

An approach to the hospitalized patient with urticaria and fever

ROBERT MICHELETTI & MISHA ROSENBACH

Departments of Dermatology and Internal Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

ABSTRACT: Urticaria is a common skin disorder with a long differential diagnosis. Most cases are readily treated symptomatically and have no systemic implications. However, a number of diseases and syndromes, including vasculitides, immunologic disorders, infectious diseases, hematologic diseases, and autoinflammatory syndromes, can present with urticaria and systemic symptoms, which may lead to hospitalization of the patient. These urticarial syndromes are important to recognize as they often have significant health implications. A comprehensive history and physical exam is important in distinguishing cases of simple urticaria from these syndromes. The presence of atypical wheals, systemic symptoms such as fever or arthralgia, and a lack of response to antihistamine therapy are important diagnostic clues that should prompt further workup.

KEYWORDS: autoinflammatory syndromes, hospitalized patient, Schnitzler syndrome, urticaria, urticarial vasculitis

Introduction

Urticaria, or hives, is a common skin disorder with a lifetime prevalence of approximately 15% (1). Its clinical appearance is well-known – pruritic, edematous pink or red wheals of varying size and shape can occur anywhere on the body and may be associated with angioedema (FIG. 1). Urticaria occurs when effector mast cells degranulate, releasing histamine and other mediators. These molecules result in localized vasodilation, increased blood flow, and enhanced vascular permeability responsible for the redness, warmth, and edema of individual wheals.

Urticarial lesions may rarely occur as part of systemic diseases or syndromes with important health implications, including vasculitides and immunologic disorders, infectious diseases, hematologic diseases, and autoinflammatory syndromes. It is

the purpose of this review to highlight these conditions and to provide a practical approach to the diagnosis and treatment of fever and urticaria in the hospitalized patient.

Initial approach to the hospitalized patient with urticaria and fever

True urticaria must be distinguished from other inflammatory cutaneous eruptions that may present with urticarial or wheal-like lesions. These entities include arthropod bite reactions, autoimmune bullous diseases, urticaria pigmentosa, erythema multiforme, contact dermatitis, dermal hypersensitivity reactions, and pruritic urticarial papules and plaques of pregnancy. The presence of lesion morphologies other than isolated wheals suggests an alternate diagnosis, and if there is any doubt, a biopsy may be performed.

The causes of urticaria are numerous, and knowledge of at least the most common of these can help differentiate simple urticaria from systemic diseases with urticarial lesions. Viral upper respiratory tract infections are the most common

Address correspondence and reprint requests to: Misha Rosenbach, MD, Department of Dermatology, University of Pennsylvania, 3600 Spruce Street, 2nd Floor, Maloney Bldg., Philadelphia, PA 19104, or email: misha.rosenbach@uphs.upenn.edu.



FIG. 1. Urticarial morphologies: serpiginous (A), ill-defined edematous plaques (B), discrete edematous plaques (C), and classic wheals (D).

causes of acute urticaria, accounting for 28–62% of patients, whereas medication reactions account for an additional 9.2% (2). Table 1 lists additional causes of urticarial lesions relevant to the hospitalized patient with urticaria and fever. Recent review articles and comprehensive texts are available for a more exhaustive review of cutaneous eruptions that mimic urticaria and a complete discussion of the causes of urticaria (2–5).

The initial workup of the hospitalized patient with urticaria and fever should include a thorough history and physical examination, along with basic laboratory testing including a complete blood count (CBC) with differential. Patients with extensive or perioral urticaria, angioedema, or stridor should be identified quickly and monitored closely. Patient history should include comorbidities, allergies, exposures, frequency and pattern of symptoms, and family history (as outlined in Table 2), as well as a detailed timeline of medications administered in the preceding 3 weeks. Penicillin and other beta-lactam antibiotics are the most commonly implicated drugs. These agents can cause urticaria, fever, and arthralgia within 3 weeks of exposure through immunoglobulin (Ig)E or

complement-mediated pathways or as part of a serum sickness-like reaction (6).

Important historical “red flags” that may indicate the presence of systemic disease are shown in Table 3 and include the presence of atypical wheals that burn rather than itch, persist longer than 24 hours, and resolve with bruising, or are associated with systemic symptoms such as fever, arthralgia, or weight loss. Evidence of cytopenias, significant eosinophilia, or atypical lymphocytes on the CBC may also indicate systemic disease. Additional laboratory tests need not be performed routinely in all patients. The history and physical findings should dictate further testing based on the suspicion of a particular diagnosis and the pretest probability. Unguided extensive testing (including complement, immune complex, and cryoglobulin levels, rheumatoid factor, IgE, antinuclear antibody (ANA), anti-double-stranded DNA, hepatitis serologies, stool ova and parasites, smears for *Streptococcus* and *Candida*, radiographs, skin biopsies, radioallergosorbent testing, elimination diet, and more) has not been shown to contribute substantially to the diagnosis of urticaria or to the detection of underlying disorders (7).

Table 1. Differential diagnosis of urticaria; conditions typically associated with fever marked by asterisk (*)

Medications	Infectious diseases
Immunologic	Viral
Penicillin and other beta-lactam antibiotics*	Viral upper respiratory tract infection*
Vancomycin	Mononucleosis (Epstein–Barr virus)*
Other antibiotics (including cephalosporins, sulfonamides, isoniazid)	Prodromal hepatitis B*
Antiepileptic drugs	Acute human immunodeficiency virus infection*
Diuretics and laxatives	Bacterial
Chloroquine	Streptococcal pharyngitis (children)*
Quinidine	Chronic sinusitis*
Bupropion	Dental abscess*
Nonimmunologic mast cell degranulators	<i>Helicobacter pylori</i>
Aspirin and other nonsteroidal anti-inflammatory drugs	Parasitic
Opiates	Schistosomiasis*
Contrast agents	Strongyloides*
Angiotensin-converting enzyme inhibitors (angioedema)	Giardiasis*
Tubocurarine	<i>Entamoeba histolytica</i> *
Vasculitides and autoimmune diseases	<i>Plasmodium falciparum</i> *
Histamine-releasing autoantibodies to the mast cell immunoglobulin E receptor	<i>Ancylostoma</i> *
Urticarial vasculitis*	<i>Onchocerca</i> *
Other vasculitides	<i>Echinococcus</i> *
Polyarteritis nodosa*	<i>Trichinella</i> *
Churg–Strauss syndrome*	<i>Toxocara</i> *
Systemic lupus erythematosus*	<i>Fasciola</i> *
Still's disease*	Fungal (superficial infections rarely febrile)
Hematologic diseases	<i>Candida</i>
Schnitzler syndrome*	<i>Trichophyton rubrum</i>
Waldenström's macroglobulinemia*	Autoinflammatory disease
Hypereosinophilic syndrome*	Familial Mediterranean fever*
Non-Hodgkin lymphoma*	Neonatal-onset multisystem inflammatory disease or chronic infantile neurologic cutaneous and arthropathy syndrome*
Polycythemia vera*	Familial cold autoinflammatory syndrome*
	Muckle–Wells syndrome*

Table 2. Initial workup

Patient history
Comorbid conditions
Allergies and exposures
Frequency and pattern of symptoms
Family history
Complete review of systems
Medication history over preceding 21 days
Physical exam
Complete cutaneous exam
Lymph node exam
Perioral exam for signs of angioedema
Complete blood count with differential

Table 3. “Red flags” suggestive of complex urticaria

Atypical wheals
Burning sensation
Persist >24 hours
Resolve with bruising
Other coexisting skin lesions like macules, papules, livedo reticularis, or ulcers
Fever
Arthralgia
Weight loss
Lymphadenopathy
Refractory to therapy with antihistamines
Cytopenia, eosinophilia, atypical lymphocytes, or other unexplained laboratory abnormalities

Fever and other systemic symptoms are important markers of rare but serious urticarial syndromes. However, it is important to recognize that urticaria may also be an incidental finding in ill hospitalized patients, unrelated to other symptoms or due, perhaps, to concurrent infection or medications used to treat an infection. In such situations, it is the responsibility of the treating physician to gauge whether the symptoms and urticaria are related. Given the relative rarity of systemic urticarial syndromes, it is reasonable to treat the patient for common causes of urticaria if no red flags are present or if systemic symptoms can be explained by another more likely cause.

In such cases, we suggest treating any underlying causes of simple urticaria discovered during the history and physical exam. In addition, all non-essential potential culprit medications should be eliminated, and drugs with the tendency to worsen urticaria (i.e., known mast cell degranulators such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and opiates; included in Table 1) should be avoided. Nonsedating antihistamines are the mainstay of treatment and improve symptoms in 77% (1). Combination therapy with H1 and H2 antihistamines can further improve control (8,9), whereas sedating antihistamines are useful for breakthrough symptoms. We recommend this type of combination regimen, described in detail in Table 4, as initial therapy for simple urticaria. Patient response to the therapeutic trial can be an important diagnostic indicator; treatment failure is itself a red flag and may indicate the presence of an urticarial syndrome that does not respond to antihistamines. Such patients generally require further investigation to rule out systemic disease.

Approach to the patient with red flags

Vasculitides and immunologic disorders

Urticarial vasculitis is the most common of the urticarial syndromes, comprising 5–10% of cases of chronic urticaria (3). Atypical urticarial lesions that last longer than 24 hours, burn rather than itch, or resolve with bruising, are suggestive of the diagnosis but are not always present (FIG. 2). Roughly 40–60% of patients lack these findings and present with typical wheals (10,11). Whether typical or atypical, urticarial lesions that are chronic or unresponsive to oral antihistamines should be biopsied to rule out urticarial vasculitis and assess the makeup of the inflammatory infiltrate. Of 312

patients biopsied for refractory urticaria, 15% had histologically confirmed urticarial vasculitis. More than half of those patients had no atypical urticarial lesions. Extracutaneous symptoms like fever (38%) and arthralgias (36%) were present in 81%, however (11).

Histologic findings of a small vessel vasculitis, leukocytoclasia, perivascular neutrophilic infiltrate, red blood cell extravasation, and fibrin deposition in and near blood vessels support the diagnosis of urticarial vasculitis. Once diagnosed, the patient should be evaluated for specific organ involvement, as the lymph nodes, liver, spleen, synovia, kidneys, gastrointestinal tract, respiratory tract, eyes, central nervous system, peripheral nerves, and heart can be affected. A thorough review of systems, CBC with differential, basic metabolic panel, liver function tests, fecal occult blood, and urinalysis should be performed to look for involvement of other organs.

Urticarial vasculitis is caused by immune complex deposition in blood vessel walls. It may be idiopathic or associated with serum sickness, connective tissue disease such as systemic lupus erythematosus (SLE) or Sjögren's syndrome, hematologic malignancies, infections, medications, Schnitzler syndrome, or physical urticarias (4). Screening labs in addition to those previously mentioned should be performed to look for these disorders. A reasonable starting point includes testing for ANA, C3 and C4 complement levels, antineutrophilic cytoplasmic antibodies, and erythrocyte sedimentation rate (ESR), along with any screening tests for diseases suggested by specific symptoms or laboratory findings. Elevated ESR is the most frequently abnormal lab finding, present in 43% of patients (11). Patients with low complement levels (hypocomplementemic urticarial vasculitis) more frequently show signs of systemic involvement, particularly renal and pulmonary disease, than their normocomplementemic counterparts. They are also more likely to meet criteria for SLE and may develop late systemic manifestations of disease such that long-term follow-up is important (2). All patients with a new diagnosis of urticarial vasculitis should be evaluated for SLE.

The treatment of urticarial vasculitis should be tailored to any specific underlying disorder, but generally therapy begins with systemic steroids at a dose of 1 mg/kg prednisone daily, or its equivalent. If there is significant extracutaneous involvement, particularly vasculitis of the kidneys, additional therapy may be required, and the patient should be evaluated by both nephrology

Table 4. List of antihistamines and adjunctive agents with doses

A. Nonsedating H1 blockers	B. H2 blockers	C. Sedating H1 blockers	D. Adjunctive medications
Cetirizine (Zyrtec)	Ranitidine (Zantac)	Diphenhydramine (Benadryl)	Montelukast (Singulair) ^a
Adult (6–11): 5–10 mg daily	Adult (≥ 16): 150 mg twice daily	Adult (≥ 12): 25–50 mg every 6 hours or as needed	Adult (≥ 15): 10 mg daily
Child (2–5): 2.5 mg daily or twice daily	Child (≤ 16): 1–2 mg/kg twice daily	Child (6–11): 12.5–25 mg every 6 hours or as needed	Child (6–14): 5 mg daily
Infant (0.5–2): 2.5 mg daily		Child (2–5): 6.25 mg every 6 hours or as needed	Child (1–5): 4 mg daily
Fexofenadine (Allegra)	Cimetidine (Tagamet)	Hydroxyzine (Atarax)	Zafirlukast (Accolate) ^a
Adult (≥ 12): 60 mg twice daily	Adult: 400 mg twice daily	Adult (≥ 12): 25 mg every 6 hours or as needed	Adult (≥ 12): 20 mg twice daily
Child (6–11): 30 mg twice daily	Child: 5–10 mg/kg every 6 hours	Child (6–12): 12.5–25 mg every 6 hours or as needed	Child (5–11): 10 mg twice daily
Loratadine (Claritin)		Chlorpheniramine (Chlor-Trimeton)	Doxepin ^b
Adult (≥ 6): 10 mg daily		Adult (≥ 12): 4 mg every 6 hours or as needed	Adult (≥ 12): 10 mg–150 mg daily
Child (2–5): 5 mg daily		Child (6–11): 2 mg every 6 hours or as needed	Child (≤ 12): not recommended
Desloratadine (Clarinex)		Cyproheptadine (Periactin)	
Adult (≥ 12): 5 mg daily		Adult (≥ 15): 4 mg three times daily or as needed	
Child (6–11): 2.5 mg daily or twice daily		Child (7–14): 4 mg twice to three times daily or as needed	
Child (1–5): 1.25 mg daily		Child (2–6): 2 mg twice to three times daily or as needed	
Infant (0.5–1): 1 mg daily		Clemastine (Tavist)	
Levocetirizine (Xyzal)		Adult (≥ 12): 1–2 mg twice daily or as needed	
Adult (≥ 12): 5 mg daily		Child (6–11): 1 mg twice daily or as needed	
Child (6–11): 2.5 mg daily			

^aSelect patients, particularly those with asthmatic or allergic respiratory symptoms, may benefit from the addition of a leukotriene inhibitor.

^bIn refractory cases, sedating tricyclic antidepressants such as doxepin may be added at night.

For initial combination therapy, select one medication from each of columns A, B, and C; column D shows adjunctive medications.

and rheumatology. Once clinical remission is achieved, systemic steroids should be slowly tapered. To avoid relapses with steroid tapering, a steroid-sparing agent is often added to help maintain disease control and avoid long-term complications of hypercortisolism. The type of histopathologic infiltrate may help guide the selection of a steroid-sparing agent, as some believe urticarial vasculitis with a significant neutrophilic infiltrate may respond to targeted antineutrophilic therapy with dapsone or colchi-

cine. Dapsone (up to 100 mg twice daily), colchicine (0.6 mg twice daily initially and up to four times daily), hydroxychloroquine (initial dose 200 mg twice daily), and mycophenolate mofetil (initial dose 500 mg twice daily) have all shown efficacy in treating urticarial vasculitis. As mentioned, it does not respond to therapy with antihistamines.

Rarely, urticarial lesions may occur in other vasculitides, such as polyarteritis nodosa (6%) and Churg–Strauss (less than 10%) (3). In these cases,



FIG. 2. Urticarial vasculitis: edematous, erythematous plaques on the anterior shins which leave ecchymotic patches upon resolution.

other cutaneous findings like palpable purpura, petechiae, livedo reticularis, macules, papules, or nodules, as well as systemic symptoms suggesting multiorgan involvement, may be present. A skin biopsy is crucial for diagnosis. A workup for signs of systemic involvement, as previously mentioned, is important. Treatment should commence with immunosuppressive therapies aimed at controlling the underlying pathology.

Still's disease, a subset of juvenile rheumatoid arthritis, classically affects children but may also occur in adults. It is characterized by recurrent high spiking fevers and arthritis with a transient, non-pruritic, salmon-colored macular or papular rash that may sometimes appear urticarial. Though rare, Still's disease should be considered in the differential diagnosis of patients with recurrent fever and urticaria (12,13). A markedly elevated ferritin level in the presence of characteristic symptoms and the classic rash is supportive, though not diagnostic, of this condition.

Infectious diseases

Viral upper respiratory tract infections are the most frequent cause of acute urticaria in children and adults (2,14,15), but other viral, bacterial, fungal, and parasitic infections may result in hives. Though less common, these infections are nonetheless important to consider in the hospitalized patient with localizing symptoms or laboratory findings. Among other viral infections, hepatitis B is the most common. The prodromal phase of infection may include an urticarial rash occurring together with serum sickness-like sys-

temic symptoms (16). Infectious mononucleosis due to Epstein-Barr virus and acute human immunodeficiency virus (HIV) infection are other reported viral causes of urticarial lesions (2,17–19).

Among bacteria, streptococcal pharyngitis is an especially common cause of urticaria, particularly in children (20). Chronic sinusitis and dental abscesses as well as subclinical *Helicobacter pylori* infection have also been implicated. Though causal relationships may be difficult to establish, treatment of these infections with antibiotics often leads to resolution of urticaria. Meanwhile, such patients respond poorly to treatment with antihistamines (2,4,21,22).

Fungal infection with *Candida* and *Trichophyton rubrum* has been associated with urticaria in the literature, but these data show no clear causal role (2). Numerous parasitic infections may cause urticaria (Table 2), likely due to their induction of an IgE immune response. Schistosomiasis, known as “urticarial fever” in parts of East Asia, frequently results in urticaria, fever, arthralgias, diarrhea, and hepatosplenomegaly 4–8 weeks after penetration of the skin by schistosomal larvae (4). Strongyloides infection may be associated with urticarial lesions, either diffusely or localized to the perianal area. As this helminth can complete its life cycle within a single human host, subclinical infection may persist for years.

Most infectious causes of urticaria other than upper respiratory infections are sufficiently rare that routine specific testing adds nothing to diagnostic yield (6). However, one should consider infectious causes in a patient with refractory urticaria and localizing infectious symptoms. Patients with a history of travel to endemic locations (which may include parts of the Southeastern United States) and an unexplained peripheral eosinophilia, for example, should be screened for stool ova and parasites. It may also be worthwhile to screen for evidence of infection in patients with urticaria of unknown cause prior to starting an immunosuppressive agent, which may lead to disseminated disease. Discussion of the treatment of these diseases is beyond the scope of this article but is readily available in reference texts.

Hematologic diseases

Schnitzler syndrome is a rare disease defined by the combination of chronic urticaria and a monoclonal IgM gammopathy. Cutaneous lesions are those of typical urticaria, though without significant pruritus, lasting less than 24 hours, and

disappearing without sequelae. Historical red flags include systemic symptoms of intermittent fever in 88%, bone pain in 72%, arthralgia or arthritis in 82%, weight loss in 64%, lymphadenopathy in 44%, and a failure to respond to therapy with antihistamines. Elevated ESR and white blood cell count are present in nearly all patients, whereas complement levels are normal (23).

Schnitzler syndrome is a chronic disease which typically has a benign course. However, at least 15% of patients eventually develop a lymphoproliferative disorder, most often Waldenström's macroglobulinemia (22,24). Initial workup should include bone marrow biopsy, immunoelectrophoresis of serum and urinary proteins, and analysis of immunoglobulin subtypes; biannual follow-up with an experienced hematologist is recommended.

Historically, there has been no consistently effective treatment for Schnitzler syndrome. Corticosteroids, colchicine, hydroxychloroquine, interferon- α , and thalidomide have all shown partial efficacy, though often with limiting side effects. Phototherapy with psoralen + ultraviolet A has been used to reduce urticaria and bisphosphonates to reduce bone pain, though neither effectively treats systemic symptoms like fever. More recently, anakinra, a synthetic interleukin (IL)-1 receptor antagonist, has brought complete remission in all eight patients treated with a daily dose of 100 mg injected subcutaneously. Remission has reportedly occurred within 24 hours and has been durable without significant side effects (22,23). We recommend initial symptomatic therapy with NSAIDs for bone pain and arthralgia along with colchicine. Steroids and immunosuppressive agents should be tried when systemic symptoms like fever or arthralgia are disabling. Anakinra is a promising therapeutic option limited by its high cost.

Monoclonal gammopathy of undetermined significance may mimic Schnitzler syndrome if present in a patient with chronic urticaria due to other causes. Waldenström's macroglobulinemia, a low-grade plasma cell malignancy characterized by a circulating IgM paraprotein and lymphoid proliferation in the bone marrow, may uncommonly manifest with urticaria, as well as purpura, edema, ulceration, or cutaneous signs of systemic amyloidosis. Non-Hodgkin lymphoma and polycythemia vera are other hematologic disorders that may be associated with urticaria (3,4,22).

Hypereosinophilic syndrome is defined by peripheral eosinophilia ($>1500/\text{mm}^3$ for more than 6 months) with clinically significant invasion of

tissues by eosinophils. It is a diagnosis of exclusion, so other causes of eosinophilia, such as allergic reactions, parasitic infections, Loeffler syndrome, Churg–Strauss disease, and eosinophilic leukemia must be ruled out. Cutaneous lesions include nodules and plaques from infiltration of eosinophils. An immediate pressure urticaria may also occur with prompt wheal formation at sites of pressure. Eosinophil infiltration of the heart, lungs, and nervous system are common causes of morbidity. Once the diagnosis has been made, further testing is performed to classify the disorder into myeloproliferative and lymphocytic variants to help guide therapy (4,25–27).

Autoinflammatory syndromes

Autoinflammatory syndromes are characterized by recurrent episodes of multisystemic inflammation due not to infection or autoimmunity, rather, to mutations in genes that control inflammatory signaling. This rare group of diseases includes many entities, but those that commonly present with fever and urticarial lesions are hyperimmunoglobulinemia D with periodic fever syndrome and the cryopyrinopathies: neonatal-onset multisystem inflammatory disease, otherwise known as chronic infantile neurologic cutaneous and arthropathy syndrome; familial cold autoinflammatory syndrome; and Muckle–Wells syndrome. These diseases, which are described in greater detail elsewhere (28), feature recurrent episodes of fever with skin lesions, arthralgia or arthritis, and other systemic symptoms such as abdominal pain, myalgia, ocular symptoms, headaches, neurological symptoms, amyloidosis, and elevated acute phase reactants.

A detailed family history is essential, as the majority of cases are familial and present in infancy or childhood, only rarely in adulthood. They share a common cause, resulting from defects in cryopyrin, pyrin, or pyrin-binding protein that lead to activation of the IL-1 β pathway. When an autoinflammatory syndrome is suspected in a young patient with a history of periodic fever, genetic testing can be performed to confirm the diagnosis. High-dose corticosteroids (1 mg/kg/day of prednisone or equivalent) and colchicine have shown efficacy in treating autoinflammatory syndromes. Etanercept, infliximab, cyclosporine, and intravenous immunoglobulin have been used successfully as steroid-sparing agents and in refractory cases. However, the IL-1 receptor antagonist anakinra has shown the most promise in rapid resolution of inflammation by

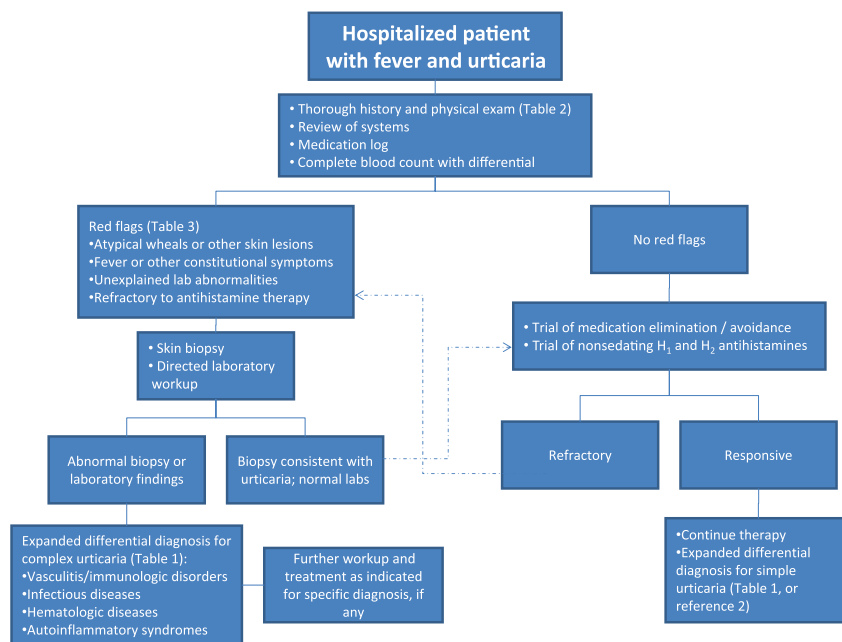


FIG. 3. Diagnostic approach to the hospitalized patient with fever and urticaria.

blocking the IL-1 β pathway (29). A more specific antihuman IL-1 β antibody, canakinumab, shows similar potential (30).

Conclusion

Urticarial lesions are extremely common in the general public, and the hospitalized patient is no exception. Of the numerous triggers and diseases potentially associated with urticaria, many have significant implications for the overall health of the patient. It is therefore important for dermatologists to be familiar with these conditions and to be able to recognize atypical presentations requiring more thorough investigation. Luckily, the vast majority of cases are routine, readily treated symptomatically and without lasting health consequences. Yet, in the febrile or otherwise ill hospitalized patient, even routine cases of urticaria may not always appear straightforward. Accordingly, we offer a diagnostic and therapeutic algorithm to guide the directed workup of urticaria in the hospitalized patient so that the diagnosis – rare or mundane – may be made with greater confidence (FIG. 3). A comprehensive history and physical examination is chiefly important. Red flag physical findings or systemic symptoms should guide further workup without the need for exhaustive and indiscriminate laboratory testing.

References

- Humphreys F, Hunter JA. The characteristics of urticaria in 390 patients. *Br J Dermatol* 1998; **138** (4): 635–638.
- Greaves MW, Kaplan A, eds. *Urticaria and angioedema*. New York, NY: Marcel Dekker, 2004: 143.
- Peroni A, Colato C, Schena D, et al. Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria: part I. Cutaneous diseases. *J Am Acad Dermatol* 2010; **62** (4): 541–555.
- Peroni A, Colato C, Schena D, Girolomoni G. Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria: part II. Systemic diseases. *J Am Acad Dermatol* 2010; **62** (4): 557–570.
- Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. *Urticaria: clinical, diagnostic and therapeutic aspects*. New York, NY: Springer, 1998.
- Heckbert SR, Stryker WS, Coltin KL, et al. Serum sickness in children after antibiotic exposure: estimates of occurrence and morbidity in a health maintenance organization population. *Am J Epidemiol* 1990; **132** (2): 336–342.
- Kozel MM, Mekkes JR, Bossuyt PM, et al. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. *Arch Dermatol* 1998; **134** (12): 1575–1580.
- Bleehen SS, Thomas SE, Greaves MW, et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. *Br J Dermatol* 1987; **117** (1): 81–88.
- Paul E, Bodeker RH. Treatment of chronic urticaria with terfenadine and ranitidine. A randomized double-blind study in 45 patients. *Eur J Clin Pharmacol* 1986; **31** (3): 277–280.
- Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. *J Am Acad Dermatol* 1992; **26** (3 Pt 2): 441–448.

11. Tosoni C, Lodi-Rizzini F, Cinquini M, et al. A reassessment of diagnostic criteria and treatment of idiopathic urticarial vasculitis: a retrospective study of 47 patients. *Clin Exp Dermatol* 2009; **34** (2): 166–170.
12. Adams A, Lehman TJ. Update on the pathogenesis and treatment of systemic onset juvenile rheumatoid arthritis. *Curr Opin Rheumatol* 2005; **17** (5): 612–616.
13. Setterfield JF, Hughes GR, Kobza Black A. Urticaria as a presentation of adult Still's disease. *Br J Dermatol* 1998; **138** (5): 906–908.
14. Mortureux P, Leaute-Labreze C, Legrain-Lifermann V, et al. Acute urticaria in infancy and early childhood: a prospective study. *Arch Dermatol* 1998; **134** (3): 319–323.
15. Zuberbier T, Ifflander J, Semmler C, et al. Acute urticaria: clinical aspects and therapeutic responsiveness. *Acta Derm Venereol* 1996; **76** (4): 295–297.
16. Cribier B. Urticaria and hepatitis. *Clin Rev Allergy Immunol* 2006; **30** (1): 25–29.
17. Soter NA. Acute and chronic urticaria and angioedema. *J Am Acad Dermatol* 1991; **25**: (1 Pt 2): 146–154.
18. Dover JS, Johnson RA. Cutaneous manifestations of human immunodeficiency virus infection. Part I. *Arch Dermatol* 1991; **127** (9): 1383–1391.
19. Friedman D, Picard-Dahan C, Grossin M, et al. Chronic urticaria revealing an HIV infection. *Eur J Dermatol* 1995; **5**: 40–41.
20. Schuller DE, Elvey SM. Acute urticaria associated with streptococcal infection. *Pediatrics* 1980; **65** (3): 592–596.
21. Sakurai M, Oba M, Matsumoto K, et al. Acute infectious urticaria: clinical and laboratory analysis in nineteen patients. *J Dermatol* 2000; **27** (2): 87–93.
22. Tebbe B, Geilen CC, Schulzke JD, et al. *Helicobacter pylori* infection and chronic urticaria. *J Am Acad Dermatol* 1996; **34** (4): 685–686.
23. De Koning HD, Bodar EJ, van der Meer JW, et al. Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. *Semin Arthritis Rheum* 2007; **37** (3): 137–148.
24. Lipsker D, Veran Y, Grunenberger F, et al. The Schnitzler syndrome. Four new cases and review of the literature. *Medicine* 2001; **80** (1): 37–44.
25. Roufosse FE, Goldman M, Cogan E. Hypereosinophilic syndromes. *Orphanet J Rare Dis* 2007; **2**: 37–48.
26. Simon D, Simon HU. Eosinophilic disorders. *J Allergy Clin Immunol* 2007; **119** (6): 1291–1300.
27. James W, Berger T, Elston D, eds. *Andrews' diseases of the skin: clinical dermatology*, Tenth ed. Philadelphia, PA: Elsevier, 2006: 746.
28. Farasat S, Aksentijevich I, Toro JR. Autoinflammatory diseases: clinical and genetic advances. *Arch Dermatol* 2008; **144** (3): 392–402.
29. Gattorno M, Sormani MP, D'Ossualdo A, et al. A diagnostic score for molecular analysis of hereditary autoinflammatory syndromes with periodic fever in children. *Arthritis Rheum* 2008; **58** (6): 1823–1832.
30. Lachmann HJ, Lowe P, Felix SD, et al. In vivo regulation of interleukin 1 beta in patients with cryopyrin-associated periodic syndromes. *J Exp Med* 2009; **206** (5): 1029–1036.