Nedeni Bilinmeyen Ateş
Enfeksiyon dışı nedenler

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Sunum planı

- NBA, enfeksiyon dışı nedenler
- Epidemiyoloji
- Enfeksiyon dışı NBA nedenleri, ne kadar tanıyabiliyoruz?
- İpucu bilgiler
- Tanı yöntemleri
- …
- Eve gidecek notlar

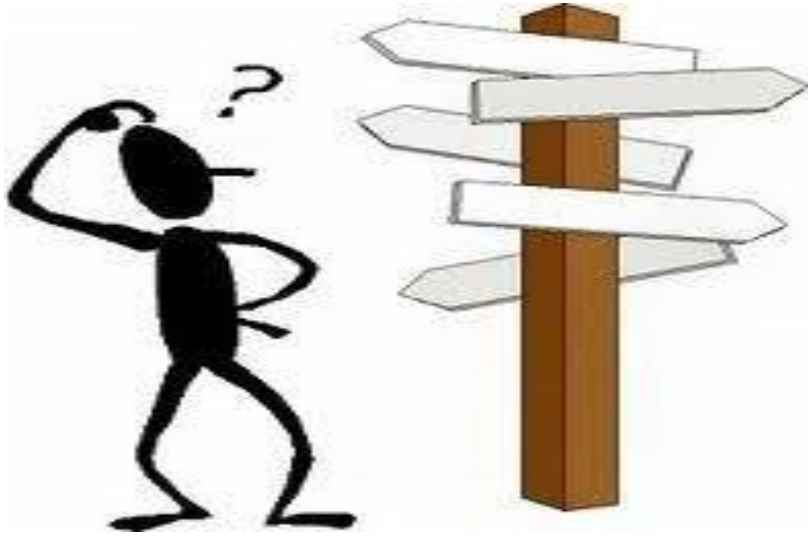
The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

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

Fever of Unknown Origin

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



Nedeni bilinmeyen ateş

- Etioloji
  - Enfeksiyonlar
    - Sistemik
    - Fokal
  - Malignensiler
    - Hematolojik
    - Solid tümörler
  - Kollojen vasküler hastalıkları (non enfeksiyoz enflamatuvar hast-NIID)
    - Erişkin Still hastalığı
    - SLE
    - Temporal arterit
  - Misellenoz (Diğer)
    - Subakut tiroidit, ilaç ateşi
  - Tanı konmayan

Table 3. Selected Malignant, Autoinflammatory and Autoimmune, and Miscellaneous Causes of FUO.*

Cancers

Lymphomas (including Hodgkin's and intravascular lymphomas); widespread metastatic carcinomas; tumors with liver metastases; colon, hepatocellular, and renal-cell carcinomas; acute leukemias; brain tumors with thermoregulatory disorders

Autoinflammatory and autoimmune disorders

Autoinflammatory: familial Mediterranean fever, Muckle–Wells syndrome, familial cold autoinflammatory syndrome

Autoimmune: autoimmune lymphoproliferative syndrome, autoimmune polyendocrinopathy syndrome

Variable autoinflammatory and autoimmune expression or mixed-pattern diseases†: giant-cell and Takayasu's arteritis, inflammatory bowel disease, certain types of uveitis, Behçet's syndrome, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis

Miscellaneous causes

Granulomatous, idiopathic, familial: idiopathic granulomatous hepatitis, granulomatosis with polyangiitis, chronic granulomatous disease, Rosai–Dorfman disease, adjuvant or silicone-induced granulomas, lipogranulomas (e.g., from mineral oil ingestion), Kikuchi–Fujimoto disease (histiocytic necrotizing lymphadenitis), Kawasaki's disease, sclerosing mesenteritis

Vascular: atrial myxoma, aortic dissection, deep-vein thrombosis, pulmonary emboli, hematoma, thrombophlebitis, intracranial hemorrhage and strokes

Endocrine: Addison's disease, thyrotoxicosis, thyroid storm, thyroiditis, pheochromocytoma

Hematologic: hemolytic–uremic syndrome, thrombotic thrombocytopenic purpura

Others: cirrhosis, pancreatitis, hemophagocytic lymphohistiocytosis, intravesical bacillus Calmette–Guérin, lipid overload syndrome (from lipid emulsion therapy), factitious fever, retroperitoneal fibrosis, crowned dens syndrome (calcium pyrophosphate deposition disease)

* Not all entities that may be associated with fever are shown; many other causes are described as case reports. Data are from Gaeta et al.,[17] Pannu et al.,[18] Loizidou et al.,[37] Sun and Singh,[38] and van Kempen et al.[39]

† These disorders may have both autoinflammatory and autoimmune components.

Epidemiyoloji

Fever of Unknown Origin in Turkey

F. Tabak, A. Mert, A.D. Celik, R. Ozaras, M.R. Altiparmak, R. Ozturk, Y. Aktuglu

Table 1
Cases of FUO in our clinic (1984–2001).

Diseases	No. (%)
Parvovirus B19 meningitis	1
Collagen–vascular diseases	**27 (23)**
Adult-onset Still's disease	13
SLE	3
Temporal arteritis	3
ARF	2
Wegener's granulomatosis	2
Polymyalgia rheumatica	1
PAN	1
Juvenile rheumatoid arthritis	1
Systemic vasculitis	1
Neoplasms	**22 (19)**
Hodgkin's disease	8
Non-Hodgkin's lymphoma	7
Hairy cell leukemia	1
Primary liver cancer	1
Peritonitis carcinomatosis	1
Lung cancer	1
Multiple myeloma	1
Ewing's sarcoma	1
Skin cancer	1
Miscellaneous diseases	**12 (10)**
Subacute thyroiditis	4
Sarcoidosis	2
Cirrhosis	2
Sweet's syndrome	1
Weber-Christian disease	1
Ulcerative colitis	1
Histiocytosis X disease	1
Undiagnosed	**16 (14)**

SLE: systemic lupus erythematosus; ARF: acute rheumatic fever; PAN: polyarteritis nodosa

Infection J, 2003

1984-2001

117 NBA hasta

- %23 kollojen vasküler hastalık
- %19 neoplazm
- %10 miscellaneous hastalık
- %14 tanı konmamış

Tabak F et al. Infection 2003; 31: 417–420

Journal of Infection (2004) 48, 81–85

Table 1 Causes of fever unknown origin.

Diagnostic category	No of patients ($n = 87$)	%
Infections	51	58.6
Collagen vascular disease	16	18.3
Neoplasm	12	13.7
Miscellaneous	2	2.2
No diagnosis	6	6.8

Fever of unknown origin in Turkey: evaluation of 87 cases during a nine-year-period of study

Nese Saltoglu*, Yesim Tasova, Durdane Midikli, Hasan S.Z. Aksu, Aslihan Sanli, Ismail H. Dündar

Table 3 Non-infectious causes of FUO and diagnosis.

Aetiology	Diseases	Diagnostic methods
Collagen vascular disease ($n = 16$)	($n = 6$) Vasculitic syndromes	Clinical follow-up, Skin biopsy ANA (−), AntiDNA (−)
	($n = 4$) Adult Still's disease	Clinical follow-up; ANA/antiDNA (−), high serum ferritin level, leucocytosis, Rash
	($n = 3$) Systemic lupus erythematosus	Clinical findings; ANA (+), antiDNA (+) in serial
	($n = 2$) Behçet's disease	Immunological investigation; skin biopsy
	($n = 1$) Juvenile ankylosing spondylitis	Radionuclide bone scan with technetium; cervical MRI, immunological investigation
Neoplasm ($n = 12$)	($n = 4$) Non-Hodgkin lymphoma	Bone marrow biopsy; CT
	($n = 1$) Hodgkin lymphoma	
	($n = 4$) Chronic myeloid leukemia	Bone marrow biopsy
	($n = 2$) Gastrointestinal tractus Ca	CT; colon graphy, rectal biopsy
	($n = 1$) Pons glioma	Cerebral CT; biopsy
Miscellaneous ($n = 2$)	($n = 1$) Subacute thyroiditis	Thyroid ultrasonography; clinical signs
	($n = 1$) Granulomatous hepatitis	Liver biopsy

International Journal of Infectious Diseases (2008) 12, 71—79

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INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

http://intl.elsevierhealth.com/journals/ijid

The spectrum of diseases causing fever of unknown origin in Turkey: a multicenter study

Yasar Kucukardali [a], Oral Oncul [b], Saban Cavuslu [b], Mehmet Danaci [a], Semra Calangu [c], Hakan Erdem [d,*], Ayse Willke Topcu [e], Zuhal Adibelli [f], Murat Akova [f], Emel Azak Karaali [e], Ahmet Melih Ozel [a], Zahit Bolaman [g], Bulent Caka [h], Birsen Cetin [i], Erkan Coban [j], Oguz Karabay [k], Cagla Karakoc [c], Mehmet Akif Karan [h], Selda Korkmaz [e], Gulsen Ozkaya Sahin [f], Alaaddin Pahsa [d], Fatma Sirmatel [l], Emrullah Solmazgul [a], Namik Ozmen [a], Ilyas Tokatli [h], Cengiz Uzun [h], Gulsen Yakupoglu [j], Bulent Ahmet Besirbellioglu [d], Hanefi Cem Gul [d]

Fever of Unknown Origin Study Group

Table 2 The final diagnosis in patients with fever of unknown origin

Infectious diseases (53)	Malignant diseases (22)	Non-infectious inflammatory diseases (47)	Miscellaneous (8)
Tuberculosis (21)	**Hematological malignancies (12)**	**Collagen tissue disease (31)**	Drug fever (2)
Pulmonary tuberculosis (6)	Hodgkin lymphoma (4)	Adult Still's disease (21)	FMF (2)
Disseminated tuberculosis (5)	Non-Hodgkin lymphoma (1)	Subacute thyroiditis (3)	Ulcerative colitis (1)
Tuberculosis lymphadenitis (5)	Splenic lymphoma (2)	SLE (2)	Crohn's disease (1)
Pleural tuberculosis lymphadenitis (2)	Multiple myeloma (2)	Dermatomyositis (1)	Thrombosis (1)
Pericardial tuberculosis (1)	CML (1)	Rheumatoid arthritis (1)	Gout (1)
Renal tuberculosis (1)	MDS (1)	Polymyositis (1)	
Peritoneal tuberculosis (1)	AML (1)	Polymyalgia rheumatica (1)	
Other (32)	**Solid cancer (10)**	Interstitial pulmonary fibrosis (1)	
CMV pneumonia (5)	Adenocarcinoma (2)	**Vasculitis (14)**	
Abscesses (5)	Stromal tumor (1)	Unclassified vasculitis (5)	
Brucellosis (5)	Hypernephroma (1)	Temporal arteritis (4)	
Toxoplasmosis (4)	Castleman disease (1)	PAN (3)	
Salmonellosis (3)	Metastatic carcinoma (1)	HSP (2)	
Pyelonephritis (2)	Testis tumor (1)	**Granulomatous disease (2)**	
PID (2)	Colon carcinoma (1)	Sarcoidosis (2)	
Urinary infection (2)	Pancreatic carcinoma (1)		
Endocarditis (1)	Gastric carcinoma (1)		
Systemic candidiasis (1)			
Leptospirosis (1)			
Meningitis (1)			
	Undiagnosed (24)		

CMV, cytomegalovirus; PID, pelvic inflammatory disease; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; AML: acute myeloid leukemia; SLE, systemic lupus erythematosus; PAN, polyarteritis nodosa; HSP, Henoch—Schönlein purpura; FMF, familial Mediterranean fever.

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DOI: 10.1111/ijcp.14138

ORIGINAL PAPER

INFECTIOUS DISEASES

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Fever of unknown origin (FUO) on a land on cross-roads between Asia and Europa; a multicentre study from Turkey

Ercan Yenilmez[1] | Deniz Kakalicoglu[1] | Fatma Bozkurt[2] | Mine Filiz[3] | Aysegul Akkol Camurcu[4] | Elif Ozge Damar Midik[5] | Hande Berk Cam[6] | Eren Arkali[7] | Seval Bilgic Atli[2] | Ahmet Sahin[8] | Sibel Yorulmaz Goktas[9] | Halil Erkan[10] | Mehmet Resat Ceylan[11] | Merve Kacar Eker[12] | Hava Kaya[13] | Zehra Karacaer[3] | Ersin Tural[1] | İlyas Dokmetas[14] | Levent Gorenek[1] | Sukran Kose[7]

- 2015-2019
- 13 merkez
- 214 NBA hasta
- Retrospektif

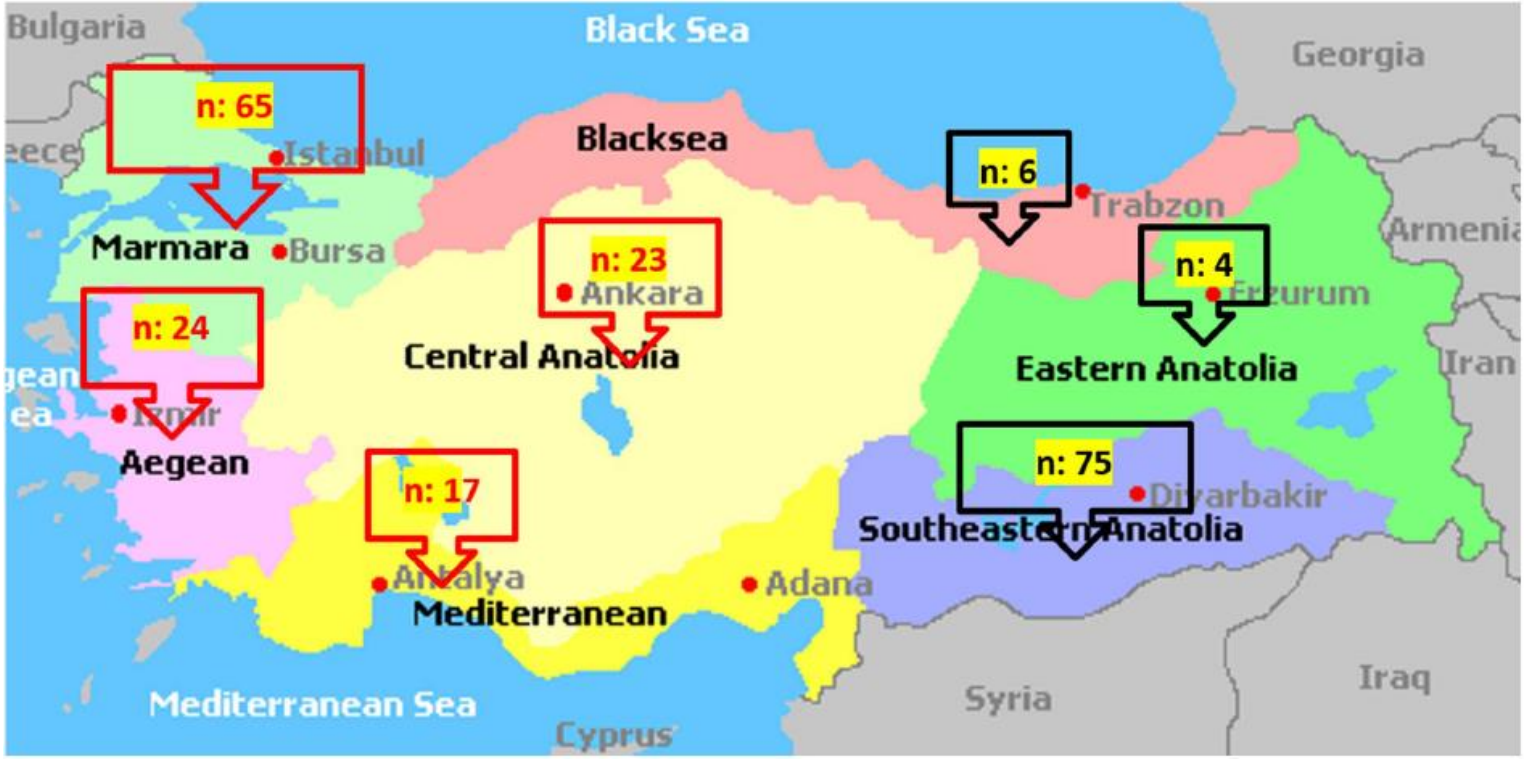


TABLE 5 Etiologic spectrum of the FUO cases in literature reported from Turkey

Reference	Year of publishing Region	Methodology	Number of cases	Diagnosis				
				Infection %	Autoimmune/ inflammatory %	Malignancy %	Miscellaneous %	Undiagnosed (True FUO) %
Pehlivan[9]	1998 Izmir	Retrospective Single centre	62	50	21	11	6	11
Araz[10]	2000 Gaziantep	Retrospective Single centre	30	47	20	17	3	13
Kucukardali[11]	2001 Istanbul	Retrospective Single centre	82	59	7	10.9	2.4	19.5
Goktas[12]	2002 Istanbul	Prospective Single centre	35	40	23	14	8.5	14.5
Tabak[13]	2003 Istanbul	Retrospective Single centre	117	34	23	19	10	14
Oncu[14]	2003 Istanbul	Retrospective Single centre	66	43.9	39.4	7.6	1.5	7.6
Saltoglu[15]	2004 Istanbul	Retrospective Single centre	87	58.6	18.3	13.7	2.2	6.8
Ozer[16]	2004 Istanbul	Retrospective Single centre	86	52.3	5.8	14	8.1	19.8
Ergonul[17]	2005 Ankara	Prospective Single centre	80	52	13	18	6	11
Erten[18]	2005 Istanbul	Retrospective Single centre	57	42	30	18	0	10
Onal[19]	2006 Ankara	Retrospective Single centre	97	36.1	8.2	15.5	5.2	35.1
Colpan[20]	2007 Ankara	Prospective Single centre	71	45.1	26.8	14.1	5.6	8.5
Satilmis[21]	2008 Konya	Retrospective Single centre	27	40.8	25.9	22.2	7.4	3.7
Kucukardali[22]	2008 Multicentre	Prospective Multicentre	154	34.4	30.5	14.3	5.2	15.6
Alpat[23]	2009 Eskisehir	Retrospective Single centre	53	31.1	18.9	9.4	15.1	24.5
Mete[24]	2012 Istanbul	Retrospective Single centre	100	26	38	14	2	20
Solay[25]	2013 Ankara	Prospective Single centre	43	45.2	23.8	16.7	14.3	2.3
Present study	2020 Multicentre	Retrospective Multicenter	214	44.9	11.68	15.42	8.41	19.62

TABLE 3 Association of age category (A) and geographic region (B) with FUO aetiology (n: 214)

	Age ≥ 65		Age < 65		Total			95%CI	
A. Age category	n	%	n	%	n	P	OR	Lower	Upper
Infections	10	34.48	86	46.49	96	.227	0.61	0.27	1.37
Malignancies	5	17.24	27	14.59	32	.710	1.22	0.43	3.47
Autoimmune/inflammatory	2	6.90	23	12.43	25	.388	0.52	0.12	2.34
Miscellaneous	2	6.90	15	8.11	17	.823	0.84	0.18	3.88
Undiagnosed	10	34.48	34	18.38	44	.046	2.34	1.00	5.48
	Western Turkey		Eastern Turkey		Total			95%CI	
B. Geographic region	n	%	n	%	n	P	OR	Lower	Upper
Infections	45	34.62	51	60.71	96	<.001	0.34	0.19	0.60
Malignancies	21	16.15	12	14.29	33	.826	1.09	0.50	2.37
Autoimmune/Inflammatory	20	15.38	5	5.95	25	.036	2.87	1.03	7.98
Miscellaneous	11	7.69	7	8.33	18	.866	0.92	0.33	2.51
Undiagnosed	33	26.92	9	10.71	42	.004	3.07	1.39	6.78

NBA, enfeksiyon dışı nedenler

- Yaş (<65 yaş ve 65 yaş>)

  65 yaş üstü hasta grubunda tanı konmayan oranı daha yüksek

- Doğu-Batı bölgeleri

  Batı bölgesinde otoimmun hastalıklar daha sık

  Tanı konmayan hasta oranı daha sık

Retrospective analysis of 1,641 cases of classic fever of unknown origin

Guanyu Zhou, Ying Zhou, Cejun Zhong, Hui Ye, Zhenzhen Liu, Yanbin Liu, Guangmin Tang, Junyan Qu, Xiaoju Lv

2011-2017, 1641 NBA

- %48 enfeksiyöz (en sık tüberküloz)
- %19 kollojen doku hastalığı (en sık ESH)
- %16 neoplastik hastalıklar (en sık lenfoma)
- %6 diğer
- %8 tanı konamayan

Tüberküloz ve lenfoma tanısı konan hastalar arasında,

Yaş, cinsiyet, klinik ve laboratuvar parametreleri açısından anlamlı bir fark bulunmamıştır.

Ann Transl Med 2020;8(11):690

Retrospective analysis of 1,641 cases of classic fever of unknown origin

Guanyu Zhou, Ying Zhou, Cejun Zhong, Hui Ye, Zhenzhen Liu, Yanbin Liu, Guangmin Tang, Junyan Qu, Xiaoju Lv

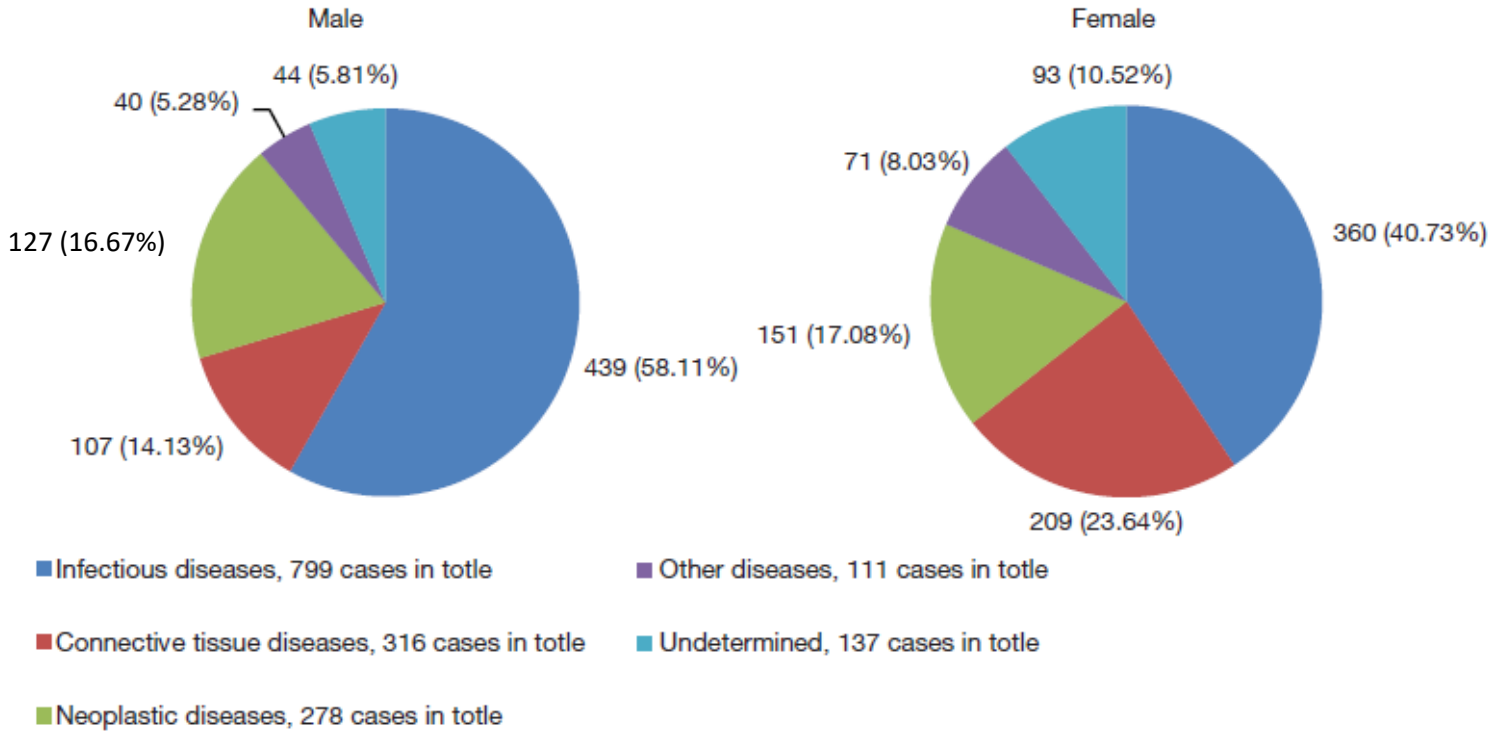


Figure 1 The relationship between the distribution of etiology and gender in patients with fever of unknown origin.

Ann Transl Med 2020;8(11):690

Open access Original research

BMJ Open

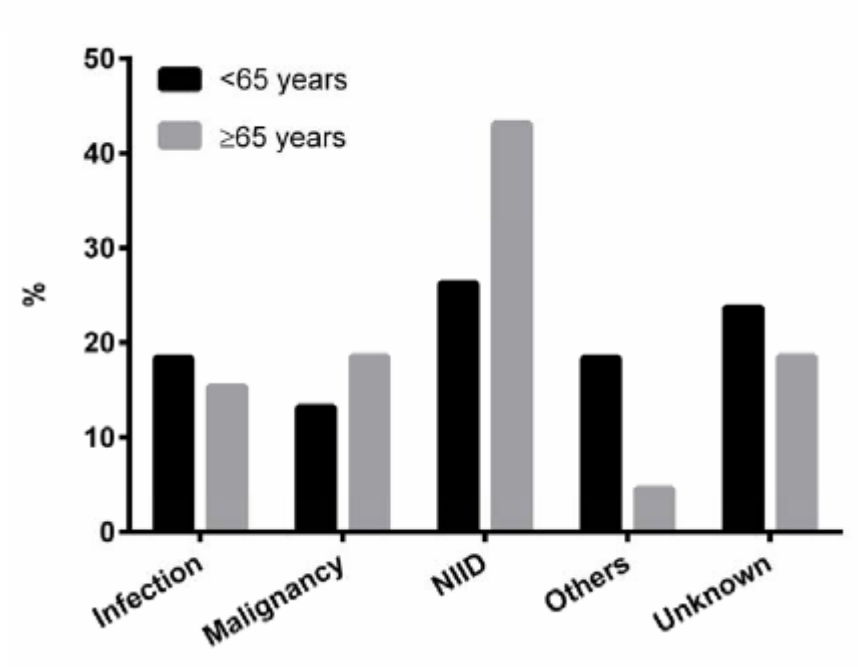
Key diagnostic characteristics of fever of unknown origin in Japanese patients: a prospective multicentre study

Toshio Naito ,[1] Mika Tanei,[1] Nobuhiro Ikeda,[2] Toshihiro Ishii,[3] Tomio Suzuki,[4] Hiroyuki Morita,[5] Sho Yamasaki,[6] Jun'ichi Tamura,[7] Kenichiro Akazawa,[8] Koji Yamamoto,[9] Hiroshi Otani,[10] Satoshi Suzuki,[11] Motoo Kikuchi,[12] Shiro Ono,[13] Hiroyuki Kobayashi,[14] Hozuka Akita,[15] Susumu Tazuma,[16] Jun Hayashi[17]

Table 1 Description of final diagnosis of fever of unknown origin

Final diagnosis	N (%)
Infectious disease	24 (17.0%)
Viral infection	5
Infective endocarditis	4
Tuberculosis	2
Malignancy	22 (15.6%)
Malignant lymphoma	11
Non-infectious inflammatory disease	48 (34.0%)
Adult-onset Still disease	7
Polymyalgia rheumatica	6
ANCA-associated vasculitis	6
Rheumatoid arthritis	4
Others	17 (12.1%)
Histiocytic necrotising lymphadenitis	3
Subacute thyroiditis	2
Unknown	30 (21.3%)

Japonya, çok merkezli, 2016-2017 yılı
141 hasta



Naito T, *et al*. *BMJ Open* 2019;9:e032059

Fusco et al. BMC Infectious Diseases (2019) 19:653
https://doi.org/10.1186/s12879-019-4285-8

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Fever of unknown origin (FUO): which are the factors influencing the final diagnosis? A 2005–2015 systematic review

Francesco Maria Fusco[1*], Raffaella Pisapia[2], Salvatore Nardiello[3], Stefano Domenico Cicala[4], Giovanni Battista Gaeta[5] and Giuseppina Brancaccio[6]

Neoplasms (out of 289 cases from 15 case-series where details are available)	
Lynphomas (including Hodgkin, Non-Hodgkin, not specified)	169 (58.5%)
Solid tumors (not specified)	25 (8.7%)
Leukemias	17 (5.9%)
Other cancers (not specified)	14 (4.8%)
Myelodysplastic syndrome	11 (3.8%)
Colon cancers	10 (3.5%)
Multiple mieloma	8 (2.8%)
Gastric cancers	5 (1.7%)
Mesotheliomas	5 (1.7%)
Castleman's diseases	4 (1.4%)
NIIDs (out of 642 cases from 17 case-series where details are available)	
Adult-onset Still's disease	177 (27. 6%)
Systemic Lupus Erythematosus	71 (11.1%)
Vasculitis	63 (9.8%)
Rheumatic Polymyalgia	44 (6.9%)
Giant Cells Arteritis	32 (5.0%)
Mixed connective diseases (not specified)	31 (4.8%)
Sarcoidosis	21 (3.3%
Rheumatoid Arthritis	17 (2.6%)
Wegener Granulomatosis	14 (2.2%)
Polyarteritis nodosa	13 (2.0%)

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Table 4 Comparison of main diagnostic categories among FUO case-series in 2005–2015 and FUO case-series in 1995–2004

	Old case-series (1995–2004)	New case-series (2006–2014)	*p*-value
N° of patients	1488	3164	–
Male (%)	56,2	49,6	–
Mean age	40,6	45,8	–
Infectious Diseases	545 (37%)	1197 (38%)	0,428
Neoplasm	167 (11%)	366 (12%)	0,731
NIID	236 (16%)	661 (21%)	**< 0,001**
Others	155 (10%)	206 (7%)	**< 0,001**
No diagnosis	385 (26%)	734 (23%)	0,051

Variables with significant statistical association ($p < 0,05$) are in bold

Fusco et al. BMC Infectious Diseases (2019) 19:653
https://doi.org/10.1186/s12879-019-4285-8

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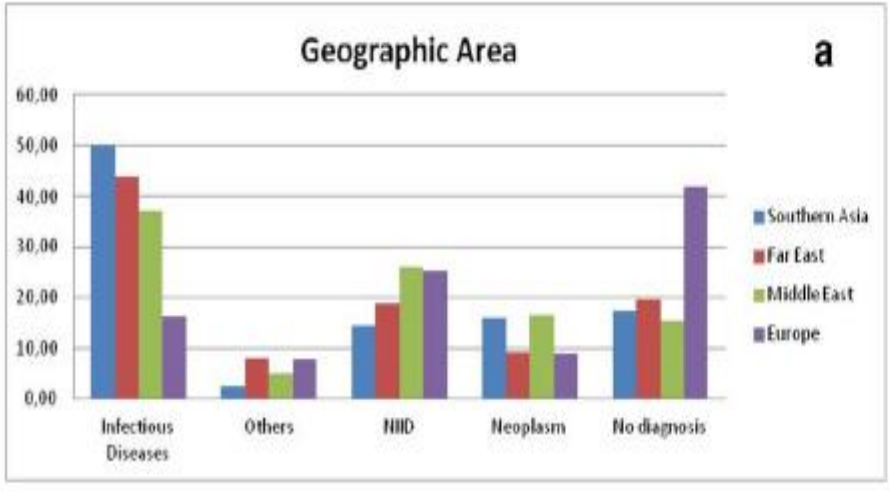
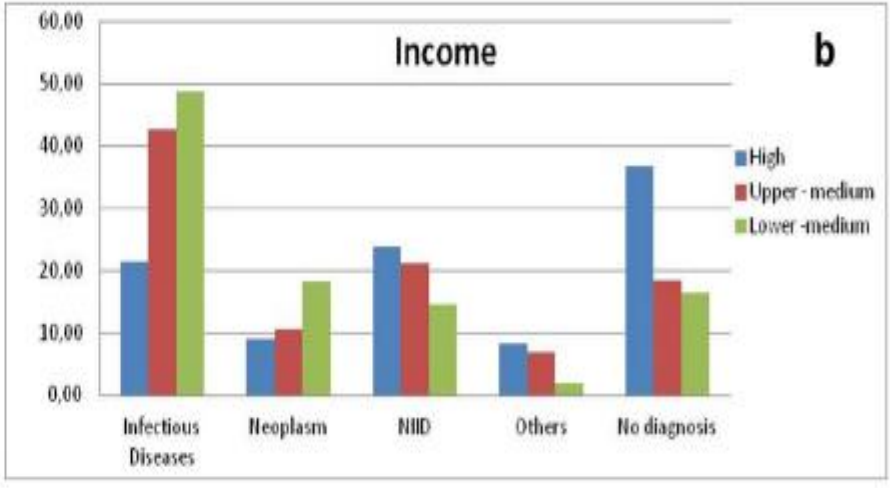




- NIID tanısı, Orta Doğu ve Uzak Doğu Asya'da, G. Asya'dan daha sık
- Avrupa'da NIID, Güney Asya'dan daha sık
- Tanı konmayan NBA, Avrupa'da sık
- Düşük gelir malignite ile ilişkili

Table 1 Fever of Unknown Origin (FUO): Classic Causes

Type of Disorder	Common	Uncommon	Rare
Malignancy/neoplastic disorders	Lymphoma* Hypernephroma/renal cell carcinoma (RCC)	Preleukemia (AML)* Myeloproliferative disorders (MPDs)*	Atrial myxoma Multiple myeloma Colon carcinoma Pancreatic carcinoma Hepatoma CNS metastases Liver metastases Systemic mastocytosis*
Rheumatologic/ inflammatory disorders	Adult Still's disease (juvenile rheumatoid arthritis [JRA])* Giant cell arteritis (GCA)/ temporal arteritis (TA)*	Periarteritis nodosa/ microscopic polyangiitis (PAN/MPA)* Late-onset rheumatoid arthritis (LORA) SLE*	Takayasu's arteritis* Kikuchi's disease* Sarcoidosis (CNS) Felty's syndrome Gaucher's disease Polyarticular gout Pseudogout Antiphospholipid syndrom (APS) Behçet's disease* FAPA syndrome* (Marshall's syndrome)
Miscellaneous disorders	Drug fever* Cirrhosis*	Subacute thyroiditis* Regional enteritis* (Crohn's disease)	Pulmonary emboli (small/multiple) Pseudolymphomas* Rosai-Dorfman disease* Erdheim-Chester disease (ECD)* Cyclic neutropenia* Familial periodic fever syndromes: FMF* Hyper-IgD syndrome* TNF receptor-1-associated periodic syndrome (TRAPS)* Schnitzler's syndrome* Muckle-Wells syndrome* Hypothalamic dysfunction Hypertriglyceridemia (type V)* Factitious fever*

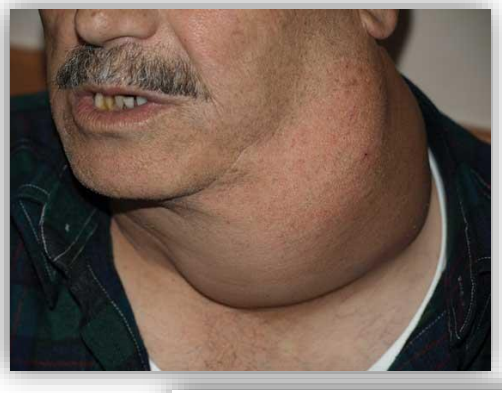
Table 1 Fever of Unknown Origin (FUO): Classic Causes

Type of Disorder	Common	Uncommon	Rare
Malignancy/neoplastic disorders	Lymphoma* Hypernephroma/renal cell carcinoma (RCC)	Preleukemia (AML)* Myeloproliferative disorders (MPDs)*	Atrial myxoma Multiple myeloma Colon carcinoma Pancreatic carcinoma Hepatoma CNS metastases Liver metastases Systemic mastocytosis*

Neoplastik nedenler

Sık

- Lenfoma
- Renal hücreli karsinom

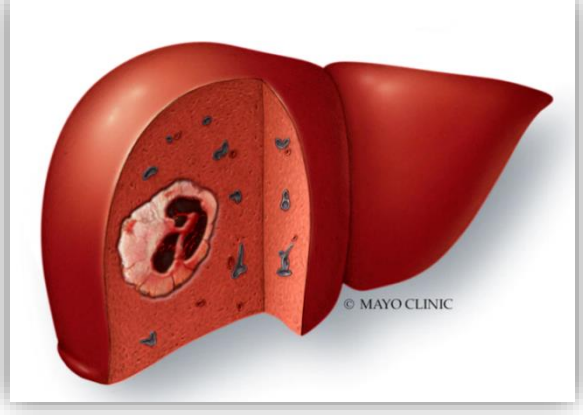


Orta sıklıkta

- AML
- Miyeloproliferatif hastalıklar

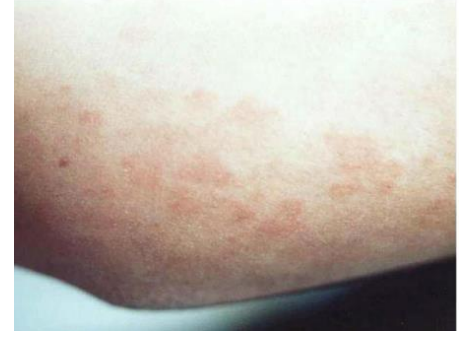
Nadir

- Atrial miksoma
- Hepatoma
- Kolon karsinomu
- Karaciğer metastazı



Rheumatologic/ inflammatory disorders	Adult Still's disease (juvenile rheumatoid arthritis [JRA])* Giant cell arteritis (GCA)/ temporal arteritis (TA)*	Periarteritis nodosa/ microscopic polyangiitis (PAN/MPA)* Late-onset rheumatoid arthritis (LORA) SLE*	Takayasu's arteritis* Kikuchi's disease* Sarcoidosis (CNS) Felty's syndrome Gaucher's disease Polyarticular gout Pseudogout Antiphospholipid syndrom (APS) Behçet's disease* FAPA syndrome* (Marshall's syndrome)

Romatolojik/enflamatuvar nedenler

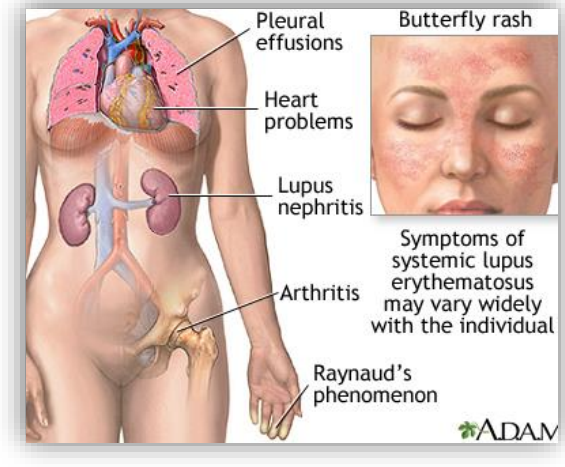


Sık

- Erişkin Still Hastalığı
- Sistemik Lupus (SLE)
- Giant cell arteritis (Temporal arterit)

Orta sıklıkta

- Poliarteritis nodosa (PAN)



Nadir

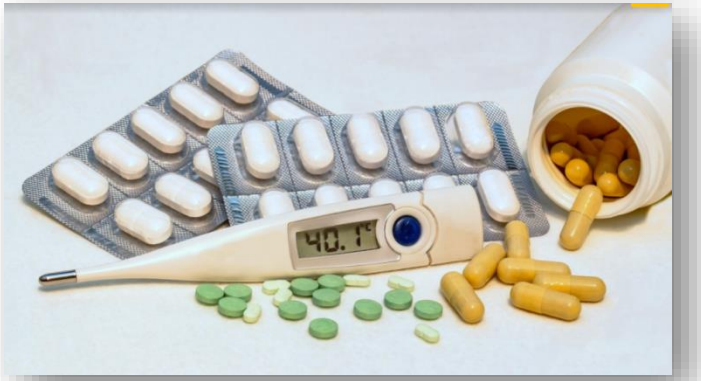
- Takayasu arteriti
- Kikuchi hastalığı
- Sarkoidoz
- Behçet hastalığı

Miscellaneous disorders	Drug fever*	Subacute thyroiditis*	Pulmonary emboli (small/multiple)
	Cirrhosis*	Regional enteritis* (Crohn's disease)	Pseudolymphomas*
			Rosai-Dorfman disease*
			Erdheim-Chester disease (ECD)*
			Cyclic neutropenia*
			Familial periodic fever syndromes:
			FMF*
			Hyper-IgD syndrome*
			TNF receptor-1-associated periodic syndrome (TRAPS)*
			Schnitzler's syndrome*
			Muckle-Wells syndrome*
			Hypothalamic dysfunction
			Hypertriglyceridemia (type V)*
			Factitious fever*

Çeşitli-Diğer nedenler

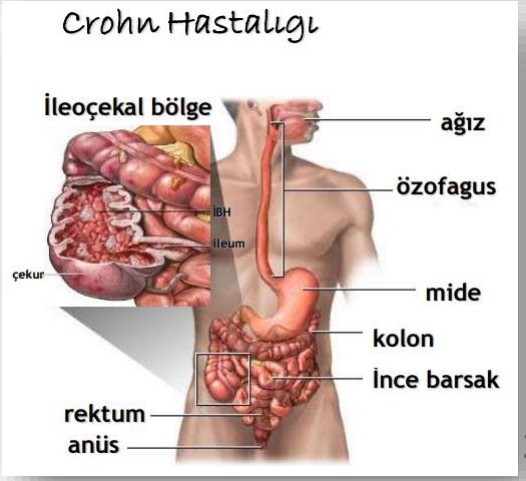
Sık

- İlaç ateşi



Orta sıklıkta

- Subakut tiroidit
- Crohn hastalığı



Nadir

- Pulmoner emboli
- Siklik nötropeni
- Familyal periyodik ateş sendromları
  - FMF, Hiper Ig D sendromu
- Yalancı ateş

Table 1. Broad Categories of Fever of Unknown Origin (FUO).*

Category	Definition and Causes
Classic FUO	FUO despite reasonable initial investigations in the inpatient or outpatient setting; includes FUO in persons with HIV infection who are virally suppressed, with CD4 counts >200 cells/mm^3; causes fall into four categories: infections (e.g., tuberculosis, endocarditis, occult abscesses, Whipple's disease, enteric fever, syphilis [mainly secondary], various zoonoses, and histoplasmosis), cancer, autoimmune and autoinflammatory disorders, and miscellaneous causes
Nosocomial FUO	FUO that develops in hospitalized persons
ICU patients	Causes include infections (bacteremia, pneumonia, *Clostridioides difficile* infection, fungemia, catheter-associated infections, decubitus ulcers), thromboembolic events, acalculous cholecystitis, drug-associated fever, strokes, cerebral hemorrhages, and bleeding
Non-ICU patients	Similar causes to those listed for FUO in ICU setting, although patients are not critically ill
Immunodeficiency-associated FUO	Causes are highly variable, depending on the type of underlying immunodeficiency
Organ-transplant recipients	Causes include viruses, donor-derived infections, *Strongyloides stercoralis* hyperinfection, opportunistic fungal infections, rejection, and in rare cases, GVHD, graft intolerance syndrome (from retained kidney grafts in situ after graft failure), old nonfunctioning arteriovenous grafts after kidney transplantation (may cause occult infection or fever), hemophagocytic lymphohistiocytosis, and ureaplasma-related hyperammonemia syndrome
Patients with neutropenia	High-risk patients with neutropenia are considered to have FUO if they have been febrile for >5 days despite appropriate empirical antibiotic therapy; etiologic diagnosis affected by duration of neutropenia, immunosuppression for GVHD treatment or prophylaxis, and prophylactic antimicrobial therapy
Hematopoietic-cell transplant recipients	Causes before engraftment: similar to causes of neutropenic FUO Causes in early period after engraftment: engraftment itself, opportunistic herpesvirus infections, adenovirus infection, hyperacute GVHD, infectious pneumonia, idiopathic pneumonia syndrome Causes in late period after engraftment: multiple causes, including relapsed cancer; immune reconstitution is not fully restored for approximately 24 mo, and patients remain at risk for infection (e.g., from encapsulated organisms) during that period
Patients with HIV infection not receiving ART, patients with AIDS	Causes include acute retroviral syndrome, mycobacterial infection, endemic mycoses, toxoplasmosis, cryptococcosis, HHV-8 infection (e.g., Kaposi's sarcoma, primary effusion lymphoma, Kaposi's sarcoma herpesvirus inflammatory cytokine syndrome), and lymphoma
Travel-associated FUO	Causes include malaria, enteric fever, leptospirosis, viral hemorrhagic fevers, typhus, and acute undifferentiated febrile illness of tropical countries[24]

NBA, Enfeksiyon dışı nedenler İpuçları-1

- ❑ Ateş, NBA'in her klinik kategorisinde farklılık gösterir

Malignitelerde,

- Ateş nedeni,
  - Pirojenik sitokin üretimi veya
  - Spontan tümör nekrozu (ikincil enfeksiyonlarla birlikte veya bunlar olmadan)
- Kilo kaybı (2kg/hf) ve erken anoreksi ön planda
- ❑ Bazı klinik ipuçları
- Sinovit, Romatizmal/enflamatuvar tanı için düşündürücü
- ❑ Organ tutulum paterni, her hastalıkta tanıyı düşündüren veya dışlayan bir organ tutulumu oluşur
- Karaciğerin korunduğu organ tutulumu, SLE
- Tek başına hepatomegali, subakut IE dışlanır (splenomegali olur)

NBA, Enfeksiyon dışı nedenler İpuçları-2

- Öyküde;
- Sıcak banyo sonrası kaşıntı malignite akla getirmeli!!!
- Adenopatide malignite!!
- Belirgin artralji-miyalji, romatizmal/enflamatuvar hastalık
- Kuru öksürük, dev hücreli arterit/temporal arterit için ipucu!!!!
- Oral ülser varlığı, Behçet veya SLE…
- Eklem semptomları ve jeneralize LAP, ESH veya SLE
- Taşlı kolesistit varlığı, PAN veya SLE için ipucu!!!!
- Behçet hastalığında aile hikayesi önemli

NBA, Enfeksiyon dışı nedenler İpuçları-3

- ❑ Öykü; belirli bir kategoriye yönlendirmedi ise
- Periyodik ateş; siklik nötropeni ipucu olabilir
- LAP; Kikuchi veya Rosai Dorfman
- Boyun-çene ağrısı; subakut tiroidit
- Tıbbi personelde yapay ateş????
- Rejionel enterit (IBS), ilaçlar (uyuşturucu dahil..) ve alkolizm (siroz) sorgulanmalı
- Bilinmeyen bazı ateşler ailesel olabilir, FMF veya Hiper Ig D sendromu

❑ Hektik lenfoma ateşi, enfeksiyon ile karışabilir???

❑ Rölatif bradikardi lenfoma ve SSS tümörü olabilir

❑ Göz muayenesi önemli,

- Roth lekesi; lenfoma, atrial miksoma
- Sitoid cisim, atrial miksoma
- Retinal kanama, prelösemi

Tanı için fundoskopik muayene erken dönemde önerilir

NBA, Enfeksiyon dışı nedenler İpuçları-4

- Romatizmal/enflamatuvar NBA ipuçları????

- Sabah ateşi varlığı; PAN için önemli…
- Günde iki kez yükselen ateş; SLE
- Döküntü varsa; SLE, Sarkoidoz düşünülmeli….
- Nabızda eşitsizlik, azalma, kladikasyo; Takayasu arteriti
- Lakrimal bez büyümesi; geç başlangıçlı RA, SLE
- Retina arteri oklüzyonu; Takayasu arteriti, Temporal arterit, PAN, SLE
- Kan kültürü negatif olan bir üfürüm; Libman-Sacks endokarditi???
- Epididimit, epididimal nodul; PAN, SLE veya Sarkoidoz

NBA, Enfeksiyon dışı nedenler İpuçları-5

- Sternal hassasiyet, Kİ boz. işareti, prelösemi
- İzole HM; hepatoma, renal hc Ca ve KC metastazı????
- Splenomegali, rejyonel enterit, siroz ve Hiper Ig D sendromu için ipucu !!
- Yalancı ateşte, ateşe rağmen iyi görünüm, birden fazla hastaneye yatış, kadın
- Öncesinde viral enfeksiyon hikayesi ve sedimantasyon yüksekliği; subakut tiroidit
- 21-28 gün aralık ile tekrarlayan ateş ve nötropeni, siklik nötropeni
- İlaç ateşi ve yapay ateşte rölatif bradikardi!!!

Table 4. Drug-Related Causes of Classic FUO.*

Type of Drug Reaction	Usual Time to Onset of Fever	Commonly Implicated Drugs or Other Agents
Hypersensitivity reaction	7–10 days	Antimicrobial agents (beta-lactams, sulfonamides, minocycline), allopurinol, anticonvulsants (phenytoin, carbamazepine), methyldopa, heparin, quinidine, quinine
Chemotherapy-related reaction	3–19 hr	Chemotherapeutic agents (cytosine arabinoside, bleomycin, chlorambucil, vincristine, cisplatin), molecular targeting agents for melanoma (dabrafenib, trametinib)
Infusion-related reaction	0.5–3.0 hr	Amphotericin B formulations, vancomycin, bleomycin, vaccines, monoclonal antibodies
DRESS	2–6 wk	Sulfonamides, carbamazepine, allopurinol, lamotrigine, phenytoin
Hyperthermia syndromes		
Serotonin syndrome	6 hr–several days†	Selective serotonin-reuptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline Serotonin–norepinephrine reuptake inhibitors: duloxetine, trazodone, desvenlafaxine, levomilnacipran, milnacipran, venlafaxine Tricyclic antidepressants: amitriptyline, nortriptyline MAO inhibitors: nonselective irreversible inhibitors (phenelzine, tranylcypromine), nonselective reversible inhibitors (linezolid), selective irreversible MAO type A inhibitor (methylene blue), selective irreversible MAO type B inhibitor (selegiline) Antiemetic agents: ondansetron, metoclopramide Serotonin receptor agonists: psychedelics (LSD), fentanyl, buspirone, triptans, lithium Herbal products: St. John's wort, Syrian rue (harmine and harmaline) Cytochrome P-450 inhibitors‡: fluoxetine, ciprofloxacin, ritonavir, fluconazole, sertraline
Malignant hyperthermia	0.5–2.0 hr	Depolarizing muscle relaxants: succinylcholine Inhalation anesthetics: halothane, sevoflurane, isoflurane, desflurane
Neuroleptic malignant syndrome	1–2 wk	Antipsychotic agents: haloperidol, quetiapine, olanzapine, risperidone Antiemetic agents: metoclopramide, prochlorperazine Parkinsonism–hyperpyrexia syndrome: abrupt withdrawal of dopamine agonists or nondopaminergic agents (amantadine)
Adrenergic fever	Variable	Sympathomimetic agents and MAO inhibitors: theophylline, cocaine, MDMA (ecstasy)
Anticholinergic fever	About 2 hr	Anticonvulsants: carbamazepine Antiemetics: scopolamine, promethazine, prochlorperazine Muscle relaxants: cyclobenzaprine, methocarbamol, carisoprodol Herbal agents: belladonna, jimsonweed (datura), lupin Antidepressants: amitriptyline, imipramine, nortriptyline
Mitochondrial uncoupling of oxidative phosphorylation	0.5–3.0 hr	Pesticides and toxins: organochlorine compounds, snake venom–derived phospholipases Salicylates: high-dose aspirin

İlaç ateşine neden olabilen ilaçlar

Kardiovasküler	• **Alfametildopa** • **Kinidin**	• **Prokainamid** • **Hidralazin**	• **Nifedipin** • **Oksprenolol**
Antimikrobiyal	• Penislin G • Ampisilin • Metisilin • Kloksasilin • Sefalotin • Sefamandol • Sefapirin	• Tetrasiklin • Linkomisin • Sulfonamid • TMP-SXT • Streptomisin • Vankomisin	• Kolistin • İzoniazid • Paraaminosalisilik asit • Nitrofurantion • Mebendazol
Antineoplastik	• Bleomisin • Daunorubisin • Prokarbazin	• Sitarabin • Streptozosin • 6-merkaptopurin	• L-Asparaginaz • Klorambusil • Hidroksiüre
MSS ilaçları	• Difenilhidantoin • Karbamazepn • Klorpromazin • Nomifensin	• Haloperidol • Triamteren • Benztropin • Thioridazin	• Trifluoperazin • Amfetamin • Liserjik asit
Anti-inflamatuar	• İbuprofen	• Tolmetin	• Aspirin
Diğerleri	• İodide • Simetidin • Levamizol • Metklopramid	• Klofibrat • Allopurinol • Folat • Prostoglandin E2	• Ritodrin • İnterferon • Propiltiyourasil

Klinik bulguların enfektif ve non-enfektif ayırıcı tanıdaki yeri?

Table 2

Patients' demographic characteristics, history, symptoms and signs in the derivation cohort. Values represent number of subjects (%) or mean ± standard deviation (OR, odds ratio; MD, mean difference for infectious versus non-infectious cause; 95% CI, 95% confidence intervals).

Patients' characteristics	Overall ($n=112$)	Infectious ($n=34$)	Non-infectious ($n=78$)	p value	OR or MD	95% CI
Age (years)	56.5 ± 11.2	55.2 ± 8.7	57.0 ± 10.4	0.19	−1.8 ± 0.7	−3.7, 1.1
Male sex (%)	61 (54.5)	17 (50)	44 (56.4)	0.53	0.78	0.34, 1.73
Duration of fever before admission (days)	32.1 ± 11.9	30.0 ± 8.3	33.1 ± 9.5	0.09	−3.1 ± 0.8	−5.2, 1.0
Duration of hospitalization (days)	25.5 ± 14.8	24.5 ± 11.9	26.2 ± 11.9	0.13	−1.7 ± 1.1	−4.9, 1.2
History						
Episodic fever	37 (33.0)	8 (23.5)	29 (37.2)	0.19	0.52	0.21, 1,30
High risk travel	16 (14.3)	7 (20.6)	9 (11.5)	0.24	1.99	0.67, 5.87
Contact with animals	15 (13.4)	5 (14.7)	10 (12.8)	0.50	1.17	0.37, 3.73
Symptoms and signs						
Murmur	31 (27.7)	15 (44.1)	16 (20.5)	0.01	3.05	1.28, 7.32
Rash	20 (17.9)	2 (5.9)	18 (23.1)	0.03	0.21	0.05, 0.96
Arthritis	33 (29.5)	4 (11.8)	29 (37.2)	0.01	0.22	0.07, 0.70
Lymph node enlargement	29 (25.9)	4 (11.8)	25 (32.1)	0.03	0.28	0.09, 0.89
Hepatomegaly	27 (24.1)	5 (14.7)	22 (28.2)	0.15	0.44	0.15, 1.28
Splenomegaly	25 (22.3)	6 (17.6)	19 (24.4)	0.47	0.67	0.24, 1.85
Vein thrombosis	9 (8.0)	2 (5.9)	7 (9.0)	0.72	0.63	0.12, 3.22
Cough	10 (8.9)	3 (8.8)	7 (9.0)	0.64	0.98	0.24, 4.04
Headache	21 (18.8)	5 (14.7)	16 (20.5)	0.60	0.67	0.22, 2.00
Muscle pain	23 (20.5)	4 (11.8)	19 (24.4)	0.20	0.41	0.13, 1.33

Tanı yaklaşımı

NBA, Enfeksiyon dışı nedenler
Tanı yaklaşımı

- Dikkatli bir öykü, fizik muayene ve nonspesifik temel laboratuvar testleri
  - Tam kan
  - Biyokimya
  - Sedim, CRP, Ferritin…
- Radyolojik tetkikler
  - Grafi, USG, MR, BT, Galyum-Indium sintigrafi
  - PET CT, 18 FDG PET-CT tarama
  - Eko
- İnvaziv prosedürler
  - Biyopsi, laparotomi..
- Yeni tanı yöntemleri
  - Yeni jenerasyon exon dizileme, genetik mutasyon belirleme

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Minimal başlangıç NBA

Cilt, eklemler, lenf bezi, ilaç geçmişi (antibiyotikler dahil), seyahat, besin maruziyeti (örn. pastörize edilmemiş süt) ve hayvan maruziyetine dikkat edilerek ayrıntılı hasta öyküsü ve fizik muayene

↓

Hasta stabil ve nötropenik değil ise antibiyotiği stoplayın
Hastaneye yatış ihtiyacını değerlendirin

↓

Minimal NBA değerlendirme

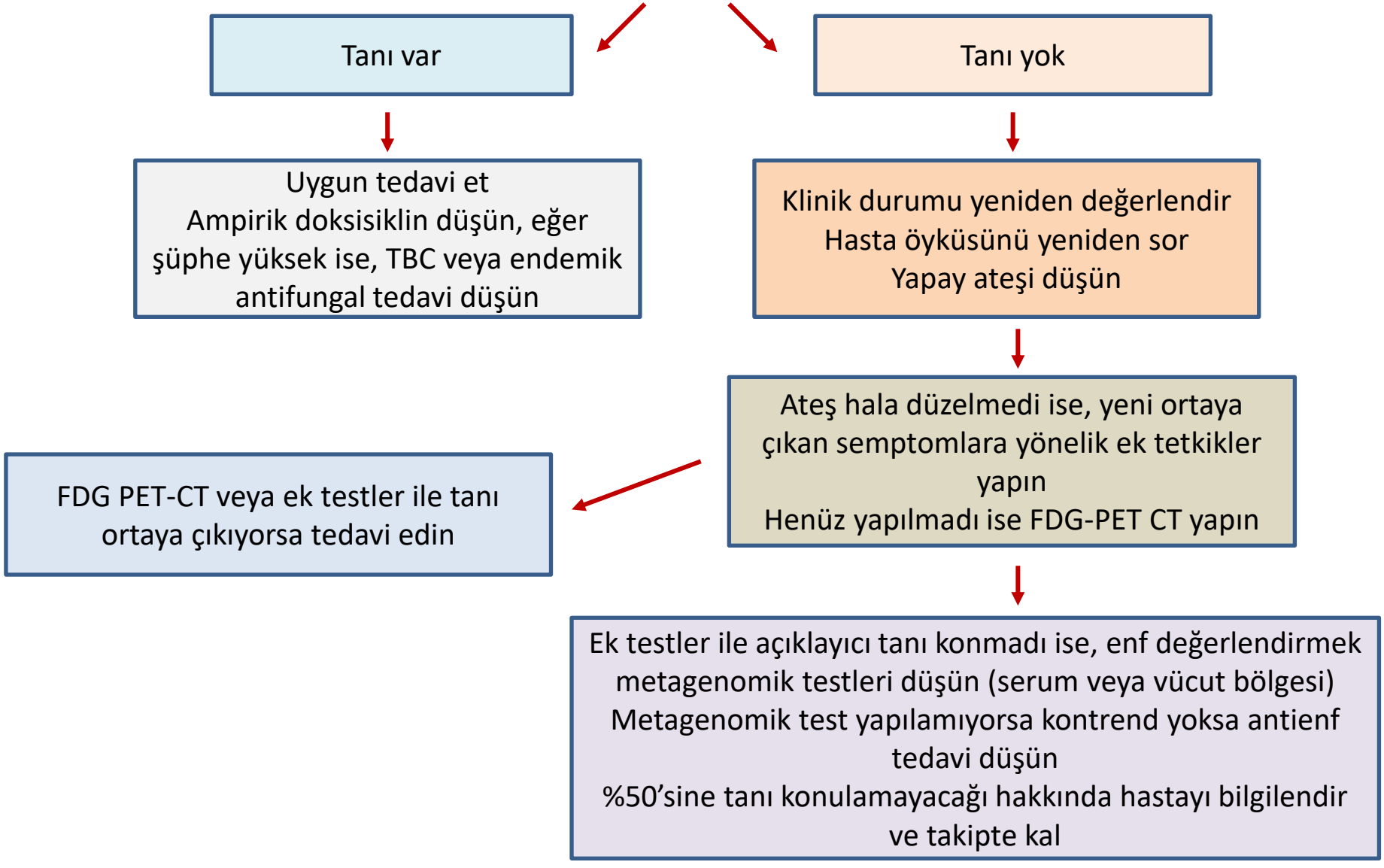
Temel lab testleri (CBC, metabolik panel), kan kült, HIV için seroloji, EKO, semptom ve muayene temelinde göğüs, batın, pelvis ve diğer bölgelerin BT görüntüleme, ESR ve CRP
Yeni ve potansiyel rahatsız edici ilaçları kesmeyi düşün

İleri NBA değerlendirme

Öykü, FM, epidemiyoloji, maruziyet, minimal lab testleri ve görüntüleme, zoonotik ve endemik mikoz, hepatit virüs testlerine ek olarak TBC testleri veya romatolojik veya tiroid hast. için tetkikler (RF, ANA, TSH..)
Biyopsi düşün (Rash, temporal arter, lenf nodu, kitle veya diğer lezyonlar)

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE



Laboratuvar testler

FUO Infectious Disease Tests	FUO Neoplastic Disease Tests	FUO Rheumatic/Inflammatory Tests	Miscellaneous Other Tests
Blood tests (if suspected by history and physical examination)			
• Q fever IgM/IgG titers	• Ferritin*	• ANA*	• TFTs
• *Brucella* IgM/IgG titers	• LDH*	• Ds DNA	(Thyroid function tests)
• *Bartonella* IgM/IgG titers	• B_{12} levels	• ACE*	If subacute thyroiditis suspected
• *Salmonella* IgM/IgG titers	• ACE*	• Antiphospholipid antibodies	ATAs
• EBV IgM/IgG titers	• β_2 microglobulins	• Anti-CCP titers	(Antithyroid antibody tests)
• CMV IgM/IgG titers		• Ferritin*	If subacute thyroiditis suspected
• HHV-8 IgM/IgG titers			• GGTP
Culture-positive endocarditis (SBE)			If alcoholic cirrhosis suspected
Blood Cultures			• B_{12} levels
Culture-negative endocarditis (CNE)			If alcoholic cirrhosis suspected
TTE shows a vegetation			• MEFV gene studies
plus			If FMF suspected
negative blood cultures			
plus			

*Repeat if already done.

Radyolojik testler

FUO Infectious Disease Tests	FUO Neoplastic Disease Tests	FUO Rheumatic/Inflammatory Tests	Miscellaneous Other Tests
Radiologic tests (if suspected by history, physical examination, or nonspecific tests) • TTE If blood cultures positive for endocarditis pathogen • TEE If PVE, atrial myoma, or CNE marantic endocarditis suspected • CT/MRI abdomen/pelvis† If intra-abdominal/pelvic infection suspected • Gallium/indium scan If occult infection suspected • Panorex film of jaws If apical root abscess suspected	• CT/MRI abdomen/pelvis If intra-abdominal/ pelvic neoplasm suspected • Gallium/indium scan If neoplasm suspected • PET-CT scan If occult neoplasm suspected	• CT/MRI abdomen If hepatomegaly/ splenomegaly or retroperitoneal adenopathy suspected	• Abdominal CT scan If regional enteritis (Crohn's disease) suspected • Gallium/indium scan If regional enteritis (Crohn's disease) suspected • Chest CT (pulmonary embolus protocol) If pulmonary emboli suspected • CT-PET scan If Erdheim-Chester disease suspected (bone involvement, periaortic fibrosis or "coated aorta")

İnvaziv işlemler

Table 3 Continued

FUO Infectious Disease Tests	FUO Neoplastic Disease Tests	FUO Rheumatic/Inflammatory Tests	Miscellaneous Other Tests
• Naprosyn test If FUO DDx *infection* vs *Malignancy* suspected • Anergy panel/PPD or T-spot If TB suspected • BM biopsy/culture If miliary TB, SBE, brucellosis, Q fever, typhoid/enteric fevers suspected	• Naprosyn test If FUO DDx infection vs *malignancy* suspected • BM biopsy If myelophthisic anemia/ abnormal WBCs • β-2 microglobulins If lymphoma suspected	• Temporal artery biopsy If GCA/TA suspected • Low-dose steroids If PMR suspected (prednisone 10 mg/day diagnostic for PMR) • ASA therapy If adult Still's disease (JRA) suspected	

- Naprosyn testi, tartışmalı !!!
- Ampirik steroid tedavisi,
  - Ateş ve döküntüyü maskeleyebilir
  - Temporal arterit veya Polimiyaljika romatika düşünülüyorsa başla *

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Original article

Fever of unknown origin: Discrimination between infectious and non-infectious causes

Stamatis P. Efstathiou *, Angelos V. Pefanis, Aphrodite G. Tsiakou, Irini I. Skeva, Dimitrios I. Tsioulos, Apostolos D. Achimastos, Theodore D. Mountokalakis

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- **C-reaktif protein, ferritin ve eozinofil sayısı** kombinasyonu, klasik FUO nedeniyle hastaneye yatırılan hastalarda enfeksiyöz ve enfeksiyöz olmayan nedenleri ayırt etmede faydalı
- ≥2'sinin varlığı %91,4 duyarlılık ve %92,3 özgüllük ile enf lehine

Table 4
Multiple regression analysis for diagnosis of infection in the derivation cohort (OR, odds ratio; 95% CI, 95% confidence intervals).

Variables	Parameter estimate	Standard error	*p* value	OR	95% CI
Positive antinuclear antibodies	0.48	0.29	0.09	1.61	0.88, 2.82
Hypergammaglobulinemia	−0.56	0.31	0.08	0.57	0.31, 1.52
C-reactive protein>60 mg/L	2.49	0.63	<0.001	6.02	2.50, 9.75
Ferritin<500 μg/L	0.98	0.39	0.01	2.51	1.30, 5.21
Eosinophils<40/mm^3	1.51	0.38	<0.001	4.10	2.02, 7.34
Murmur	−0.17	0.22	0.44	0.85	0.55, 1.49
Arthritis	−0.57	0.30	0.07	0.66	0.24, 1.11
Lymph node enlargement	−0.66	0.32	0.08	0.61	0.28, 1.14
Rash	−0.19	0.22	0.39	0.83	0.54, 1.68

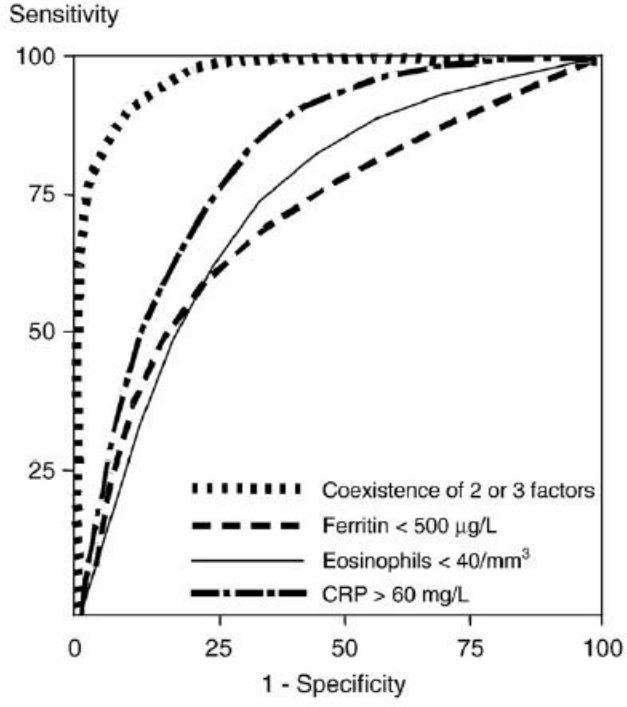

Fig. 1. Discriminatory capacity of the model and its components in the validation cohort.

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Diagnostic use of serum ferritin levels to differentiate infectious and noninfectious diseases in patients with fever of unknown origin

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Table 3
Laboratory findings [median (IQR)], (Kruskal–Wallis test)

	Infectious diseases ($n = 11$)	Hematologic diseases ($n = 13$)	Noninfectious inflammatory diseases ($n = 20$)	p-value*
ESR (mm/hr)	60 (24–71)	60.5 (32.3–90.8)	84.5 (44–102.8)	0.28
CRP (mg/dL)	7.6 (2.8–15.0)	8.0 (3.3–19.3)	11.1 (3.2–17.7)	0.89
Ferritin (ng/mL)	282.4 (149.0–951.8)	1818.2 (485.4–4789.5)	563.7 (399.6–1927.2)	0.048†
Hemoglobin (g/dL)	9.5 (9.4–10.1)	9.6 (9.4–9.8)	9.5 (9.4–10.7)	0.58
WBC count ($\times 10^3/mm^3$)	11.5 (10.3–14.3)	11.1 (9.1–13.3)	11.7 (9.2–13.2)	0.76
Granulocyte count ($\times 10^3/mm^3$)	7.7 (5.4–15.0)	6.9 (3.55–16.15)	7.45 (3.78–11.48)	0.78
Lymphocyte count ($\times 10^3/mm^3$)	5.12 (4.0–11.82)	4.5 (1.67–12.93)	5.8 (2.01–8.93)	0.80
Monocyte count ($\times 10^3/mm^3$)	1.5 (0.92–1.81)	1.33 (0.7–1.88)	1.27 (0.81–1.56)	0.59
Eosinophil count ($\times 10^3/mm^3$)	0.6 (0.31–1.1)	0.62 (0.32–1.22)	0.49 (0.2–0.77)	0.71
Platelet count ($\times 10^3/mm^3$)	0.02 (0.0–0.67)	0.02 (0.0–0.55)	0.02 (0.0–0.1)	0.12

*Statistical analysis was performed using the Kruskal–Wallis test; †Statistically significant differences were found between infectious diseases and hematologic diseases ($p = 0.049$), as well as infectious diseases and non-infectious inflammatory diseases ($p = 0.04$) using the Mann–Whitney test. However, there was no significant difference between hematologic diseases and NIID ($p = 0.25$).

- **Ferritin** testinde, bulaşıcı hastalıklar ve hematolojik hastalıklar (p = 0.049)
- Bulaşıcı ve bulaşıcı olmayan enflamatuar hastalıklar (p = 0.04) arasında istatistiksel olarak anlamlı farklılıklar saptandı

Table 3 General characteristics of infectious and non-infectious diseases in retrospective population

Variables	ID (*n*=157)	NID (*n*=118)	*P* value
Age (years), median (interquartile range)	48 (34, 58)	43 (26, 59)	0.107
Male, *n* (%)	88 (56.1%)	49 (41.5%)	0.017
White blood cell count (×1000/mm^3)	6.37 (4.56, 10.82)	6.36 (3.72, 10.06)	0.298
Percentage of neutrophil (%)	73.60 (64.20, 84.80)	72.45 (60.05, 83.60)	0.497
Erythrocyte sedimentation rate (mm/h)	38.0 (14.0, 74.0)	43.5 (14.3, 74.0)	0.639
C-reactive protein (mg/L)	58.8 (25.0, 109.0)	53.8 (18.0, 110.9)	0.629
Procalcitonin (ng/ml)	0.25 (0.10, 0.60)	0.22 (0.12, 0.47)	0.627
Ferritin (μg/L)	474.0 (250.5, 1240.0)	1114.2 (463.5, 5655.8)	<0.001
Lactate dehydrogenase (U/L)	211.0 (164.0–331.0)	373.5 (197.3, 608.5)	<0.001
T-SPOT.TB positivity, *n* (%)	43 (27.4%)	8 (6.8%)	<0.001
Antinuclear antibodies positivity, *n* (%)	4 (2.5%)	27 (22.9%)	<0.001
Anti-neutrophilcytoplasm antibodies positivity, *n* (%)	1 (0.6%)	3 (2.5%)	0.317
Rheumatoid factor positivity, *n* (%)	5 (3.2%)	5 (4.2%)	0.749
Chills, *n* (%)	64 (40.8%)	37 (31.4%)	0.109
Muscle pain, *n* (%)	43 (27.4%)	43 (36.4%)	0.109
Lymph node enlargement, *n* (%)	25 (15.9%)	43 (36.4%)	<0.001
Hepatomegaly and/or splenomegaly, *n* (%)	37 (23.6%)	48 (40.7%)	0.002
Multi-cavity effusion, *n* (%)	33 (21.0%)	37 (31.4%)	0.051

ID: infectious diseases; NID: non-infectious diseases

Non-enfeksiyoz hastalıklarda;
- Ferritin yüksek
- LDH yüksek
- ANA yüksek

Enf ve non-enfeksiyoz hastalıklar arasında;
- WBC, nötrofil yüzdesi
- Sedimantasyon
- CRP, PCT açısından fark yok

Man-zhi ZHAO, Current Medical Science. 2019, 39(4):589-596

Retrospective analysis of 1,641 cases of classic fever of unknown origin

Guanyu Zhou, Ying Zhou, Cejun Zhong, Hui Ye, Zhenzhen Liu, Yanbin Liu, Guangmin Tang, Junyan Qu, Xiaoju Lv

Table 5 Methods by which the diseases were diagnosed

Type of disease	Laboratory investigation (%)	Radiographic investigation (%)	Invasive investigation (%)	Diagnostic treatment (%)	Total
Infectious diseases	257 (32.16)	216 (27.03)	90 (11.26)	236 (29.55)	799
Connective tissue diseases	164 (51.90)	0 (0)	74 (23.42)	78 (24.68)	316
Neoplastic diseases	0 (0)	53 (19.06)	225 (80.94)	0 (0)	278
Other diseases	19 (17.12)	27 (24.32)	5 (4.50)	60 (54.06)	111
Total	440 (29.25)	296 (19.68)	394 (26.19)	374 (24.88)	1,504

Note: diagnostic treatment includes drug discontinuance and clinical observation.

- Kollojen doku hast.'da lab tetkikler,
- Neoplastik hast.'da invaziv yöntemler daha fazla oranda tanı konduğu saptanmış

Non-enfektif NBA'de ^{18}FDG- PET CT yeri

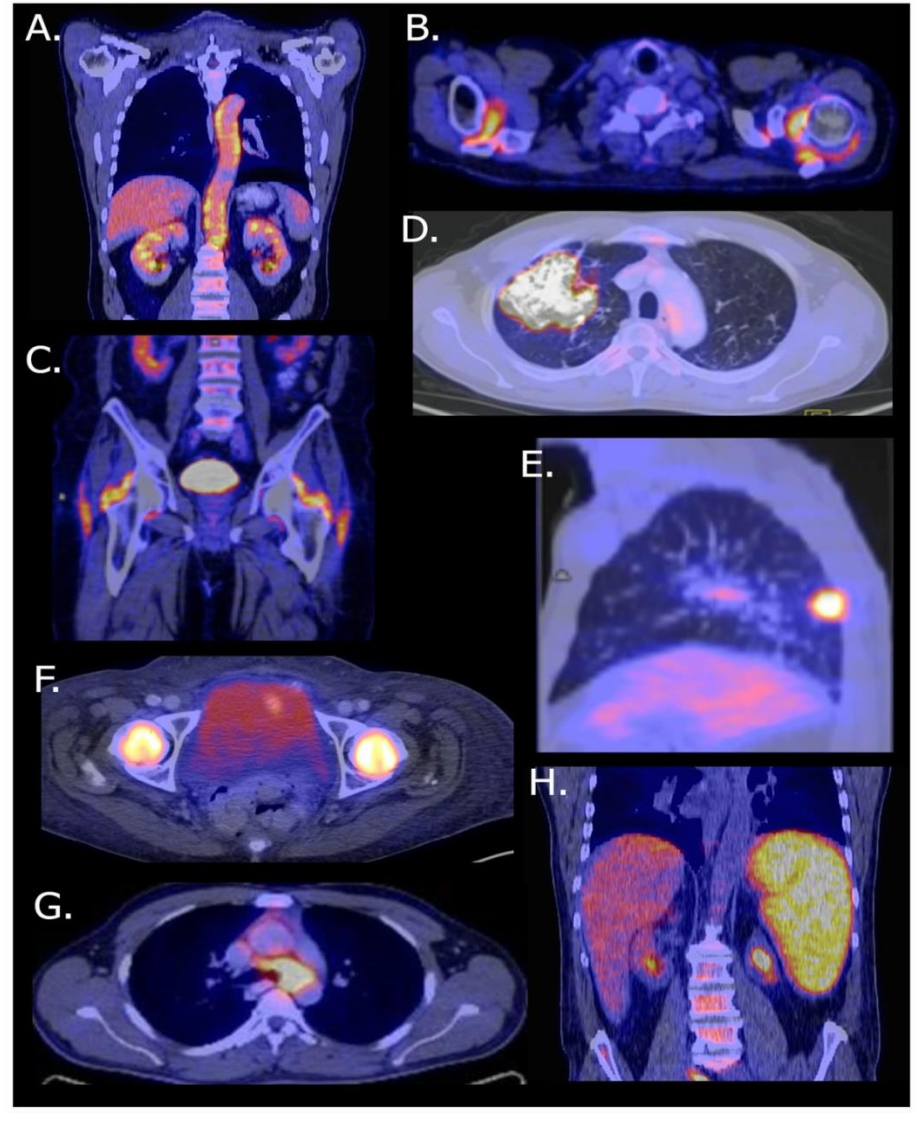
- Non invaziv görüntüleme yöntemi
- NBA tanısında, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG- PET CT), enfeksiyon ve malignitelerde artan glikolizi tespit eder
  - Duyarlılığı %86-98
  - Özgüllüğü %52-85
- Performans, enfeksiyon veya neoplazm olan hastalarda, otoimmün rahatsızlıkları olanlara göre daha iyi
- FDG PET-CT ayrıca BT'siz PET ve galyum veya lökosit sintigrafisi gibi diğer nükleer görüntüleme yöntemlerinden daha üstün
- Anatomik lokalizasyonu iyi gösterir
- Dezavantajı, maliyeti ve her merkezde olmaması

Non-enfektif NBA'de ^{18}FDG- PET CT yeri

Ga, In ve Tc işaretli lökosit sintigrafileri ile kıyaslandığında;

- Santral iskelet tutulumunu göstermede daha etkin
- Enjekte edildiği zaman ile kısa sürede tanı konma imkanı
- Daha az radyasyon
- Daha az nefrotoksisite
- Daha erken tanı konmasına olanak sunar

Temporal arteritte negatif sonuç olması, biyopsi yapmayı dışlatmaz



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journal homepage: www.elsevier.com/locate/ijid

Diagnostic contribution of ^{18}F-FDG-PET/CT in fever of unknown origin

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[b] School of Medicine, Koç University, Istanbul, Turkey

- 25 hasta;
- 18 F-FDG-PET tetkiki ile hastaların %60'ında ateş nedeni kesin olarak saptandı
- Testin tahmini doğruluk oranı %90,5, duyarlılık %93.8, özgüllük %80
- Vaka sayısı az, geniş çalışmalara gereksinim

Journal of
Clinical Medicine

MDPI

Article

Place of the ^{18}F-FDG-PET/CT in the Diagnostic Workup in Patients with Classical Fever of Unknown Origin (FUO)

Simon Letertre [1], Pierre Fesler [1,2], Laetitia Zerkowski [1], Marie-Christine Picot [3], Jean Ribstein [1], Philippe Guilpain [4,5], Vincent Le Moing [6], Denis Mariano-Goulart [2,7] and Camille Roubille [1,2,*]

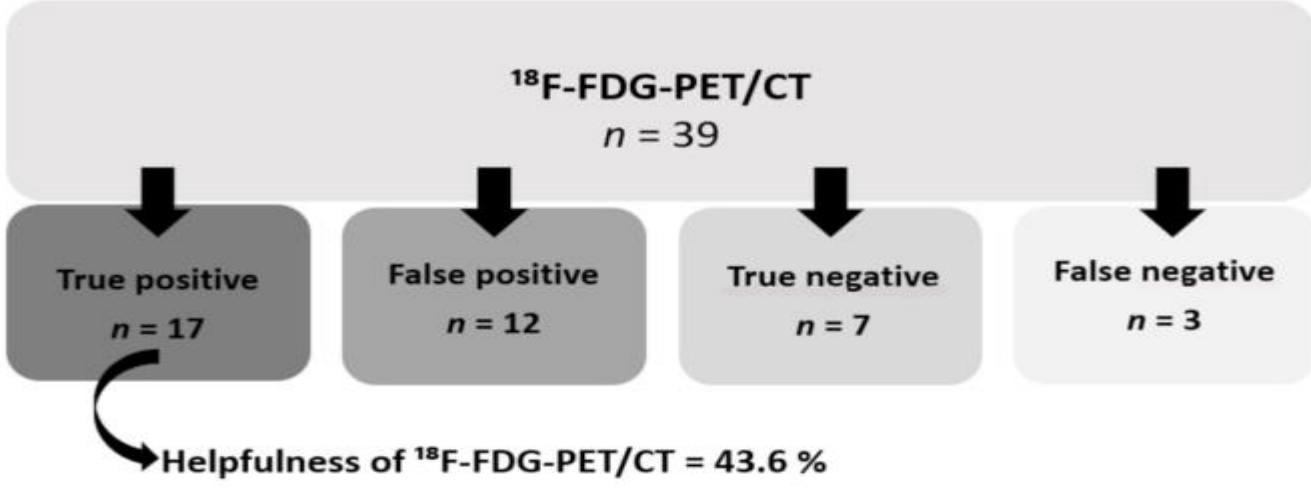

Figure 3. Diagnostic contribution of ^{18}F-FDG-PET/CT.

^{18}F-FDG-PET/CT,

- NIID %41'i,
- Enfeksiyon hast %66,7'si,
- Malignitelerin tümüne tanıda katkı sağladı

J Clin Med. 2021 Sep; 10(17): 3831

İnvaziv yöntemler

Biyopsi,

Cilt, periton, lenf nodu, kemik iliği, organ, temporal arter…

- 2012 yılındaki bir çalışmada, biyopsi ile tanı oranı %42
- Biyopsiler için NPV ve PPV sırasıyla %85 ve %100

Mete B. *Int J Med Sci* 2012; 9(8):682-689

Laparatomi/laparaskopi,

- Gelişmiş tanısal görüntüleme sonrası artık sık uygulanmıyor
- Solid kanser, peritoneal karsinomatozis ve lenfoma'da

Özet olarak aklımızda ne kalmalı?

- NBA non-enfektif etiolojiler; coğrafi bölge, yaş, cinsiyet ve yıllara göre değişkenlik göstermekte
- Öykü, fizik muayene ve ipucu semptomları non-enfektif tanılar için de önemli
- Multidisipliner yaklaşım, Dahiliye ve radyoloji bilgisi !!!!

- Tanısal laboratuvar tetkikler, görüntüleme (USG, BT, MR) yöntemleri, gerekli durumda biyopsi ve tanısal invaziv işlemler
- 18FDG PET-CT, enfeksiyon ve malignitelerde tanı oranı daha iyi ve erken bakılmalı

- Neoplastik hastalıklarda; lenfoma, renal hücreli karsinom
- Non-enfektif enflamatuvar hastalıklarda; gençlerde ESH ve SLE, yaşlılarda TA
- Çeşitli nedenler; İlaç ateşi, subakut tiroidit, yalancı ateş
- Yoğun bakım hastalarında tromboemboli, ilaç ateşi, hemoraji