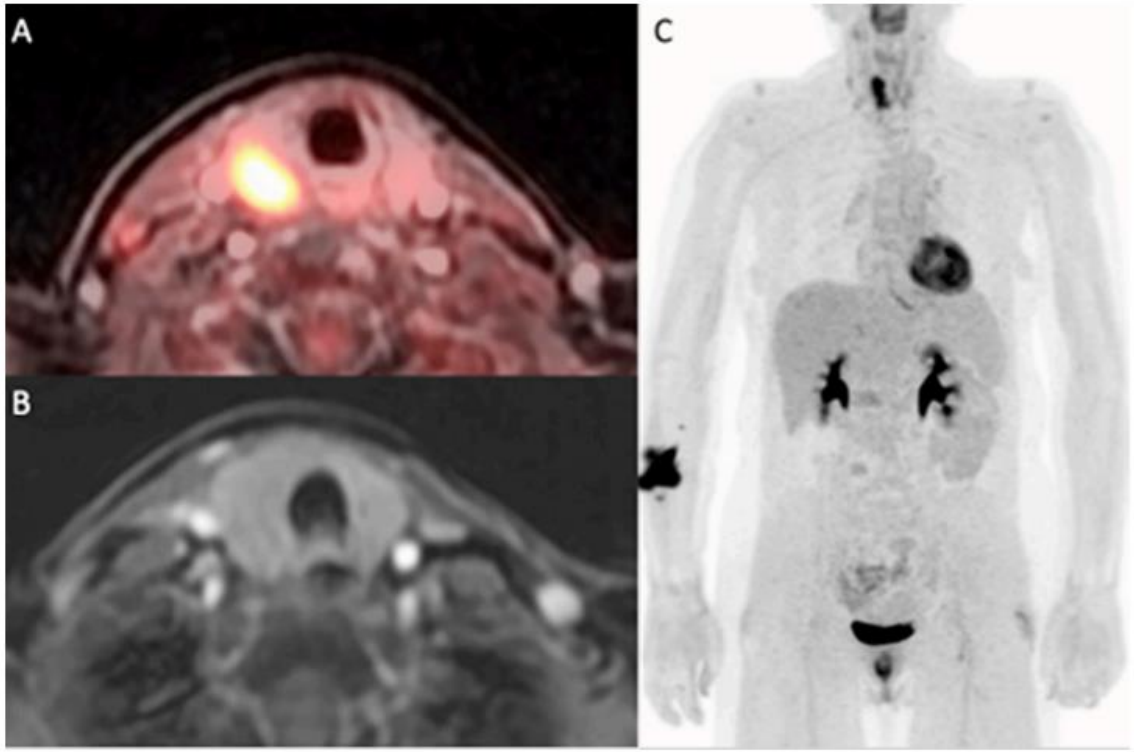


Fig. 3. Example of patient classified as Likert 3. The F-18 FDG PET/MRI fusion image (A) and PET 3D image (C) show an increased FDG uptake in the right lobe of thyroid gland. No lesion of thyroid gland was visible on LAVA WATER image (B). Finally, subacute thyroiditis was diagnosed.

Subacute thyroiditis (L1190)

Invasive tests-1, Lymph node biopsy

Invasive Tests

- Lymph node biopsy is the most frequent invasive test.
- More likely to be diagnostic are posterior cervical, supra/infraclavicular, or epitrochlear node biopsies.
- Hilar, mediastinal, or retroperitoneal node biopsies have a high diagnostic yield.

❖ **Bone marrow biopsy** may be diagnostic, for example,

- **myeloproliferative disorders,**
- **preleukemias (due to acute myelogenous leukemia),**
- **Gaucher's disease,**
- **lymphoma,**
- **Erdheim-Chester disease,**
- **miliary tuberculosis,**
- **disseminated histoplasmosis,**
- **multicentric Castleman's disease,**
- **Whipple's disease, or**
- **typhoid/enteric fever.**

Typhoid fever/enteric fever

Liver Biopsy and Bone Marrow Biopsy

Diagnostic yield of liver biopsy has ranged from 14% to 17%.

- Physical exam finding of hepatomegaly or abnormal liver
- profile are not helpful in predicting abnormal biopsy result.
- Complication rate is 0.06% to 0.32%

The diagnostic yield of bone marrow cultures in immunocompetent individuals has been found to be 0% to2 %

Volk et al. J Clin Pathol 1998;110:1502
Riley et al. J Clin Pathol 1995:48:706
Mourand et al. Arch Intern Med 2003;163:545

❖ **Epididymal nodule biopsy** may be diagnostic of

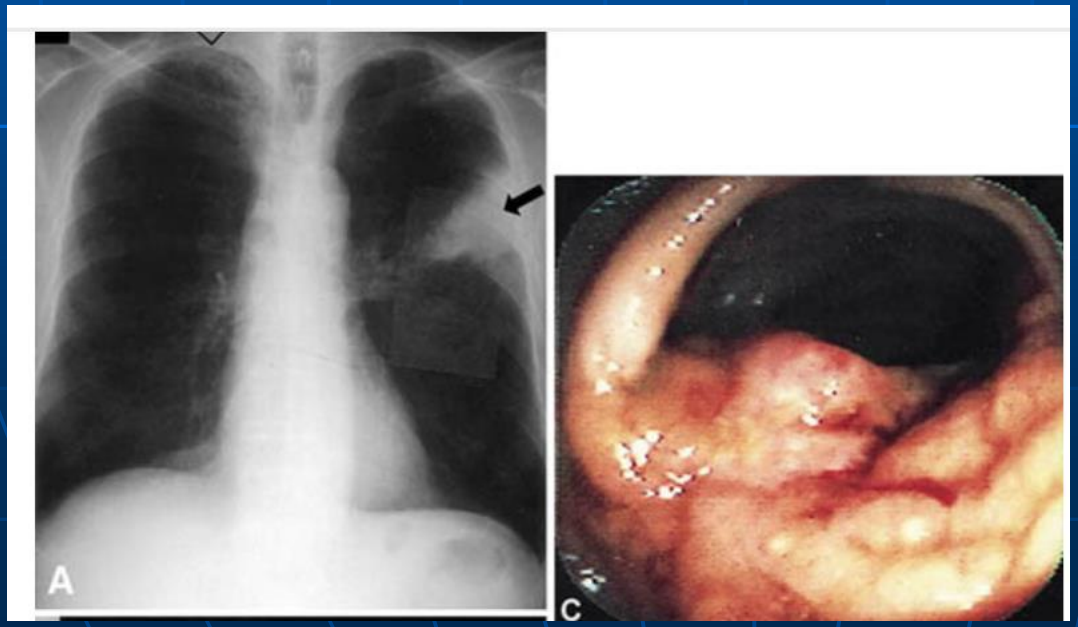
- **brucellosis,**
- **tuberculosis,**
- **leptospirosis,**
- **rat bite fever,**
- **relapsing fever,**
- **lymphoma,**
- **systemic lupus erythematosus,**
- **periarteritis nodosa,**
- **sarcoidosis, or**
- **familial Mediterranean fever.**

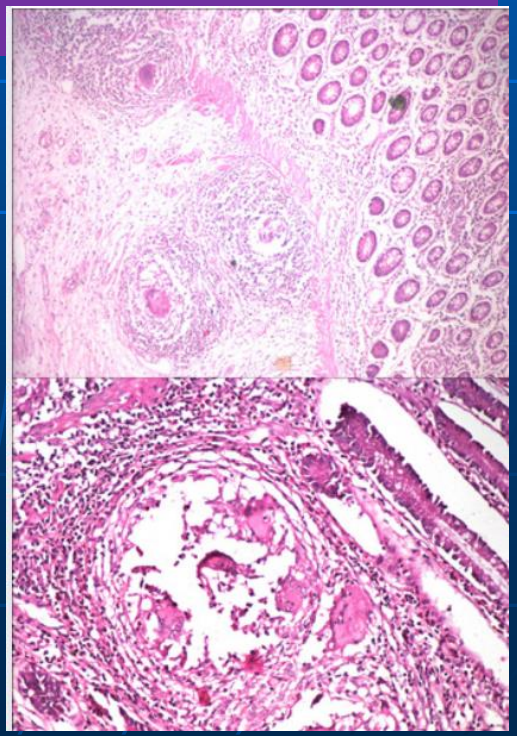
Ileocecal TB

❖ **Ileal biopsy** can be done for suspected

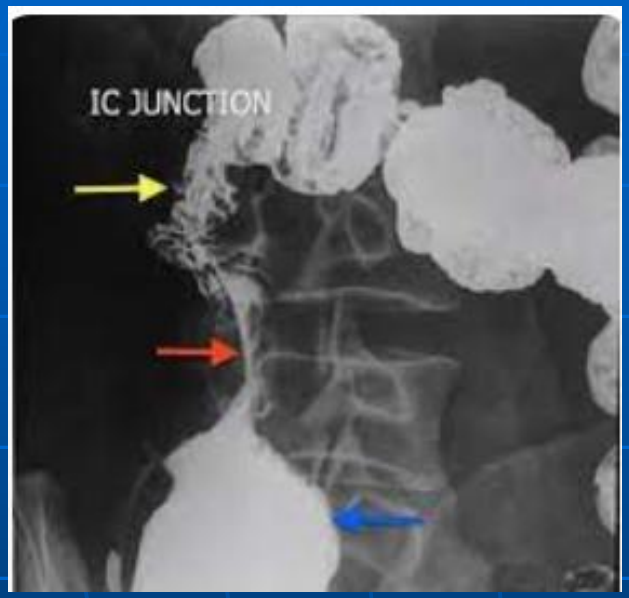
- **ileocecal tuberculosis or**
- **regional enteritis.**

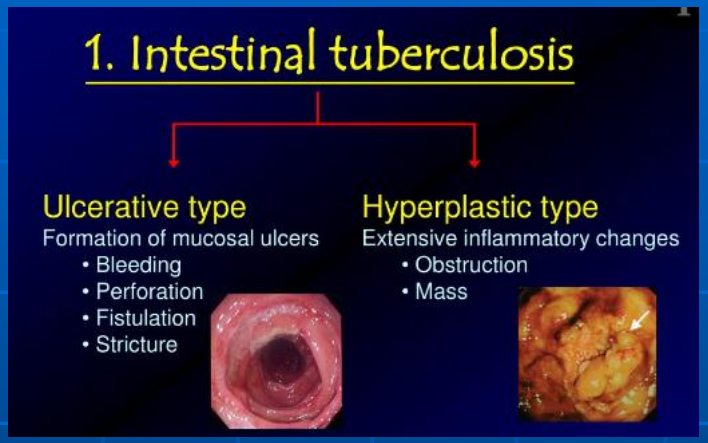
Ileocecal tuberculosis is the most common site of gastrointestinal tuberculosis, which in turn is the third most common site of extrapulmonary tuberculosis.

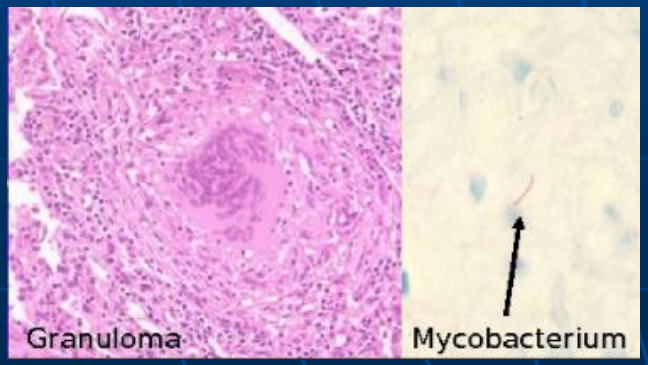


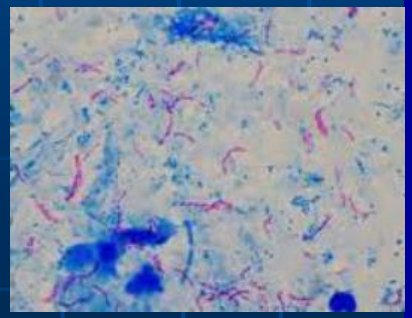


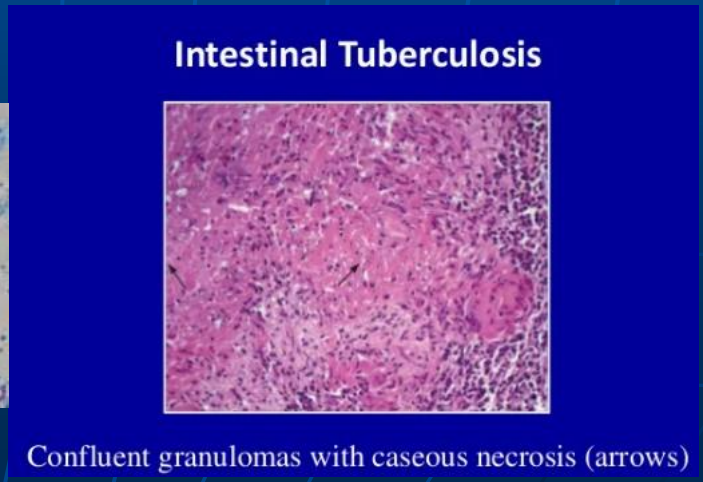
Intestinal TB











Management--principle

- There is no single standard FUO management protocol given the variety of possible etiologies**.**
- **The most important thing is to investigate and rule out all possible diagnoses.**
- Specific treatment should be started, once a diagnosis is made. Please note that empiric antibiotics are not indicated unless the patient with **FUO is neutropenic**. Antibiotics may delay the diagnosis of some occult infections. Empiric glucocorticoids are also not indicated unless there is strong clinical suspicion for a **specific rheumatologic diagnosis**.
- However, in patients whose condition is deteriorating empiric therapeutic trials of antibiotics, steroids, or antituberculous agents may be considered

Management -2

- @@Patients with FUO rarely need surgical treatment.
- **@@Specific Examples of Treatment--steroid**

- In patients with **hepatic granulomas**, 50% respond to corticosteroid treatment while the other 50% resolve spontaneously.
- Patients with **giant cell arteritis** are treated with high doses of steroids, and if the patient is very ill or has a significant ocular compromise, intravenous steroids should be administered.
- **In polymyalgia rheumatica**, the treatment is steroid therapy.
- **@@When drug fever is suspected, discontinue the implicated drug. The patient would be afebrile after two days of stopping the causative drug.**

Management-3

- **腫瘤和惡性腫瘤占 FUO 病因的 18%。**
- 與FUO相關的最常見腫瘤是：

- 淋巴瘤
- 腎細胞癌
- 急性髓系白血病
- 骨髓增生性疾病
- 心房粘液瘤
- 多發性
- 腸癌
- 胰腺癌
- 肝癌
- CNC轉移
- 肝轉移
- 系統性肥大細胞增多症 systemic mastocytosis

Cunha BA, Lortholary O, Cunha CB. Fever of unknown origin: a clinical approach. Am J Med. 2015 Oct;128(10):1138.e1-1138.e15. (L1196)

Prognosis determined primarily by the underlying disease.

- Outcome is worst for neoplasms.
- FUO patients who remain undiagnosed after extensive evaluation generally have a favorable outcome and the fever usually resolves after 4-5 weeks.

Larson et al. Medicine 1982;61:269

Summary

- **FUO is often a diagnostic dilemma.**
- Infections comprise ~30% of cases. Bone marrow biopsies are of low diagnostic yield. Diagnostic approach should occur in a step-wise fashion based on the H & PE. Patient's that remain undiagnosed generally have a good prognosis

Epidemiology

- Epidemiology of fever of unknown origin (FUO) varies based on etiology of fever, age group, geography, environmental exposure, and immune/HIV status. In developing countries, an infectious etiology of FUO is most prevalent whereas, in developed countries, FUO is likely due to non-infectious inflammatory disease.

2003年的結論-不明原因的持續發燒仍然是醫生面臨的更艱鉅的挑戰

- 在21世紀初，不明原因的持續發燒仍然是醫生面臨的更艱鉅的挑戰之一。
- 流行疾病和診斷類別的不斷變化需要定期更新譜系，因為對一系列原因的了解構成了合理方法的基礎。
- 診斷技術的日益複雜性仍然未能提高診斷的敏銳度。
- 一些長時間的發燒仍然是個謎，但這不應引起沮喪，而應激發正在進行的研究，以揭示潛在的病理生理機制

From Prolonged Febrile Illness to Fever of Unknown OriginThe Challenge Continues
Steven Vanderschueren, MD, PhD; Daniël Knockaert, MD, PhD; Tom Adriaenssens, MD al
Arch Intern Med. 2003;163(9):1033-1041.

2024的review還是認定是一個困難的問題

- 青少年不明原因發熱是一種具有挑戰性的疾病狀態，其潛在病因可能包括感染性、非感染性炎症和惡性腫瘤過程。對這些患者來說，仔細和全面的病史（包括暴露史）、連續檢查以及有針對性的實驗室和影像學檢查至關重要。
- 在發現病因的青少年中，感染性病因仍然是最普遍的，其次是非感染性炎症性疾病。在總體上令人放心的非診斷性檢查患者中，預後通常為自限性和良好。

Ryan K (Infectious Disease, Department of Pediatric, Medical College of Wisconsin & Children's Hospital of Wisconsin)
Fever of Unknown Origin, MCNA 2024 Jan;108(1):79-92.
doi: 10.1016/j.mcna.2023.05.016. Epub 2023 Jul 18.

結論(2024.02.23)

1. 發燒原因不明是臨床上一個困難的問題.
2. 發燒原因不明有很複雜的原因包括感染,惡性腫瘤以及非感染的各項原因.
3. 詳細問病史還是非常重要的手段. 注意身體的一些特別的異常可以找出發燒不明原因的疾病或原因.
4. 檢驗及醫學影像是進一步確認發燒不明原因的手段.
5. 必須經常注意發燒不明原因的原因累積經驗就可以比較容易做出診斷