KEY FACTS

- No single diagnostic algorithm can be universally applied to all patients with fever of unknown origin (FUO).
- Geographic location significantly influences the diagnostic differentials of FUO in any patient.
- Arthrocentesis should be performed in all dogs with FUO.

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Fever of Unknown Origin: A Systematic Approach to Diagnosis

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ABSTRACT: Fever of unknown origin (FUO) is by definition a diagnostic challenge. Fortunately, a diagnosis can be made in most cases if a logical and thorough diagnostic plan is developed. This article outlines the pathogenesis of fever and presents several options for the development of an investigative approach to FUO. Data from several case series are compared and show that infection, immune-mediated diseases, and neoplasia are important causes of FUO in small animals. Finally, selected diagnostic tests are discussed in detail and therapeutic approaches are reviewed.

Fever of unknown origin (FUO) provides a significant diagnostic challenge in both human and veterinary medicine. In human medicine, FUO was originally defined as an illness of more than 3 weeks’ duration with a fever higher than 101°F (38.4°C) on several occasions and an uncertain diagnosis after 1 week of hospital investigation.1 The last component of this definition has recently been modified to allow investigation as an outpatient or investigation for at least 3 days as an inpatient.2 A more general definition of FUO is that it is fever that does not resolve spontaneously in the period expected for self-limited infection and its cause cannot be ascertained despite considerable diagnostic effort.3 This definition emphasizes two important points about FUO:

- The fever is of sufficient duration that many common, simple, or self-limiting causes are ruled out. Examples in veterinary practice include viral infections, simple abscesses, other infections that resolve spontaneously or respond to antibiotics, and postsurgical fever.
- Initial testing and diagnostic investigations do not reveal the cause of fever. These diagnostic tests are likely to include a complete history and physical examination, complete blood cell count (CBC), serum chemistry profile, urinalysis, and thoracic and abdominal radiography. These tests identify the cause of fever in most patients, and therefore most animals with fever do not have FUO. Failure to respond to short courses of antibiotic therapy is often considered to be part of the definition of FUO in veterinary patients.4

However the clinician chooses to define FUO, it is important to bear in mind that many patients ultimately have an unusual or uncommon manifestation of a
Therefore, it is necessary to develop a diagnostic approach to these patients that allows the detection of both common and uncommon causes of fever. The goal in investigating FUO in a patient is to convert the problem of FUO into a definitive diagnosis while minimizing expense, invasiveness of testing, and patient discomfort. This article provides a framework for the development of a logical diagnostic plan and critically addresses the selection and interpretation of specific diagnostic tests.

TEMPERATURE REGULATION AND PATHOPHYSIOLOGY OF FEVER

The hypothalamus is responsible for thermoregulation and essentially acts as a thermostat. It receives afferent information from several sensory receptors and controls heat loss or heat production in order to maintain normal body temperature. Fever occurs when the hypothalamus is “reset” to a higher set point so that heat loss and heat production mechanisms act to raise the body temperature. Fever is defined by this resetting of the thermostat, whereas hyperthermia and pyrexia refer to any abnormal elevation of body temperature. This includes true fever but also conditions in which the hypothalamic set point is not altered (e.g., heat stroke, exercise-induced hyperthermia, malignant hyperthermia, hyperthermia associated with seizures). These conditions lead to hyperthermia through abnormalities of heat production or dissipation. These causes of hyperthermia should be ruled out during the initial history and physical examination of the pyretic patient and are not considered to be diagnostic differentials for FUO.

Dogs and cats with true fever usually have body temperatures in the range of 103°F to 106°F (39.5°C to 41.1°C). Temperatures consistently above 105°F (40.6°C) are not common in FUO, and temperatures above 106°F (41.1°C) are more frequently seen with other nonfebrile causes of hyperthermia. It can be useful to monitor the pattern of fever while investigating a patient with FUO as knowledge of how the temperature varies in an individual patient can assist in interpreting the response to any subsequent therapies. However, the fever pattern probably has little value in predicting the underlying disease mechanism.

In febrile conditions, inflammation and bacterial toxins (e.g., endotoxin) increase the hypothalamic set point. These pyrogenic stimuli cause monocytic cells to release cytokines, including interleukin (IL)-1, IL-6, β- and γ-interferon (IFN), and tumor necrosis factor (TNF)–α. These cytokines are called endogenous...
Pyrogens and appear to induce local release of prostaglandins in the hypothalamus, which then elevate the set point.\(^6,11\)

**CAUSES OF FEVER OF UNKNOWN ORIGIN**

The causes of FUO are often divided into categories based on the underlying disease process.\(^7,9\) Table 1 shows typical disease categories, with examples of each. Similar information is available from many sources\(^4,7-9,12\) (it is beyond the scope of this article to discuss in detail all potential diagnostic differentials for FUO). Table 2 outlines a different approach that considers the diagnostic differentials of FUO in terms of the body system affected. This approach can be helpful in choosing diagnostic tests, particularly if the clinical signs of the body system involved are subtle or occult. By combining a disease mechanism and body system approach, clinicians can plan a diagnostic evaluation that allows for the detection of most causes of FUO.

In the human literature, 30% to 40% of cases of FUO are caused by infection, 20% to 30% are caused by neoplasia, 10% to 20% are the result of rheumatologic diseases, 15% to 20% have miscellaneous causes, and 5% to 15% remain undiagnosed.\(^3,13\) A similar distribution has also been reported in veterinary patients.\(^7\)

In 1995, Bennett\(^8\) noted that of 45 cases of FUO seen at a

<table>
<thead>
<tr>
<th>Body System or Region</th>
<th>Selected Examples</th>
<th>Diagnostic Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and hematopoietic</td>
<td>Leukemia, myelodysplasia, bacteremia, ehrlichiosis, haemobartonellosis</td>
<td>CBC, blood smear evaluation, bone marrow aspirate and/or core biopsy, FeLV and FIV tests, other serology, blood culture</td>
</tr>
<tr>
<td>Lymphoid</td>
<td>Lymphoma, lymphadenitis, fungal infection</td>
<td>Palpation of lymph nodes, lymph node aspiration or biopsy</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Endocarditis, vasculitis, pericarditis</td>
<td>Auscultation, radiography, angiography, electrocardiography, echocardiography, blood vessel biopsy, blood culture</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Bronchial foreign body, pneumonia, fungal infection, other granulomatous disease</td>
<td>Radiography, transtracheal or endotracheal wash, fine-needle aspiration, bronchoscopy, bronchoalveolar lavage (BAL), CT, biopsy</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Toxoplasmosis, fungal infection, steroid-responsive meningitis</td>
<td>Fundic and neurologic examination, radiography, CT, MRI, cerebrospinal fluid analysis</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Immune-mediated arthritis, panosteitis, discospondylitis</td>
<td>Radiography, blood culture, arthrocentesis, synovial membrane biopsy, RF, ANA</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Fungal disease, neoplasia, abscess, pancreatitis</td>
<td>Radiography, abdominal ultrasonography, fecal cytology, fecal culture, oral and dental radiographs, lipase and amylase, trypsinlike immunoreactivity, endoscopy, exploratory surgery, biopsy</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Prostatitis, pyelonephritis, stump pyometra, orchitis</td>
<td>Urine culture, radiography, abdominal ultrasonography, IV pyelography, prostatic wash, fine-needle aspiration, biopsy, vaginoscopy</td>
</tr>
<tr>
<td>Pleural or peritoneal cavity</td>
<td>Pyothorax, peritonitis, neoplasia</td>
<td>Radiography, ultrasonography, fine-needle aspiration, fluid analysis, microbial culture</td>
</tr>
<tr>
<td>Skin</td>
<td>Fungal infection, neoplasia</td>
<td>Physical examination, biopsy</td>
</tr>
</tbody>
</table>
veterinary referral hospital, 21 (47%) were due to infectious or parasitic causes and 18 (40%) were due to immune-mediated polyarthritis. Of the remaining cases, 4 (9%) were due to myeloproliferative disease and 2 (4%) were due to metaphyseal osteopathy. In a larger canine case series, Dunn and Dunn\textsuperscript{14} reported that 22% of 101 patients with unexplained pyrexia were diagnosed with immune-mediated disease, with immune-mediated polyarthritis accounting for 20% of those cases. Another 22% of patients were diagnosed with primary bone-marrow disease; 16% with infectious disease; 9.5% with neoplasia; and 11.5% with miscellaneous conditions, including metaphyseal osteopathy, meningitis, portosystemic shunt, and lymphadenitis. (A diagnosis was not established in the remaining 19%.) When considering these reports, it is important to recognize the influence of the specific areas of interest of the authors and the particular areas of specialization of the referral centers to which the cases were presented. For example, Bennett has a specific interest in immune-mediated arthritis,\textsuperscript{8} and the cases reported by Dunn and Dunn were investigated at a hospital with a large oncology caseload.\textsuperscript{14} However, while there may be some differences in the distribution of cases seen by different clinicians, the overall implication is that infection, immune-mediated disease, and neoplasia are important causes of FUO in small animals. Table 3 summarizes 24 cases of FUO that I saw at an internal medicine referral practice over approximately 3 years. For this small series, infectious disease accounted for 42% (10 of 24) of the cases. These data emphasize the importance of geographic location when considering infectious causes of fever. I practice in a state with a high incidence of blastomycosis, which is reflected in the fact that 25% of the cases of FUO were ultimately attributed to this fungal infection. In comparison, systemic mycoses are extremely rare in the United Kingdom, as demonstrated in the data of Dunn and Dunn\textsuperscript{14} and Bennett.\textsuperscript{8}

### Diagnostic Approach

In human medicine, it has been said that “patience, compassion, equanimity, and intellectual flexibility are indispensable attributes for clinicians in dealing successfully with FUO.”\textsuperscript{15} This statement is certainly also applicable to veterinarians dealing with FUO. It should also be remembered that the investigation of FUO demands patience and equanimity from the pet owner and often also requires considerable financial commitment. When planning the diagnostic investigation of a patient with FUO, it is essential for clinicians to explain the following to clients:

- Investigation of FUO can be time consuming and frustrating.
- Many diagnostic tests may be necessary.

Table 3. Diagnoses in 24 Cases of Fever of Unknown Origin (23 Dogs and 1 Cat)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-mediated polyarthritis</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>Neoplasia\textsuperscript{a}</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1 (4%)</td>
</tr>
<tr>
<td><em>E. canis</em> infection</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>FIP</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Lymphadenitis</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Panosteitis</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Included splenic hemangiosarcoma, splenic fibroma with a necrotic center, lymphoblastic leukemia, and malignant histiocytosis.

- Tests may often be repeated several times.

However, clinicians should also reassure clients of the following:

- The fever itself is rarely harmful to patients.
- A diagnosis is ultimately obtained in most cases.
- Many causes of FUO prove to be treatable or manageable.\textsuperscript{14}

The importance of good client communication in these cases cannot be overstated. The goal is not to dissuade clients from pursuing an exhaustive workup but to ensure that the client is a willing partner who is prepared for the necessary commitment of time and money. Four factors should be considered when developing a diagnostic plan for FUO:

1. The plan should begin with tests that are safe, simple, inexpensive, and easy to interpret.
2. Each clinician should choose a plan that minimizes the chances of overlooking any potential diagnostic differentials. Depending on the preferences of a clinician, the plan may be based on the consideration of disease processes (Table 1), a body-system approach (Table 2), a stepwise approach to testing (Table 4), or a combination of these.
3. The plan should evolve as results of each diagnostic test become available. For example, bone marrow aspiration should be performed early in the course of investigation if a CBC reveals cytopenia. This
same test is likely to be conducted at a later stage in a patient with FUO and an unremarkable CBC.

4. The plan should allow for repetition of simple and basic diagnostic tests, including physical examinations, in-depth history taking, CBCs, fine-needle aspiration, cultures of fluids, radiography, and infectious disease titers.

Table 4 outlines my approach to diagnostic testing in patients with FUO. Similar staged approaches are available from other sources, and the exact details are likely to depend on clinician preference, geographic location, client compliance, and whether the cases are investigated in a primary care or referral setting. The stages should not be rigidly defined, and the timing of specific tests should primarily be dictated by the abnormalities detected in a patient.

### History and Physical Examination

The history and physical examination should include vaccination, heartworm prevention, deworming, and other medication history. The client should be questioned closely about any subtle signs of illness because these may help localize a disease process. Travel history is particularly important as is the lifestyle and home environment of the pet. Clients should be questioned about a history of other illnesses, injuries, and surgeries as well as the response to therapies that may have initially been used in managing the fever. Concurrent illnesses in any other pets or human family members should be noted. It is important to spend a significant amount of time on this part of the investigation and to be prepared to readdress the patient history on several occasions.

All body systems should be examined frequently in detail. Particular attention should be paid to the lymph nodes, bones and joints, rectum, mouth, and skin. Repeated fundic examinations are also essential as they may reveal evidence of infectious disease (Figure 1). For hospitalized patients, physical examinations should be performed at least twice daily. For outpatients, a complete physical examination should be performed at every hospital visit and an appointment should be scheduled whenever a client observes a change in a patient’s status. Clients should be advised to watch for the development of skin lesions, masses or swellings, lameness, and changes in urination or defecation habits.

### Complete Blood Cell Count

The CBC should always be accompanied by an examination of the blood smear. This will allow...

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**Figure 1**—Subretinal granulomas in a cat with cryptococcosis. (Courtesy of the Comparative Ophthalmology Group, University of Wisconsin—Madison)
detection of morphologic abnormalities in blood cells as well as the possible detection of organisms (Figure 2). The latter may require the careful examination of repeated blood smears. Many patients with inflammatory or infectious causes of fever may have a neutrophilia with a left shift, but this finding does not help to localize the problem of fever. Although the CBC findings rarely lead directly to a specific diagnosis, they may provide diagnostic clues that can be pursued with further testing. Dramatic changes in the CBC (e.g., evidence of immune-mediated hemolytic anemia) usually do not meet the criteria for FUO.

**Urine Culture and Evaluation of the Urogenital Tract**

Urine should be obtained by cystocentesis whenever possible and submitted for aerobic bacterial culture with antibiotic sensitivity testing. Urine cultures should be performed in all cases of FUO, even if the urine sediment appears inactive. Urine cultures are usually used to detect pyelonephritis or prostatitis. However, a single negative culture does not rule out these diagnostic differentials. If there is a history of lower urinary tract infection or other evidence suggesting the presence of pyelonephritis, repeated urine cultures should be conducted in addition to ultrasonography and contrast radiographic evaluation of the renal collecting system. Similarly, if prostatitis is suspected, further testing may include prostatic wash, ejaculate evaluation, ultrasonography, and prostatic aspiration or biopsy.

**Radiography**

I routinely obtain thoracic and abdominal radiographs in the first stage of evaluating patients with FUO. These radiographs are simple to obtain and relatively inexpensive, and if abnormalities are detected, they can facilitate the rapid localization of the source of fever.

Figure 3 illustrates an example of a dog with blastomycosis. The patient had no historical or physical examination findings of respiratory tract disease, but thoracic radiographs revealed marked hilar lymphadenopathy. This problem was then used to generate a new list of diagnostic differentials and a more focused diagnostic plan. Because immune-mediated polyarthritis is a common finding in patients with FUO, I also obtain radiographs of multiple joints during the second stage of the diagnostic plan. Additional radiographic studies that may be useful include long bone (particularly in young dogs), vertebral, dental, and contrast radiography of specific body systems.

**Ultrasonography and Echocardiography**

Abdominal ultrasonography is a valuable tool for evaluating patients with FUO and is becoming more widely available in veterinary practice. A skilled ultrasonographer can examine most abdominal organs and often detect lesions that are not demonstrated by radiography (Figure 4). Ultrasonography of the thoracic cavity may be useful when effusions or masses are present. Ultrasonography can also be used to investigate the retrobulbar area or any other large mass or swelling that is not confined to a body cavity. This technique can facilitate the acquisition of fine-needle aspirates or biopsies from many sites.

Echocardiography should be used to evaluate the pericardium, myocardium, endocardium, heart valves, and great vessels during the early stages of the diagnostic plan for a febrile patient with a heart murmur. This modality is often used to look for vegetative valvular lesions when endocarditis is
suspected; however, it should be noted that this test is neither sensitive nor specific for this diagnosis. False-positive results may occur because other valve lesions (e.g., endocardiosis) may resemble vegetations. False-negative results occur when the vegetative lesions are very small or absent (due to embolization), when infection exists without vegetation, and when infection is localized to the mural endocardium. Therefore, the results of echocardiography should be interpreted in light of a patient’s signalment, the time of onset of the heart murmur, and the results of blood cultures.

Advanced Imaging

In human medicine, advanced imaging modalities have markedly reduced the need for exploratory surgeries in patients with FUO. In addition to ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) are increasingly used in veterinary practice. These imaging modalities are often selected with regard to specific areas or body systems of interest. For example, CT is considered to be more sensitive than standard radiographic techniques for detecting several types of pulmonary lesions and MRI is often used to evaluate the central nervous system. In human medicine, nuclear medicine is increasingly used to evaluate patients with FUO. A technique for the use of scintigraphy in localizing abscesses with labeled canine neutrophils has been described but has not yet been adapted for use in clinical veterinary practice.

Cytology and Bone Marrow Evaluation

Cytology is an essential tool for evaluating patients with FUO, particularly if it reveals the presence of abnormal cells or infectious agents (Figure 5). Cytologic preparations should always be made from aspirates of masses, abnormal organs, or fluid accumulations that are detected on physical examination or imaging studies. Joint fluid and lymph node cytology may be informative in patients with FUO when less invasive tests do not localize the source of the fever (Figure 6). Bone marrow aspiration is indicated early in the diagnostic plan if there are CBC changes suggestive of bone marrow disease. Even in the absence of such changes, bone marrow aspiration should be considered in the later stages of the diagnostic plan because bone marrow disease (e.g., lymphoid leukemia, myeloma, malignant histiocytosis) has been reported to be a relatively common cause of FUO. In cats, bone marrow slides should also be reserved for feline leukemia virus (FeLV) immunofluorescent antibody (IFA) testing as this may occasionally reveal the presence of viral antigen in the marrow despite negative tests on peripheral blood.

Arthrocentesis

In my practice and according to previously reported case studies, immune-mediated polyarthritis is a common cause of canine FUO. Since affected patients do not consistently demonstrate lameness or significant periarticular pain or swelling on physical examination, arthrocentesis is recommended in the second stage of the diagnostic plan for all cases of FUO. Several joints should be sampled; I generally obtain synovial fluid from at least the carpi and tarsi. Arthrocentesis is well described elsewhere. Samples obtained should be inspected for cloudiness, discoloration, or loss of normal viscosity. If small fluid samples are collected, the highest priority is to make direct smears for cytologic examination. Larger samples can be transferred to EDTA tubes (taking care to use the
optimum fluid:anticoagulant ratio) and used for both cytology and cell counts. If larger samples are obtained, it is also advisable to submit joint fluid for aerobic, anaerobic, and mycoplasma culture.

**Blood Culture**

Blood cultures are recommended for evaluating all patients with unexplained pyrexia. The goal is to detect bacteremia associated with endocarditis, discospondylitis, or other foci of infection. In human medicine, it has been convincingly demonstrated that the volume of blood drawn is the single most important factor influencing the sensitivity of blood cultures for detecting bloodstream infections. As the volume of blood drawn is increased, the number of positive cultures increases; this effect is the same whether all the blood is drawn at one time or serially over 24 hours. Similar studies have not been performed in veterinary patients, but there is no reason to expect that the results would be different in dogs and cats. Therefore, it is recommended that blood culture techniques should be optimized for the collection of adequately large volumes of blood, rather than focusing on the timing of blood collections. In my practice, patient size and the size of the blood culture bottles are used to determine the volume of blood collected. For large dogs, 16 to 20 ml of blood is collected from a single site during a febrile episode and 8 to 10 ml is inoculated into an aerobic and an anaerobic culture bottle (BBL™ SEPTI-CHEK™ with Trypticase™ Soy Broth, Becton Dickinson Microbiology Systems, Sparks, Maryland [70 ml]). For cats and small dogs, approximately 5 ml of blood is collected and divided between blood culture bottles designed for pediatric patients (BBL™ SEPTI-CHEK™ with Brain Heart Infusion [20 ml]).

If the size of the patient allows, a second blood sample is immediately drawn from a different site and again divided between aerobic and anaerobic culture bottles. The use of separate sites assists in determining whether positive cultures are due to true bacteremia or contamination. Contamination should be minimized by proper sterile technique, and identification of the organisms cultured also assists in identifying contaminants. For patients that have recently received antibiotic therapy, blood culture bottles containing resins are used (Figure 7; BBL™ SEPTI-CHEK™ with Resins Culture Bottle).

**Serology**

Antibody titers (and sometimes antigen tests) are frequently obtained to look for evidence of infectious disease in patients with FUO. When selecting and interpreting these tests, it is important to consider the clinical signs in the patient (although these are often not present in FUO) and understand the sensitivity and specificity of the tests selected. For example, in diagnosing fungal disease, cryptococcal antigen titers are sensitive and specific. In contrast, I have detected Blastomyces dermatitidis in many patients with negative antibody titers, implying that this test is not very sensitive. An example of low specificity is the use of feline coronavirus titers in diagnosing feline infectious peritonitis (FIP). Positive titers imply exposure to one of several related coronaviruses but cannot be used to make a specific diagnosis of FIP. Low specificity can be advantageous in some tests. For example, antibodies to *Ehrlichia canis* cross-react with *Ehrlichia ewingii* and *Ehrlichia chaffeensis*; thus *E. canis* serology can be used to detect infection with any one of these organisms.

Specificity, sensitivity, and disease prevalence in the population of interest determine the predictive value of a test. Disease prevalence is often influenced by geographic location. It should also be remembered that...
evidence of an immune response to an organism does not necessarily imply the presence of disease, as high antibody titers can be associated with asymptomatic infections. For example, elevated antibody titers to *Borrelia burgdorferi* in areas where Lyme disease is endemic do not prove that this infection is the cause of clinical illness. Clinicians can enhance the sensitivity and specificity of serologic testing by choosing the most appropriate test available. For example, when diagnosing toxoplasmosis, elevated IgM antibody titers are suggestive of recent infection, whereas elevated IgG titers can persist for months or years after exposure. If infectious disease is suspected and initial antibody titers are negative, it is advisable to repeat the serology in 2 to 4 weeks to allow time for development of an antibody response. During this time, specific therapy may be instituted if there is convincing evidence of infectious disease. However, convalescent titers should still be obtained in order to confirm the initial presumptive diagnosis. If possible, the acute and convalescent titers should be run together to minimize the effects of any variation in laboratory technique. Finally, vaccination can induce antibody production that will limit the value of certain serologic tests. In some cases (e.g., infection with *B. burgdorferi*), specific tests are available to distinguish between antibodies induced by vaccination and natural infection. In all cases, a careful vaccination history is essential for evaluating patients with FUO.

**Immune Panels**

I do not recommend the indiscriminate use of immune panels or autoantibody screens for patients with FUO. These panels typically include antinuclear antibody (ANA), rheumatoid factor (RF), and Coombs tests. The ANA test is used in the investigation of suspected systemic lupus erythematosus (SLE). However, patients with many other diseases can have abnormal ANA titers, and a positive ANA test alone is never sufficient for a diagnosis of SLE. The diagnosis of this multiorgan immune-mediated disease requires the presence of several diagnostic criteria, one of which may be an abnormal ANA titer, with affected patients often presenting with skin and oral lesions, polyarthritis, renal disorders, and/or hematologic disorders. Rheumatoid arthritis is uncommon in dogs and rare in cats. Diagnosis of this erosive arthritis requires joint radiographs, synovial fluid cytology, and sometimes synovial membrane biopsy. RF tests are reported to show poor sensitivity and specificity in diagnosing canine rheumatoid arthritis. The Coombs test is used to detect antibodies against a patient’s erythrocytes. This test is used in diagnosing suspected immune-mediated hemolytic anemia, which is unlikely to fit the criteria for FUO.

**Biopsy**

Tissue biopsies may be obtained percutaneously, with or without imaging guidance; during surgery; or with techniques such as endoscopy, laparoscopy, or thoracoscopy. The selection of the tissue for the biopsy is usually dictated by the results of preliminary diagnostic tests, but in some cases, biopsies of organs or tissues may be performed in the absence of any localizing signs. It is important to maximize the value of these biopsies by obtaining adequate tissue samples and conducting several tests on the tissues obtained. For example, during exploratory laparotomy in patients with FUO with unlocalized gastrointestinal signs, biopsies should be obtained from several organs, including the stomach, small intestine, liver, pancreas, and lymph nodes. In addition to submitting samples for histopathologic examination and special stains, unfixed specimens should also be cultured for aerobic and anaerobic bacteria, mycobacteria, other atypical bacteria, mycoplasma, and fungi.

**Therapeutic Trials**

The goal in all cases of FUO is to obtain a specific diagnosis and treat accordingly. This may not be possible in some patients because the complete diagnostic evaluation is curtailed or because a diagnosis cannot be achieved despite an exhaustive investigation. In these cases, therapy with antibiotics, antifungal agents, or corticosteroids may be considered. Antibiotic trials should be based on the agents most likely to be present and their known antibiotic sensitivity patterns. For example, doxycycline is used whenehrlichiosis is suspected, fluoroquinolones are often selected for cases of prostatitis, and metronidazole or clindamycin are used for anaerobic infections. In areas where systemic mycoses are prevalent, trials with antifungal agents may be used in patients with typical signs of fungal infection but in which the diagnosis cannot be confirmed. Corticosteroid trials are used when immune-mediated disease is suspected; however, every attempt should be made to first rule out infectious disease.

When planning a therapeutic trial, it is important to follow these guidelines:

- Begin with a tentative diagnosis.
- Use effective doses of appropriate medications for an adequate length of time.
- Define parameters to be monitored and follow them closely.
- Use predetermined criteria to determine the success or failure of therapy.
For example, if immune-mediated polyarthritis is suspected, immunosuppressive doses of corticosteroids should be used and a dramatic response should be expected within 24 to 48 hours. These patients should be hospitalized during this period to allow for detection of infectious disease that may be worsened by the therapy. If fungal disease is suspected, the response to antifungal therapy may take days to weeks and changes in radiographic or ophthalmologic findings may occur very slowly. It is also important to remember that the response to therapy may be coincidental or nonspecific. For example, fever may wax and wane in a patient with FUO; therefore, monitoring should continue for sufficient time to confirm that resolution of the fever can be attributed to the selected therapy. Corticosteroids have antiinflammatory effects that may be of nonspecific benefit in many cases of FUO, metronidazole is known to have immunomodulatory properties, and doxycycline may have beneficial effects in certain patients with noninfectious arthritis. These effects may further confuse the interpretation of the response to a therapeutic trial.

When selecting a treatment for any problem or for a specific disease, it is important to consider the risks and benefits of therapy. For patients with FUO, potential benefits include the possibility of a resolution or control of the underlying disease, the chance to rule out certain diagnostic differentials, and the relief of clinical signs associated with fever or the underlying disease. However, the many risks associated with therapeutic trials in patients with FUO should be considered carefully before therapy (Table 5).

**NONSPECIFIC THERAPY**

Body temperatures in excess of 106°F (41.1°C) may cause organ damage, electrolyte and acid–base disturbances, disseminated intravascular coagulopathy, and death. Fortunately, temperature elevations of this magnitude are more likely to be associated with nonfebrile causes of hyperthermia and are not common in patients with FUO. It is likely that fever has beneficial effects in patients with infectious disease, leading to enhanced resistance to infection and improved immune function. However, in some patients, fever can also lead to reduced appetite, dehydration due to reduced fluid intake and increased insensible losses, and significant lethargy or obtundation. The common medical advice to “get lots of rest and drink plenty of fluids” is not always easy to apply to veterinary patients. Therefore, clinicians may need to select nonspecific therapies for canine and feline patients with FUO, specifically for the purpose of improving patient comfort or quality of life, while working through a diagnostic plan. For hospitalized patients, I routinely use intravenous (IV) crystalloid fluid therapy in patients with FUO with a body temperature above 103.5°F (39.8°C). Fluids are given at a rate of 1.5 to 2 times maintenance to allow for

### Table 5. Risks Associated with Therapeutic Trials

<table>
<thead>
<tr>
<th>Risk Description</th>
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<tbody>
<tr>
<td><strong>Exacerbating an undiagnosed disease</strong> is a risk, particularly when using corticosteroids (e.g., administering immunosuppressive doses of corticosteroids to a patient with an undiagnosed fungal infection could lead to marked clinical deterioration or even death).</td>
</tr>
<tr>
<td><strong>Continued progression of an undiagnosed disease</strong> occurs when the therapeutic trial is unsuccessful (e.g., use of an ineffective antibiotic in a patient with pyelonephritis; failure to treat appropriately could ultimately lead to irreversible organ damage).</td>
</tr>
<tr>
<td><strong>Drug toxicity</strong> (e.g., nephrotoxicity of gentamicin or amphotericin, central nervous system toxicity of metronidazole) may occur.</td>
</tr>
<tr>
<td><strong>Undesirable side effects</strong> (e.g., polyuria, polydipsia, and polyphagia associated with corticosteroid therapy) are possible. It can be difficult for clients to comply with treatment recommendations when side effects are intolerable and there is no clear diagnosis or endpoint to define the course of therapy.</td>
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<td><strong>Inducing antibiotic resistance</strong> is a concern when using trial courses of antibiotics in patients with suspected bacterial infection. If antibiotic selection is not based on culture and sensitivity results and an inappropriate antibiotic or dose is selected, this may contribute to antibiotic resistance in bacterial populations. This is now recognized as an increasing problem in both human and veterinary medicine.</td>
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<td><strong>Interfering with future diagnostic tests or therapies</strong> is a particular concern when diagnosing neoplasia (e.g., use of corticosteroids in a patient with lymphoma). Therapy may be successful in the short term but could interfere with future attempts to confirm the diagnosis and also lead to resistance to other chemotherapeutic agents.</td>
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<td><strong>Poor owner compliance due to the expense of therapy</strong> is a particular concern with antifungal agents and certain antibiotics (e.g., third-generation cephalosporins). This is a significant risk for some patients with FUO because many clients have already made a significant financial investment in the rest of the diagnostic evaluation. A trial course of therapy with an expensive medication and without a confirmed diagnosis may, therefore, be unacceptable in some cases.</td>
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increased water requirements and insensible losses associated with fever. For outpatients, low doses of aspirin can be used (10 mg/kg bid for dogs; 10 mg/kg q48h for cats). Use of dipyrone or flunixin is not recommended in either species. For hyperthermia with temperatures in excess of 106°F (41.1°C), mechanical cooling methods such as cool water baths and fans should accompany IV fluid support.

SUMMARY

The problem-oriented approach to medicine involves identifying and verifying a problem, localizing the problem, and considering the appropriate diagnostic differentials, which are then used to generate the diagnostic plan. Because FUO is, by definition, not easily localized, there are no simple algorithms that provide an inclusive approach to diagnosing all patients. The goal of the diagnostic plan should be to use simple tests to identify an abnormality and then use that as the basis for targeted diagnostic testing. With this approach, clinicians should be able to replace the problem of FUO with a more specific diagnosis.

ACKNOWLEDGMENTS

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REFERENCES


1. Which of the following statements about FUO is true?
   a. FUO can be diagnosed only in a hospitalized patient.
   b. The pattern of fever in FUO is very useful in determining the underlying cause.
   c. In human medicine, 5% to 15% of cases of FUO remain undiagnosed.
   d. Neoplasia rarely causes fever in humans or dogs.

2. Which of the following is an example of true fever?
   a. elevated body temperature after prolonged seizure activity
   b. elevated body temperature associated with necrosis of a tumor
   c. elevated body temperature due to heat stroke
   d. malignant hyperthermia

3. Which of the following are involved in the pathogenesis of fever?
   a. IL-1
   b. IL-6
   c. prostaglandins
   d. all of the above

4. Which of the following have been reported to cause fever in dogs?
   a. portosystemic shunt
   b. lymphadenitis
   c. metaphyseal osteopathy
   d. all of the above

5. Which of the following tests are useful in investigating suspected prostatitis?
   a. abdominal ultrasonography
   b. evaluating ejaculate
   c. urine culture
   d. all of the above

6. Which of the following statements regarding the evaluation of FUO patients is true?
   a. Urine culture is indicated only in the presence of an active urine sediment.
   b. Fundic examinations should always be performed.
   c. Thoracic radiographs are indicated only when signs of respiratory disease are present.
   d. Bone marrow cytology is not recommended if the CBC is normal.

7. Which of the following statements regarding the use of echocardiography in diagnosing endocarditis is true?
   a. Echocardiography is highly sensitive but not specific for diagnosing endocarditis.
   b. Echocardiography is highly specific but not sensitive for diagnosing endocarditis.
   c. Echocardiography is neither sensitive nor specific for diagnosing endocarditis.
   d. none of the above

8. Which of the following statements regarding immune-mediated polyarthritis is false?
   a. Cytologic examination of joint fluid can be performed on direct smears or on samples preserved in EDTA.
   b. Dogs with immune-mediated polyarthritis always have lameness and joint swelling on physical examination.
   c. Immune-mediated polyarthritis is a common cause of canine FUO.
   d. If immune-mediated polyarthritis is suspected, arthrocentesis should be performed on more than one joint.

9. Which of the following statements regarding blood cultures is true?
   a. Studies in humans have shown that the sensitivity of blood cultures in detecting bloodstream infections is greatest when blood samples are evenly spaced throughout a 24-hour period.
   b. Blood cultures should never be conducted in patients on antibiotic therapy.
   c. Volume of blood drawn is the most important factor in determining the sensitivity of blood cultures for detecting bloodstream infections in humans.
   d. Blood cultures are rarely indicated in the workup of dogs with FUO.

10. Which of the following statements regarding serologic testing is true?
    a. A negative Blastomyces dermatitidis titer rules out the diagnosis of blastomycosis.
    b. An abnormal ANA titer can be detected in patients that do not have SLE.
    c. Elevated IgG titers are seen only after recent exposure to toxoplasmosis.
    d. An elevated Borrelia burgdorferi titer is diagnostic for Lyme disease.