



# When a Fever Is Not a URI: If It's Not in the Differential, It Won't Be in the Diagnosis

**Urgent message:** Fever in patients presenting to UC is often attributable to viral infections, urinary tract infections, otitis media, cellulitis, or pneumonia. When the source is not apparent after the initial evaluation, however, it is important to expand the differential in order to avoid missing less common, serious diagnoses.

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## Case Presentation

A 74-year-old man with a history of Parkinson's disease and diabetes presented with 2 days of fever and fatigue. He denied cough, rhinorrhea, shortness of breath, chest pain, headache, dysuria, or sore throat. He had no indwelling lines or implanted medical devices. He denied alcohol, tobacco, and injection drug use.

His vitals were temperature of 39.2°C (102.6°F), pulse 90, respiratory rate 20, BP 139/72 and oxygen sat 98% on room air.

The remainder of his general physical exam was unremarkable with no obvious source of infection. Given his age and high fever without a source, the urgent care provider encouraged further evaluation.

## Etiologies of Fever

In an urgent care setting, most fevers will have a clear source, commonly from a respiratory or urinary tract infection. But what should the UC provider do if the febrile patient denies cough, rhinorrhea, shortness of breath and urinary symptoms? The most important diagnostic tool remains a thorough history and exam.



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## Expanded Fever History

- How was the fever measured (ie, oral vs temporal vs rectal)? Does it meet the criteria for a fever, ie, 38°C (100.4°F)?
- How long has the fever been present and has there been a response to antipyretics?
- Has previous testing already been performed?

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Table 1. Categorization Of Infectious Causes of Fever <sup>2,3</sup>		
Category	Definition	Common Infections
<b>Nosocomial</b>	Infection that occurs at least 48 hours after hospital admission or within 3 days of discharge or 30 days postoperatively <sup>4</sup>	Healthcare-associated pneumonia including ventilator-associated pneumonia (if recently intubated), <i>Clostridium difficile</i> infection, fungemia, catheter-associated infection, decubitus ulcer, septic thrombophlebitis
<b>Immunocompromise</b>	History of hematopoietic or solid organ transplant, use of immunosuppressive medications for treatment of autoimmune conditions, active metastatic or hematologic malignancy	Donor-derived infections, opportunistic bacterial and fungal infections, hemophagocytic lymphohistiocytosis, disseminated viral infections (eg, HSV, CMV, EBV)
<b>HIV/AIDS</b>	Opportunistic pathogens dependent on CD4 counts and use of antiretroviral medications	Acute retroviral syndrome, toxoplasmosis, tuberculosis, <i>Cryptococcus</i> , HHV-8 infection, endemic fungal mycoses (eg, histoplasmosis, coccidioidomycosis)
<b>Travel-associated</b>	Infections related to endemic organisms specific to region of travel	Enteric fevers, leptospirosis, hepatitis A, traveler's diarrhea, viral hemorrhagic fevers, typhoid, yellow fever, zoonotic infections, Whipple's disease
<b>Other</b>	History of IV drug use, close animal contacts, high-risk sexual history, occupational exposures, history of heavy alcohol use	Aspergillosis, Q fever, brucellosis, <i>Chlamydia psittaci</i> , cat scratch disease, pelvic inflammatory disease, syphilis, bacterial endocarditis, epidural abscess, hepatitis B, hepatitis C, necrotizing fasciitis (including Fournier's gangrene of the perineum)

- Is there associated headache, chest pain, abdominal pain, pelvic pain, rash, back pain, or weight loss?
- Has there been an exposure to others with fever (meningitis, COVID-19)?
- Has there been a travel history with possible exposure to a tropical disease or tick-borne illness?
- Was there recent antibiotic use (eg, *C diff*)?
- What is the patient's immunization status and are there risk factors for immunosuppression (eg, treatment for cancer, autoimmune disease, chronic steroid use, diabetes, tobacco use)?
- Could it be a "drug fever?" Review medications and consider anticholinergic or stimulant toxicities (such as anticonvulsants, certain antidepressants, some antiemetics), serotonin syndrome, and neuroleptic malignant syndrome
- In the social history, specifically investigating for:
  - Injection drug use as a risk factor for spinal epidural abscess (SEA), endocarditis, pulmonary abscess or cutaneous or deep space abscess
  - Alcohol-use disorder with consideration of aspiration pneumonia or hyperthermia from withdrawal
  - Sexual history may reveal pelvic inflammatory disease, tubo-ovarian abscess, HIV/AIDS, syphilis

#### Expanded Fever Physical Exam

- HEENT – Ears (speculum and external ear, including the mastoid); oropharynx (erythema/exudate/tonsillar enlargement/abscess/laryngeal tenderness or hoarseness), nose (discharge)
- Neck: lymphadenopathy, nuchal rigidity
- Chest: Skin (including breast exam), lung auscultation
- Heart: Murmur, tachycardia, presence of a rub
- Abdomen: Inspection (for surgical incisions, distention) and palpation in all quadrants and costovertebral angles (CVA)
- Pelvic/GU: Scrotum/labia and perineal skin, prostate, penile or cervical discharge
- Extremities: Swelling, erythema, ulcerations
- General skin: Rashes (erythroderma, petechiae, vesicular, necrotic)

Broad categories of fever etiologies include:<sup>1,2</sup>

- Infectious
- Autoimmune/inflammatory
- Malignancy
- Other
  - Hyperthyroidism
  - Venous thromboembolism (VTE) or thrombotic thrombocytopenic purpura (TTP)
  - Drug fever
  - Serotonin syndrome
  - Malignant hyperthermia
  - Neuroleptic malignant syndrome

### Infectious

Types of infection can be further broken down based on factors such as recent travel, HIV status, recent hospitalization, and immune status. **Table 1** shows definitions and causes of the different types of fevers caused by different types of infections.<sup>2</sup>

Etiologies of infectious disease that may be more challenging to identify include bacterial endocarditis, lung abscess, SEA/diskitis, meningitis, brain abscess, and necrotizing soft tissue infection (NSTI). Including these in the differential allows for further exploration and possibility of diagnosis at the initial visit.

### Neoplasm

Common neoplastic conditions causing a prolonged fever include leukemia, lymphoma (both Hodgkin's and non-Hodgkin's), Castleman's disease, lymphoproliferative disease, multiple myeloma, myelodysplastic syndrome, renal cell carcinoma, hepatocellular carcinoma, ovarian cancer, and colorectal cancer.<sup>1,2</sup> Fever may occur in these patients due to pyrogenic cytokine production or spontaneous tumor necrosis.<sup>2</sup>

### Autoimmune

Autoimmune diseases, such as autoimmune lymphoproliferative syndrome, are typically type 1 interferon driven responses. Whereas autoinflammatory disorders, such as periodic fever syndromes are driven by innate disorders of immunity that dysregulate interleukin responses. Measuring inflammatory markers is a nonspecific diagnostic tool but can still be useful in determining whether an inflammatory response is occurring.<sup>2</sup>

The most common inflammatory conditions causing prolonged fever include rheumatoid arthritis, rheumatic fever, adult-onset Still's disease and polymyalgia rheumatica.<sup>1</sup> Autoimmune conditions can often be identified based on presenting symptoms, age of the patient, personal and/or family history of other autoimmunity. For example, adult-onset Still's disease, other variants

**Table 2. Signs and Symptoms of NSTI<sup>14</sup>**

Erythema	66%-100%
Pain beyond erythema	73%-98%
Swelling	75%-92%
Crepitus or necrosis	0%-31%
Induration	12%-45%
Bullae	23%-45%
Fluctuance	11%
Fever	32%-53%
Hypotension	11%-18%

of rheumatoid arthritis, and systemic SLE predominate in younger patients, whereas temporal arteritis/giant cell arteritis and PMR syndromes are more common in elderly patients.<sup>1</sup>

### Other

Other etiologies include thromboembolic disorders, endocrinopathies, drug- and toxin-induced fevers and idiopathic. When evaluating an undifferentiated patient without a clear etiology of elevated temperature, obtain a history of currently prescribed medications as well as OTC medications. Nearly one third of febrile episodes secondary to drug reactions are due to beta-lactam antibiotics.<sup>2</sup> Specifically, drug reaction with eosinophilia and systemic symptoms (DRESS) presents with severe rash, fever, facial edema, lymphadenopathy, eosinophilia, and end organ damage. It may progress to more serious complications, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, if left untreated. Serotonin syndrome may occur from the co-administration of multiple selective serotonin reuptake inhibitor medications or the additive effect of multiple serotonin-affecting medications (eg, tramadol, linezolid), with or without the simultaneous use of monoamine oxidase inhibitors.<sup>2</sup>

### Case Resolution

A more thorough exam showed an 8-12 cm area of tenderness, warmth, erythema in the perineum with several areas of necrosis concerning for NSTI/Fournier's gangrene. Labs revealed an elevated lactate but no leukocytosis. CT imaging confirmed Fournier's gangrene and associated abscess formation. The patient was started on broad-spectrum antibiotics and taken to the operating room emergently for debridement.

A thorough skin exam, including the GU and perineal region, performed in UC may have expedited the diagnosis and subsequent definitive management with surgery.

### Fournier's Gangrene

Fournier's gangrene is a rapidly progressing form of necrotizing soft-tissue infection of the perineal, genital, and perianal region.<sup>5</sup> The most common locations for initial infection include a colorectal source (30%-50%), a urogenital source (20%-40%), cutaneous infection (20%) or local trauma.<sup>6</sup> It was thought to be a polymicrobial infection of unknown origin that occurred in otherwise healthy men.<sup>5,7</sup> However, subsequent observations have proven that women can also be affected. Fournier's gangrene is most likely to occur in patients with underlying risk factors including diabetes, alcoholism, hypertension, smoking, immunosuppressive disease, and malignancy.<sup>8,9</sup> The mortality rate has remained unchanged over the past 25 years, remaining around 20%.<sup>10</sup>

NSTI can be broadly classified into two categories:

- **Type I** – most common (55%-75% of NSTIs)
  - Polymicrobial (average of four different organisms)
  - Common locations: Trunk and perineal area
  - Risk factors: Immunocompromise, renal insufficiency, diabetes, obesity
  - *Clostridia perfringens* now less common
- **Type II** – *S pyogenes* +/- *S aureus* - Less common than type I
  - Occurs in healthy, young, immunocompetent patients
  - Usually affects the extremities
  - Injection drug use is a risk factor for type I and II

Symptoms and physical exam findings commonly seen in Fournier's gangrene include erythema, localized tenderness and pain, and edema of the perineal region, fluctuance, systemic signs (eg, fever and hemodynamic compromises) and subcutaneous crepitation. Patients who have signs of severe sepsis upon admission have a significantly higher risk for mortality.<sup>11</sup>

Initial symptoms may be subtle and superficially undetectable, as the infection is not cellulitis (superficial) but is located in deeper soft tissues. (See **Table 2**.) NSTI, accordingly, is often not diagnosed (14%-35% of cases) on initial presentation, which significantly contributes to the associated morbidity and mortality.<sup>12,13</sup>

Although the diagnosis of Fournier's gangrene is primarily a clinical diagnosis via surgical exploration of the affected tissue, certain imaging modalities can be used if the presentation is atypical; however, surgery should not be delayed for imaging. The most sensitive imaging modality for evaluation of NSTI is CT scan. It can also prove useful for defining the extent of disease.<sup>15</sup>

Management consists of three main therapies: rapid

and aggressive surgical debridement of the necrotized tissue, hemodynamic support including fluids and possible vasopressors, and administration of broad-spectrum parenteral antibiotics.<sup>6,16,17</sup> Early, aggressive debridement has been associated with improved survival.<sup>18-20</sup>

### Conclusion

The case described here involved a patient with a high fever without an easily identifiable source. The patient was referred to the ED due to his advanced age and comorbidities, where a diagnosis of Fournier's gangrene was suspected after the clinical exam and confirmed with CT imaging. Though the diagnosis for a fever not from an easily identifiable source may be difficult and require an expanded differential and testing, in this case, in the UC setting, with limited diagnostic tools, this diagnosis could have been made with a simple expanded physical exam. Providers must rely on a thorough clinical evaluation and broad differential to reduce the risk of serious outcomes for patients with true fever and no readily apparent etiology. ■

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