Title

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Journal

Heart & lung : the journal of critical care, 16(2)

ISSN

0147-9563

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Publication Date

1987-03-01

Peer reviewed

How to differentiate neoplastic fever from infectious fever in patients with cancer: Usefulness of the naproxen test

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Fever of undetermined origin (FUO) in patients with neoplastic diseases is a major clinical challenge, requiring a great deal of the physician's time and expertise, as well as incurring much medical expense. The initial definition of FUO by Petersdorf and Beeson[1] in 1961 is generally accepted. The term has been used only in reference to patients who have a temperature elevation above 101° F for at least 3 weeks and for whom a diagnosis cannot be established during at least 1 week of an in-hospital investigation. These rigid criteria usually have excluded many identifiable fevers from the FUO category. In addition, over the past two decades the advancement of medical knowledge and technology has further diminished the number of genuine FUOs. Nevertheless, more difficult cases of FUO are often encountered now, especially in immunocompromised patients after chemotherapy.

Fever is generally an indication of infection. However, other diseases, such as neoplastic diseases, immunologic diseases, allergic reactions, granulomatous diseases, inherited diseases, and factitious disease, have been known on occasion to produce fever in the absence of infection[2-4] (Table I). These diseases occupy a more prominent position among FUOs now than in the 1950s and 1960s.

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Presented at the Integrated Grand Rounds of the Department of Medicine of Wright State University School of Medicine on Feb. 6, 1986. These rounds are under the directorship of the chairman of the department, H. Verdain Barnes, MD. Participants of the conference consisted of the faculty of the department, medical residents, and medical students.

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FEVER IN THE PATIENT WITH CANCER

In this era of intensive chemotherapeutic approaches for neoplastic diseases, infection is the most common cause of fever, but it is not uncommon to see febrile patients with cancer in whom there is no evidence of infection even after an extensive investigation.

The evaluation of cancer patients with FUO should include a careful clinical history, complete physical examination, complete blood cell and platelet counts, urinalysis and cultures, chest roentgenogram, adequate blood cultures, and other appropriate smears and cultures of sputum, stool, spinal fluid, and discharges from local lesions. Depending on the clinical findings, further specific studies, such as gallium scan, computed tomography scan, lung biopsy, bone marrow biopsy, muscle biopsy, and laparotomy, may also be necessary.

A particularly difficult situation is a febrile

Table I. Selected diseases causing fever

Diseases	*Examples*
Infections	Bacterial
	Viral
	Fungal
	Parasitic
Neoplastic diseases	Leukemias
	Hodgkin's disease
	Non-Hodgkin's lymphomas
	Solid tumors
Immunologic diseases	Systemic lupus erythematosus
	Mixed connective tissue disease
Allergic reactions	Drug fever
	Transfusion reaction
Granulomatous diseases	Regional enteritis
	Sarcoidosis
Inherited diseases	Familial Mediterranean fever
	Fabry's disease
Factitious disease	

state in a patient with severe granulocytopenia caused by either the disease itself or bone marrow suppression resulting from chemotherapy. Although the likelihood of infection is high, it is well documented that in about 30% to 50% of febrile granulocytopenic patients, the infectious cause cannot be identified,[5,6] and antibiotics have been discontinued in some of those patients without detrimental effects.[7,8]

FUO CRITERIA IN NEOPLASTIC DISEASE

In my oncology practice, I have established more specific criteria for FUO in cancer patients[9,10]: (1) a documented fever of over 101° F at least once, (2) fever duration of at least 1 week, (3) at least three negative blood cultures, (4) a negative urine culture, (5) absence of pneumonia as determined by a chest roentgenogram, (6) normal findings on neurologic examination or spinal fluid analysis, and (7) a lack of potential allergic mechanisms such as drug reaction or blood transfusion reaction.

When these criteria are used, a diagnosis of FUO is not common. Over the previous 4 years, I have evaluated 62 patients with FUO in my oncology practice. Their primary diagnoses are listed in Table II. Ten patients had acute nonlymphocytic leukemia, nine colon cancer, six lung cancer, and so on. Although FUO was prominent in patients with hematologic malignancies, it also was not uncommon in patients with solid tumors. There were four patients with nonneoplastic disease: one each with systemic lupus erythematosus, mixed connective tissue disease, juvenile rheumatoid arthritis, and peritonitis resulting from perforated bowel.

Table II. FUO study: Patient characteristics

Primary diagnosis	*No. of patients (N = 62)*
Acute nonlymphocytic leukemia	10
Colon cancer	9
Lung cancer	6
Chronic lymphocytic leukemia	5
Hodgkin's disease	4
Multiple myeloma	3
Breast cancer	3
Stomach cancer	3
Primary hepatoma	2
Ovarian cancer	2
Non-Hodgkin's lymphoma	2
Malignant melanoma	2
Chronic granulocytic leukemia	2
Myelodysplastic syndrome	2
Leiomyosarcoma	1
Bile duct cancer	1
Primary unknown metastatic cancer	1
Systemic lupus erythematosus	1
Mixed connective tissue disease	1
Juvenile rheumatoid arthritis	1
Perforated bowel	1

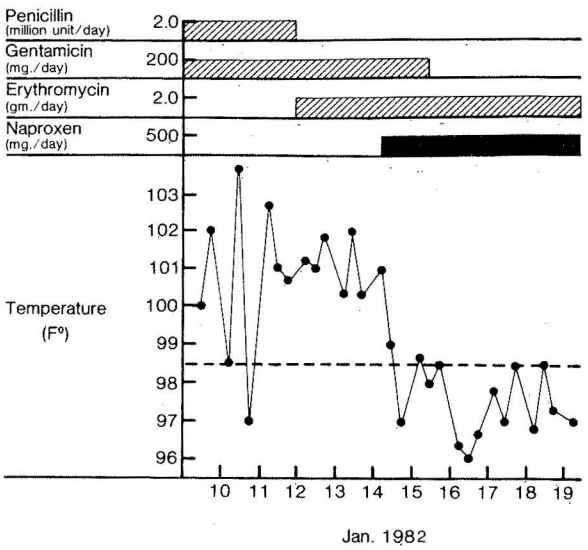

Fig. 1. Febrile course of 65-year-old white man with small cell carcinoma of the lung and *neoplastic fever.* The patient had protracted fever lasting over 2 weeks. Although antibiotics had no effect, the naproxen test resulted in prompt and complete lysis of the fever.

NAPROXEN TEST

During the course of cancer management, I have observed that naproxen has a significant antipyretic property in patients with neoplasm-related fever. In contrast, the drug has had no effect on fever caused by infection. Because of this specific effect of the drug, I was able to develop the naproxen test, which can differentiate infectious fever from neoplastic fever. The indications for the naproxen test were that the patient had fever of 101° F or more and that previously defined criteria for a diagnosis of FUO were met. For the naproxen test, a dose of 250 mg was given every 12 hours for 36 hours. If the patient showed no response, the naproxen dosage was increased to 375 mg, usually for 72 hours. The response was considered to be complete if the patient had complete lysis of fever to less than 99° F within 12 hours after the initiation of the drug and a sustained normal temperature below 99° F for at least 3 successive days while receiving the drug.

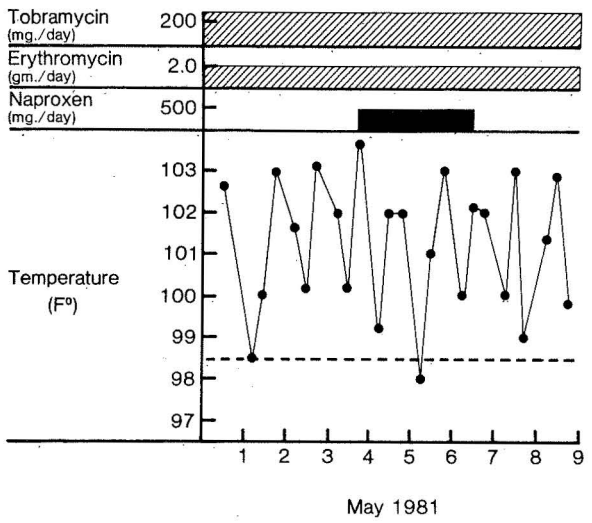

Fig. 2. Febrile course of 59-year-old white woman in a severe granulocytopenic stage after induction chemotherapy for acute myeloblastic leukemia. Antibiotics had no effect on fever, and results of the naproxen test were negative. Later a diagnosis of *infectious fever* caused by a localized left ischiorectal abscess was established.

The response was considered to be partial if the patient had a significant reduction of the fever within 12 hours of the initiation of the drug and a temperature between 99° and 100° F while receiving the drug.

As an illustration, a 65-year-old white man with known small cell carcinoma of the lung, with bone, brain, and liver metastases, had a fever spiking up to 103.8° F (Fig. 1). The patient achieved a partial remission while receiving combination chemotherapy consisting of cylophosphamide, vincristine, and doxorubicin. Since an extensive evaluation did not reveal infection, a diagnosis of FUO was established. An empiric antibiotic treatment with penicillin, gentamicin, and erythromycin was ineffective, and the febrile state continued. However, the patient showed prompt and complete lysis of the fever within 12 hours after naproxen was started. An afebrile state was sustained while the patient was taking the drug, and clinical symptoms improved. A diagnosis of neoplastic fever was established. In contrast, Fig. 2 illustrates a negative response to the naproxen test in a 59-year-old white woman who had received induction chemotherapy consisting of cytarabine, daunorubicin, and 6-thioguanine for acute myeloblastic leukemia. The patient had severe pancytopenia with agranulocytosis when she developed a fever that went up to 104° F. An extensive evaluation for infection for over 2 weeks was negative, and intensive antibiotic regimens, including tobramycin, ticarcillin, and erythromycin, failed to alter the febrile course. A neoplastic fever was suspected. Naproxen was started in addition to antibiotics, but no lysis of fever occurred. During hospitalization a further search for infection later disclosed a localized left ischiorectal abscess. The abscess was drained, and lysis of the patient's fever followed promptly.

Table III. Response of FUO to naproxen

Final diagnosis	No. of incidents	Response (No. of incidents)		
		Complete	Partial	None
Neoplastic fever	50	46	2	2
Infectious fever	13	0	1	12
Immunologic fever	4	0	2	2
Radiation-related fever	1	0	0	1

The cases cited above are typical of the responses of neoplastic fever and infectious fever to the naproxen test. Among my 62 patients there were 68 incidents of FUO. In final analysis, 50 incidents were due to neoplastic fevers, 13 to infectious fevers, four to fevers from immunologic causes, and one to radiation-related fever. The patients' responses to the naproxen test are summarized in Table III. It is remarkable that naproxen resulted in a complete response of neoplastic fevers in 46 of 50 incidents. In two of the four remaining incidents a partial response was achieved, and there was no response in the remainder. On the other hand, in none of the 13 incidents of infectious fever was there a complete response. These findings support the potential value of naproxen in discriminating between infectious and neoplastic fevers.

NAPROXEN AND NEOPLASTIC FEVER

The naproxen test has been a valuable diagnostic method for me as an oncologist. Fever is a common problem in clinical oncology practice because most patients have immunosuppression as a result of the disease itself or their chemotherapy. A source of infection is commonly identified, and an appropriate antibiotic regimen can be instituted without delay. However, in some patients an infection cannot be identified despite an extensive clinical and laboratory investigation.[6,8] In these cases the possibility of neoplastic fever must be considered. Until now there has been no effective diagnostic method for identification of a neoplastic fever. The naproxen test seems to be a safe and useful method for this purpose.

An additional advantage of the naproxen test is that it requires only a 36-hour trial with a small dosage of the drug. In most patients naproxen was

continued for about 7 days if a complete response occurred. In some cases the drug was continued longer than 3 weeks because of the definite clinical benefits from defervescence and the resulting symptomatic improvement. The withdrawal of naproxen after complete lysis of fever has resulted in a recurrence of the fever to pretreatment levels in about three fourths of the patients. I have closely examined 10 patients after withdrawal of the drug (Table IV). After the treatment, ranging from 3 days to 5 weeks, the neoplastic fever returned to the pretreatment levels in seven patients, usually within 24 hours. Three patients, however, remained afebrile during a 3-day observation period. When fever recurred, the fever-related symptoms, such as sweating, chill, excessive fatigue, and delirium, also frequently returned. This observation suggests the limited usefulness of naproxen in the treatment of neoplastic fever, but further evaluation is needed to determine the specific role.

Naproxen is known to cause gastroenteritis and functional platelet defects.[11-13] However, in my experience the side effects have been minimal because most of the patients have received a relatively short course of therapy. Mild gastrointestinal distress was observed in few patients, and no patient had clear evidence of bleeding or of coagulation abnormality directly attributable to naproxen, even though some of the patients had severe thrombocytopenia caused by their underlying neoplastic disease or treatment. One patient had rectal bleeding, and naproxen might have been a contributing factor.

OTHER ANTIPYRETIC AGENTS AND FEVER

Other antipyretic agents can be used in both infectious and neoplastic fevers. Acetylsalicylic acid and acetaminophen have been used extensively. In contrast to naproxen, these drugs usually modify a fever only moderately; they rarely produce complete lysis of neoplastic or infectious fevers and sustain normal temperature. Corticosteroids may produce prompt and complete lysis of both neoplastic and infectious fevers,[14,15] but in my experience these drugs unfortunately do not differentiate between the two.[16] Furthermore, the side effects of corticosteroid therapy are too serious and numerous to justify its use in seriously ill patients, and these drugs are usually contraindicated if patients have an infection. At this time, naproxen seems to be an ideal agent in the differential diagnosis of fever and, perhaps, in the treatment of neoplastic fever.

Other nonsteroidal anti-inflammatory drugs, such as indomethacin, ibuprofen, ketoprofen, and fenoprofen, are also known to have antipyretic activity.[17-19] However, none have been systematically evaluated for their antipyretic activity. Controlled studies are warranted to evaluate the ability of these drugs to differentiate neoplastic from infectious fever.

The precise pathogenesis of fever is unknown in both infection and neoplastic disease. In infection, an endogenous (leukocytic) pyrogen is thought to be responsible for fever by stimulating arachidonic acid release, which results in the synthesis of prostaglandin E_2 in the hypothalamus.[20,21] Prostaglandin E_2 is known to have direct pyrogenic effects.[22] Inhibitors of cyclooxygenase, such as aspirin and indomethacin, may prevent the onset of fever by suppressing prostaglandin E_2 synthesis. Naproxen has also been shown to inhibit the synthesis or release of prostaglandins in various animal models.[23,24] However, the lack of effect of naproxen on infectious fever and the specific actvity of this drug against neoplastic fever (1) suggest that the antipyretic action of naproxen may be mediated by a mechanism different from those of some other antipyretic agents and (2)

Table IV. Effect of withdrawal of naproxen on neoplastic fever*

Patient No.	*Lysis of fever with naproxen*	*Duration of naproxen therapy*	*Relapse of fever after withdrawal of naproxen*	*Lag time before relapse of fever*
1	Complete	5 wk	No	
2	Complete	3 days	Yes	3 days
3	Complete	3 days	Yes	24 hr
4	Complete	7 days	No	
5	Complete	7 days	No	
7	Complete	7 days	Yes	24 hr
9	Complete	7 days	Yes	24 hr
11	Complete	>1 wk	Yes	24 hr
17	Complete	3 wk	Yes	24 hr
19	Complete	5 days	Yes	24 hr

*From Chang JC, Groos HM. Neoplastic fever responds to the treatment of an adequate dose naproxen. J Clin Oncol 1985;3:552-8.

support the hypothesis that the mechanism of neoplastic fever may be different from that of infectious fever.[9]

In conclusion, the naproxen test appears to be a valuable tool in clinical practice, assisting in the differential diagnosis of fever in patients with cancer. Prompt and complete lysis of fever and a sustained normal temperature during naproxen dosing strongly support a diagnosis of neoplastic fever.

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QUESTIONS AND COMMENTS

Dr. Howard Wunderlich (Infectious Disease Section): I congratulate you for your excellent study and concise presentation. I have been aware of your studies on neoplastic fever. Certainly, naproxen seems to have a clinical value in evaluating fever of undetermined origin (FUO) in patients with documented cancer. However, it still seems premature to apply the naproxen test in every case of FUO, especially when a patient does not have proven cancer. In addition, I had a patient with primary hepatocellular carcinoma whose neoplastic fever failed to respond to naproxen.

Dr. Jae C. Chang: Thank you for your comments. I agree that the naproxen test has been used primarily in patients with proven cancer and has not been prospectively examined in patients with nonneoplastic diseases, or infections. Since my experience with the test is still in a preliminary stage, I do not recommend the test for every case of FUO. I believe the naproxen test should be reserved for genuine cases of FUO after an extensive evaluation and after adequate empiric antibiotic therapy. Again, I wish to emphasize that at this time, the naproxen test should be used only in patients with cancer. In regard to your case of primary hepatocellular carcinoma, may I ask whether or not you increased the naproxen dosage to 375 mg every 12 hours when the patient initially failed to respond to 250 mg twice a day?

Dr. Wunderlich: Yes, I did.

Dr. Chang: One possibility is that the patient could still have had an infectious fever even though the underlying condition was neoplastic disease. In addition, of course, the test is not 100% accurate.

Dr. Jaime Pacheco (Hematology/Oncology Section): Dr. Chang, I suspect that most of your patients were receiving chemotherapy along with the naproxen when they were in a febrile state. How, then, can you ascertain that the fever lysis was not due to the response of the neoplastic disease to chemotherapy, rather than to naproxen?

Dr. Chang: In fact, most of my patients had their chemotherapy prior to the development of FUO, and the diseases were in active stage. In the cases of acute leukemia, fever usually developed when pancytopenia became severe after an intensive induction of chemotherapy. Despite achievement of bone marrow remission, the febrile state resulting from the neoplasm did not improve in some patients until the naproxen was started. I was certain that lysis of fever was not the result of response to chemotherapy in all of my patients.

Student A: Although naproxen is effective in the defervescence of neoplastic fever, I would be reluctant to discontinue antibiotics during the naproxen test because in some patients an interruption of the antibiotic therapy might be detrimental to the course of their disease. Do you believe that the naproxen test can be done while a patient is receiving antibiotic therapy?

Dr. Chang: Absolutely, the naproxen test can be performed while the patient is taking antibiotics. The response to naproxen, as you can see in Fig. 1 and Table III, is so dramatic in neoplastic fever that within 12 hours after initiation of the drug, a prompt and complete lysis of the fever usually occurs and an afebrile state is sustained. Naturally, the test should be done only in those patients with a fever that persists while they are taking antibiotics.

Dr. Bradford Hawley (Infectious Disease Section): I wish to comment on the occurrence of neoplastic fever in patients with severe granulocytopenia after an intensive induction chemotherapy for acute nonlymphocytic leukemia. I have worked closely with Dr. Chang on these patients. It is of interest that a febrile state is common in the stage of severe bone marrow suppression, whether the fever was caused by infection or by the disease. Leukocytic pyrogen is thought to be responsible for fever by stimulating arachidonic acid release and synthesis of prostaglandin E_2. I have wondered how a patient can develop a febrile state when there is a virtual absence of granulocytes. Could there be several different mechanisms involved in the pathogenesis of fever?

Dr. Chang: Often, fever is absent when induction chemotherapy for acute leukemia is initiated, but an infectious or neoplastic fever develops when severe bone marrow suppression occurs. It is understandable that fever occurs in patients with infections. However, it is puzzling to me why the neoplastic fever occurs after intensive chemotherapy and with the patient in a state of severe granulocytopenia. In most of my patients with acute nonlymphocytic leukemia, the neoplastic fever, occurring after a complete remission of leukemia was achieved, was controlled with naproxen alone. Yes, I do suspect that different mechanisms produce fevers with different causes.

Student B: Have you observed all your patients who had a response to naproxen to see what happens when you stop naproxen? You have closely observed only the 10 patients reported.

Dr. Chang: I have not been able to observe all of the patients closely because many were discharged from the hospital while taking naproxen, and close follow-up examinations were not possible in some patients.

Dr. Barrett Bolton (Hematology/Oncology Section): Your data are impressive in that naproxen had such a dramatic antipyretic effect on neoplastic fever. We must remember, however, that in general, other antipyretic agents, such as acetylsalicylic acid and acetaminophen, partially suppress fever caused by infection or tumor and hardly modify the febrile course. The naproxen test appears to be an excellent supplementary test in the differential diagnosis of fever. However, I believe it should be used judiciously and the results interpreted carefully, along with other clinical data.

Dr. Chang: I agree with you.