Diagnostic Approach to the Febrile Patient

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Fever is defined as an elevated body temperature (>103°F [>39.5°C]) due to an altered hypothalamic set point. Fever of unknown origin (FUO) is defined in human medicine as an illness of at least 3 weeks duration with a fever, for which a cause is not identified after 3 hospitalized days or outpatient visits. A consensus veterinary definition has not been developed, but many practitioners would agree diagnosis of FUO is justified when an elevated body temperature has been documented on several occasions (typically over a period of several days) in the absence of confounding factors such as anxiety or warm ambient temperatures. Temperatures consistently >105°F (>40.6°C) are uncommon in FUO and temperatures >106°F (>41.1°C) are more common with nonfebrile hyperthermia (e.g., physical exertion, heat stroke, muscle fasciculations).

Since FUO is, by definition, not easy to localize, there are no simple algorithm to provide an inclusive approach to achieving a diagnosis in all patients. The goal of the diagnostic plan should be to begin with simple, relatively non-invasive, inexpensive, and easy to interpret tests to identify an abnormality. Once an abnormality is identified, it can be used as the basis for more targeted diagnostic testing. A stepwise approach to testing will minimize the chances of overlooking any potential diagnostic differentials. The diagnostic plan should evolve as results of each diagnostic test become available. Finally, the plan should allow for repetition of simple and basic diagnostic tests.

Practitioners should be mindful that the investigation of FUO demands patience and often also considerable financial commitment from the client. When planning the diagnostic investigation, it is essential for practitioners to explain to clients that investigation of FUO can be time consuming and frustrating. Many diagnostic tests may be necessary, and certain tests may need to be repeated. However, practitioners should also reassure clients that the fever itself is rarely harmful to patients and a diagnosis is ultimately obtained in the majority of cases.

Etiology

Infectious, immune-mediated, and neoplastic etiologies are the most common causes of FUO. There are a smattering of other diseases that can cause FUO that defy this categorization. See the chart below for a listing of frequently encountered etiologies.

Infectious

- Localized or systemic bacterial infections: diskospondylitis, osteomyelitis, bacterial endocarditis, septic arthritis, prostatitis, pyelonephritis, septic meningitis, cholangiohepatitis, abscesses, pyothorax, peritonitis, pneumonia, pyometra, catheter site infections
- Specific bacterial infections: leptospirosis, borreliosis, brucellosis, mycobacterial infections, bartonellosis, hemotropic Mycoplasma (*Haemobartonella*), tularemia, salmonellosis
- Viral: canine influenza, canine distemper virus, parvovirus/panleukopenia, feline leukemia virus, feline immunodeficiency virus, feline infectious peritonitis, systemic calicivirus
- Rickettsial: ehrlichiosis/anaplasmosis, Rocky Mountain spotted fever (*Rickettsia rickettsii*), Salmon poisoning (*Neorickettsia helminthoeca*)
- Fungal: histoplasmosis, blastomycosis, coccidioidomycosis cryptococcosis, systemic aspergillosis
- Protozoal: babesiosis, leishmaniasis, trypanosomiasis, hepatozoonosis, toxoplasmosis, cytauxzoonosis

Immune mediated

- Immune-mediated polyarthritis, systemic lupus erythematosus, rheumatoid arthritis, vasculitis, meningitis, pemphigus, immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, transfusion reaction

Neoplastic

- Histiocytic sarcoma, lymphoma, leukemia, multiple myeloma, necrotic solid tumors

Other

- Pancreatitis, drug induced (tetracyclines, penicillins, sulfas), toxins, metabolic bone disorders, hyperthyroidism, tissue necrosis

Initial database

A detailed history and comprehensive physical examination should be performed in all patients with FUO. The history should include vaccination status, heartworm preventative, other medication history, previous illnesses, and surgeries. Travel history, lifestyle, and the home environment in particular may key the clinician in to specific differentials. The examination should include a rectal examination in dogs, dilated fundic examination, thorough oral examination, full orthopedic and neurological examinations, and a

meticulous examination of the skin. Rectal examination may reveal sublumbar lymphadenopathy, prostatomegaly, and rectal or anal sac masses. Dilated fundic examination may reveal granulomas, hemorrhages, retinal detachments or chorioretinitis. Oral examination may reveal pain or difficulty opening the mouth, draining tracts, swelling caudal to the last maxillary molar or sublingual or pharyngeal masses. Orthopedic and neurologic examinations may reveal long bone pain, joint pain, joint effusion, spinal pain or cranial nerve deficits. Meticulous examination of the skin may reveal draining tracts, abscessation or masses.

The initial laboratory work-up in a febrile patient should include a CBC, serum biochemistry profile, urinalysis, and retrovirus testing in cats. A blood smear evaluation must be performed, as reliance solely on automated CBCs will miss significant abnormalities such as a degenerate left shift, toxic change, blood parasites or circulating neoplastic cells. Thoracic radiographs should be performed to evaluate for evidence of masses, effusions or pulmonary infiltrates. Abdominal radiographs should be performed to evaluate for masses, effusion or free gas. If the initial work-up fails to identify an abnormality responsible for the fever, a urine bacterial culture and sensitivity should be performed in all cases even if urine sediment is inactive.

Advanced diagnostics

If the initial database fails to identify an abnormality to direct the investigation, advanced diagnostics will need to be pursued. However, it can be rewarding to repeat the initial database and other simple diagnostic tests periodically throughout the investigation as findings can change as the underlying disease progresses. Advanced diagnostics typically progress from less invasive to more invasive as the investigation continues. Relatively less invasive advanced diagnostics appropriate for the next round of testing include abdominal ultrasound to evaluate for pyelonephritis, prostatitis, pyometra, masses or otherwise abnormal organs; echocardiogram to evaluate for vegetative valvular lesions particularly if a new murmur is present; spinal, long bone, and joint radiographs to evaluate for evidence of diskospondylitis, pre- and post-prandial bile acids testing to evaluate for portosystemic shunting; serial blood cultures to detect bacteremia associated with diskospondylitis, endocarditis or other foci of infection; cytology of lymph nodes, masses or abnormal organs to evaluate for neoplasia or infectious agents; and serology and/or PCR for infectious diseases. If infectious disease is suspected and initial titers are negative, convalescent titers should also be performed. Arthrocentesis, while a slightly more invasive test, should be considered at this stage of diagnostic testing in dogs. Immune-mediated polyarthritis is a common cause of FUO and may not always present with obvious joint effusion. The higher tier of advanced diagnostic tests consists of relatively invasive or expensive diagnostics. They include cerebrospinal fluid analysis, bone marrow aspirates and/or biopsy, bronchoalveolar lavage, CT or MRI, and exploratory surgery with biopsies.

Therapeutic trials

The goal in all cases of FUO should be to obtain a specific diagnosis and treat accordingly. A therapeutic trial should be initiated only when a specific diagnosis cannot be ascertained. This most commonly occurs because diagnostics are curtailed by the owner, but in rare instances can occur despite an exhaustive work-up. Drug therapy trials without a definitive diagnosis may interfere with future diagnotics and exacerbate the underlying condition into a life threatening one. Broad-spectrum antibiotic therapy may be initiated after all culture specimens have been collected. Therapy should be based on the agents most likely present, their known antibiotic sensitivity, and the organ or system affected. If no response is seen after 72 hours, another antibiotic may be chosen, however the practitioner should first re-evaluate if a bacterial infection may be the underlying cause. Commonly used empiric antibiotics include:

- For broad-spectrum coverage: amoxicillin-clavulanate, 10-20 mg/kg PO q 8-12 hour and enrofloxacin 5-10 mg/kg (dog), 5 mg/kg (cat) PO q 24 hour
- If anaerobic infection is suspected: metronidazole 10-15 mg/kg PO q 12 hour or clindamycin 5-15 mg/kg PO q 8-12 hour
- If tickborne disease is suspected: doxycycline, 10 mg/kg PO q 24 hour or 5 mg/kg PO q 12 hour

In areas where systemic mycoses are endemic, antifungal agents may be used in patients with typical signs of fungal infection. The response to antifungal therapy may take days to weeks. Commonly used empiric antifungals include:

- Itraconazole (Sporanox, Janssen), 5-10 mg/kg PO q 24 hour or 5 mg/kg PO q 12 hour
- Fluconazole, 5-15 mg/kg PO q 12-24 hour

A glucocorticoid trial should be used only when infectious disease has been ruled out as the immunosuppressive effects of glucocorticoids can cause a life-threatening exacerbation of an infectious disease. A dramatic response (fever reduction) should be seen within 24-48 hours. Be aware that glucocorticoids may mask clinical signs even if an immune-mediated disease is not the underlying cause due to their anti-inflammatory effects. Commonly used empiric glucocorticoids include:

- Prednis(ol)one, 1 mg/kg PO q 12 hour
- Dexamethasone, 0.2 mg/kg IV q 24 hour