

WHAT ELSE, IF NOT CHRONIC SPONTANEOUS OR INDUCIBLE URTICARIA?

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ABSTRACT

Urticaria presents to both general and specialist practitioners as a common disorder. The duration, nature of the lesions and resolution must fit the typical pattern of chronic idiopathic or inducible urticarias. Any deviation from the expected clinical pattern or failure to respond to therapy should prompt the clinician to seek an alternative diagnosis. The most common cause of urticaria in childhood is infection. This is commonly misdiagnosed as drug allergy. The systemic disorders that manifest with urticaria will present clues in the nature of the lesions and the incomplete resolution of skin signs. Autoinflammatory disorders may present with a family history of affected family members.

Urticaria has multiple synonyms – wheals, hives or even ‘bommels’ – as they are called by communities in Cape Town, South Africa. These indurated papules or plaques, which usually have surrounding erythema, may be a few millimetres to centimetres in diameter and can be intensely itchy. Urticaria is a common condition with a lifetime incidence of 15–22%.^{1,2} It is preponderant among female adults but a roughly equal male–female distribution in childhood. Acute urticaria lasts for less than six weeks. Chronic urticaria persists for longer than six weeks and may be episodic or chronic and unrelenting. This article covers the conditions that may present with urticaria but need to be differentiated from chronic spontaneous urticaria, the inducible urticarias and immune IgE-mediated urticaria.

THE COMMON CHRONIC URTICARIAS

Chronic spontaneous urticaria (CSU) presents with recurrent urticaria with or without angioedema and lasts longer than six weeks. The rash tends to migrate around the body without leaving skin changes except for scratch marks left by the patient. Histamine is the main vasoactive mediator of this lesion and may be accompanied by angioedema in 40%¹ of cases. Urticaria may occur on its own in 50% of patients, as may angioedema, which is predominantly mediated by bradykinin. Isolated angioedema requires investigation in order to exclude hereditary angioedema or drug-related angioedema before being classified as part of CSU.

The chronic inducible urticarias are recurrent and occur in response to a specific trigger or stimulus. These urticarias need exclusion by detailed history and specific office investigations.

Urticaria may manifest as part of an IgE-mediated allergy to foods, drugs, latex or venoms. This is usually apparent from the history and may progress to anaphylaxis.

CHILDHOOD INFECTION-RELATED URTICARIA

Acute urticaria in childhood is attributed to infections in up to 80% of cases.^{3–5} This may occur during an acute infection or after the symptoms have resolved. The exact pathogenesis is unknown but immune activation and immune complex formation with or without complement activation is postulated.

Viruses isolated from patients with acute urticaria include picornavirus, respiratory syncytial virus, coronavirus, adenovirus, cytomegalovirus, influenza, rhinovirus, Epstein-Barr and human immunodeficiency virus (HIV).^{1,2} Patients may develop urticaria prior to presenting with jaundice in hepatitis A, B and C infections. Mycoplasma-related urticaria is usually refractory to antihistamines and will respond to macrolide antibiotics.⁶ Other bacterial triggers may include *Group A beta-haemolytic streptococcus*, *Haemophilus Influenzae* and *Staphylococcus Aureus*.²

Patients with parasitaemia may present with urticaria and eosinophilia on differential count.⁷ Patients who have consumed fish infected with the fish tapeworm, *Anisakis*, may also present with urticaria. Important clues from the patient's history would be previous tolerance of fin fish and subsequent consumption without a clinical reaction. The specific IgE to *Anisakis* may be measured to exclude sensitisation, but it is also important to ascertain whether there is allergic sensitisation to fish by skin-prick test (SPT) to either extract, prick-to-prick or allergen-specific IgE. If no sensitisation is present, an open-food challenge will need to be performed to exclude food allergy.

The greatest concern with childhood infection-related urticaria is the possibility of an incorrect diagnosis of drug allergy, usually to penicillin. Patients will often be prescribed antibiotics for a viral infection, which will confound the diagnosis of infection-related urticaria. The usual diagnostic dilemma is:

- Is this infection-related urticaria?
- Is this drug allergy?
- Is this a combination of an infection- and a drug-related side-effect?

A recommended approach is to evaluate the patient for other signs of infection such as a pyrexia, coryzal symptoms or elevated infection markers. The patient should be taken off the drug and evaluated for evidence of a bacterial infection requiring antibiotics. If a bacterial infection is present, then a drug from a different antibiotic class will need to be prescribed until an allergy evaluation can be performed. All of these patients will require a challenge to the culprit drug after the infection has resolved. The mislabelling of patients with penicillin allergy may result in the use of expensive alternative antibiotics and the emergence of drug-resistant organisms. The majority of childhood bacterial community-acquired infections will respond to a penicillin antibiotic and do not require the broad-spectrum alternatives that may be prescribed for incorrectly labelled patients.

NON-IgE-MEDIATED FOOD URTICARIA

Food additives such as colourants, preservatives, antioxidants and artificial sweeteners may cause urticaria. However, no confirmatory tests such as SPTs exist for these additives because these reactions are non-IgE-mediated. This occurs more commonly in those patients who react to aspirin.⁸ Reactions to the natural dyes of red and yellow are well-documented causes of urticaria and anaphylaxis.⁸ Cellular antigen-stimulation tests (CAST) or basophil-activation tests (BAT) may assist with a diagnosis in these patients.

Foods such as strawberries and shellfish may cause direct histamine release from mast cells, and these patients will present with skin-prick-negative urticaria.

Scombroid food poisoning is caused by improperly stored fish that contain high quantities of histidine. This histidine is decarboxylated to histamine and results in histamine poisoning in patients who ingest the fish. This is often misdiagnosed as fish allergy because the symptoms are identical. Systematic allergy evaluation is required to diagnose or refute true allergy.

NON-STEROIDAL ANTI-FLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) may cause both urticaria and angioedema. Non-immunologic reactions to NSAIDs may be due to individual abnormalities in arachidonic acid metabolism. These patients react to drugs that inhibit cyclooxygenase-1 (COX-1) but they may tolerate acetaminophen and selective COX-2 inhibitors.

Patients allergic to specific NSAIDs may present with acute urticaria after exposure to the drug. This is on an immune basis.

No diagnostic tests are indicated for patients who present with acute urticarial, except when an IgE-mediated food allergy or an NSAID reaction is suspected.⁹

URTICARIAL VASCULITIS

Urticarial vasculitis (UV) is a rare disease which has a peak incidence in the fourth decade¹⁰ and involves mainly women.

UV may primarily involve the skin or may cause multisystem disease. This may be predominantly urticaria with minimal vasculitis or severe systemic involvement with minimum urticaria. The two components of this disease are urticaria and histopathologic evidence of leukocytoclastic vasculitis (LCV) of the dermal small vessels. UV may be hypocomplementaemic or normocomplementaemic.¹¹

Hypocomplementaemic UV syndrome is recognised as a specific autoimmune disorder present for longer than six months. Systemic features may be arthritis or arthralgias, glomerulonephritis (GN), pulmonary manifestations such as uveitis, or episcleritis. This is most likely associated with connective-tissue diseases such as systemic lupus erythematosus (SLE) or Sjogrens. Other causes of UV may be drugs such as infliximab or dermal fillers, infections such as hepatitis B or C, or lymphoproliferative disorders. A biopsy is required to show the LCV of new lesions.

UV differs from idiopathic immune urticaria in that the lesions may last for 3–7 days,¹ are poorly responsive to antihistamines and burn rather than itch. These lesions may leave residual pigmentation or purpura in up to 35% of cases.¹² Common urticaria lasts for less than 24 hours, is predominantly itchy, responds well to antihistamines and leaves no staining of the skin. Residual scratch marks may be present.

UV may present with angioedema when the vasculitis affects the deeper layers of the skin. This requires a biopsy to confirm the diagnosis. Bruising may be present.

TABLE 1: THE SYSTEMIC MANIFESTATIONS OF UV

SYSTEM	CLINICAL MANIFESTATIONS
Musculoskeletal	Arthralgia and arthritis
Renal	Proteinuria, haematuria indicative of a number of sub-types of GN
Pulmonary	Cough, dyspnoea, haemoptysis, pleuritic, pleural effusions, asthma and chronic obstructive pulmonary disease
Gastrointestinal	Abdominal pain, nausea, vomiting and diarrhoea
Ophthalmologic	Episcleritis, uveitis and conjunctivitis
Cardiovascular	Rarely pericarditis, tamponade and valvular disease
Neurologic	Idiopathic intracranial hypertension, aseptic meningitis, cranial-nerve palsies, peripheral neuropathy and transverse myelitis

Abnormal laboratory features may be an elevated erythrocyte sedimentation rate (ESR), and elevated C reactive protein (CRP), low levels of C3, C4 and C1q and positive antinuclear antibodies (ANAs).

URTICARIA PIGMENTOSA

Mastocytosis results from hyperplasia of the mast cells present in the skin, the gastrointestinal tract and the reticuloendothelial system. Lesions present before the age of two years in 90% of patients, and present as urticaria pigmentosa in 75% of cases. Twenty per cent of patients present with mastocytoma and 5% with diffuse cutaneous mastocytosis.¹³ Cutaneous lesions may be macular or maculopapular and usually spare the face and limbs.

These lesions usually have a symmetrical distribution. Systemic mastocytosis may have no haematologic involvement or may present as aggressive mast-cell leukaemia.¹⁴ Patients may present with urticaria, itching, flushing, nausea, vomiting, abdominal pain, diarrhoea and headaches. Affected patients may have more severe reactions to insect stings and drugs. The diagnosis may be suspected in patients who have a positive Darier's sign. Cutaneous mastocytomas become erythematous and urticate on pressure or scratching. Diagnosis is made on skin biopsy which shows an increase in dermal mast cells.



Figure 1: Erythema Multiforme in a paediatric patient

Mast-cell activation disorders may present with systemic symptoms and urticaria and angioedema.¹¹

AUTOINFLAMMATORY CONDITIONS

Autoinflammatory diseases (AID) are rare and can manifest as a chronic recurrent urticarial rash with systemic features such as recurrent fevers, arthralgias/arthritis, eye inflammation, fatigue and headaches. These disorders are usually associated with a delay in diagnosis and may have amyloidosis from the chronic inflammation.¹⁵ Cryopyrin-associated periodic syndrome (CAPS) includes familial cold autoinflammatory syndromes (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID).

The urticarial lesions in AID may differ in appearance from chronic urticaria in that the lesions in AID do not have dermal oedema and are flat erythematous patches. These lesions may last up to 24 hours and are burning or painful rather than pruritic. The age of onset is often during childhood and the duration is lifelong.¹⁵ Chronic idiopathic urticaria (CIU) has a shorter course. Patients with AID often have persistently elevated septic markers and systemic symptoms. There is usually a positive family history of rashes and systemic symptoms.

OTHER DISORDERS

Schnitzler's syndrome is an extremely rare disorder that presents in middle age and diagnosis may be delayed due to under-recognition. It is characterised by a recurrent urticarial rash and monoclonal gammopathy. Associated systemic symptoms may be recurrent fever, bone and joint symptoms and lymphadenopathy. Long-term sequelae may include lymphoproliferative disorders.¹⁵

Gleich syndrome is characterised by episodic angioedema and eosinophilia. Erythema multiforme (see Figure 1) may resemble urticaria and may be caused by herpes, mycoplasma or some medications.¹¹ Bullous pemphigoid may present in the pre-blistering stage as urticaria-like papules or plaques and the correct diagnosis may be made only after the blistering occurs.

CONCLUSION

Urticaria is a condition that is commonly seen in the ambulatory setting. It is predominantly an infection that occurs in children. It is frequently misdiagnosed as penicillin allergy, which has lifelong implications if it is not investigated further. UV and the rash associated with autoinflammatory disorders differ from CSU in that the lesions are of longer duration, are painful and typically leave skin pigmentation.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

This article has been peer reviewed.

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GLOBAL HEALTH THREATS IN 2019: HOW WILL THEY AFFECT OUR PATIENTS WITH ALLERGIES AND ASTHMA?

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INTRODUCTION

South Africa currently faces many healthcare issues, including HIV, obesity and access to primary healthcare. The country has recently been ranked the unhealthiest nation in the world based on the Indigo Wellness Index – an index comprising ten measurements – including life expectancy and government spend on healthcare.¹

The World Health Organisation (WHO) has listed the greatest threats to global health in 2019, ² of which the following make up the top five:

1. Air pollution and climate change
2. Non-communicable diseases
3. Global influenza pandemic
4. Fragile and vulnerable settings
5. Antimicrobial resistance.

These top five threats to health have important applicability to patients with allergies and asthma, as described below.

AIR POLLUTION AND CLIMATE CHANGE

Air pollution is a major environmental risk to health, both cardiorespiratory and central nervous system (CNS) health, and a significant cause of premature death (worldwide, seven million people die each year from pollution-related complications).² Microscopic particles of pollution can penetrate the respiratory tree and cause lung damage. The effects are exaggerated in low- and middle-income countries in which fuel use in the home often compounds emissions from agriculture, industry and transport. In those patients with asthma, air pollution can exaggerate irritability and inflammation of the airways, leading to more frequent exacerbations.² Oxidative stress has been associated with pollutant exposure, which can possibly even bring on a new onset of asthma.^{3,4} Air pollution can also act as a nasal irritant, compounding the symptoms of allergic rhinitis (AR).

The incessant burning of fossil fuels and agricultural emissions are constantly changing the world's atmosphere, leading to the 'greenhouse effect' of global warming and a shift in weather patterns.⁵ Climate change can influence allergies and asthma through:

- increased concentrations of air pollution, which can aggravate pre-existing asthma;

- increased temperatures owing to climate change, which can lead to an increase in ground-level ozone (a chemical reaction between nitrogen oxide and organic compounds when exposed to sunlight), contributing to urban smog. Ground-level ozone can lead to increased airway inflammation, which can in turn lead to asthma exacerbations;
- warmer temperatures caused by climate change, which can lead to flowers and grasses blooming earlier and longer and releasing increased concentrations of pollens within a longer pollen season. Climate change can also cause some allergen-producing plants to migrate to new areas. The result is likely to be wider areas of pollen distribution and prolonged pollen seasons, aggravating the conditions of those with pollen-sensitive AR and asthma. For example, between 1995 and 2011, the duration of the pollen season in the United States increased by 11–27 days;⁶
- more extreme weather conditions due to climate change, which can lead to complications such as 'thunderstorm asthma': here it is proposed that pollen (and perhaps also mould particles) bursts into smaller particles during a thunderstorm, which can enter and irritate the airways and trigger asthma attacks.⁷

NON-COMMUNICABLE DISEASES

Non-communicable diseases are responsible for more than 70% of deaths worldwide, owing mainly to diabetes, cancer and heart disease. Chronic lower respiratory diseases ranked ninth among the top ten causes of death in South Africa in 2018.⁸

Although not the most common causes of fatalities, atopy-related conditions such as asthma, AR and eczema have become among the most common non-communicable diseases worldwide,⁹ causing significant morbidity. This places a heavy burden on healthcare systems and budgets and will require further healthcare planning as diseases such as asthma continue to increase.

GLOBAL INFLUENZA PANDEMIC

The WHO is constantly monitoring the circulation of influenza viruses to detect pandemic strains. The organisation predicts that the world should be on high alert for another pandemic strain within the next few years. Influenza is a particular threat in those at the extremes of age, during pregnancy, and in those with chronic heart or respiratory diseases, including asthma.¹⁰ In the event of an influenza pandemic, asthmatic patients will

be at greater risk of asthma exacerbations and pneumonitis or pneumonia. Keeping up to date with annual influenza vaccines should be a regular recommendation for asthmatic patients.

FRAGILE AND VULNERABLE SETTINGS

Some 22% of the global population (1.6 billion people) lives in fragile and vulnerable settings accompanied by poverty and/or one or more examples of weak health services, drought, famine, conflict and population displacement.² South Africa has several 'vulnerable' settings in suburban areas and informal settlements. The burden of severe asthma has been found to be highest among socio-economically disadvantaged populations.¹¹ Moreover, migration from traditionally protective rural environments into urbanised environments can lead to an increase in allergic conditions, including asthma.¹²

In conclusion, fragile and vulnerable settings carry a risk of the inhabitants of these areas having asthma which may be sub-optimally controlled and vulnerable to severe exacerbations. Healthcare personnel should try to follow up with patients from vulnerable settings frequently, and take time to educate asthmatics and their caregivers carefully about asthma control and exacerbations.

ANTIMICROBIAL RESISTANCE

The overuse of antimicrobials in people, animals and in the environment is rapidly leading to antibiotic resistance. This

is of significance in populations at higher risk of infectious complications such as those with pre-existing lung disease and asthma.¹³

Patients with allergic diseases of the airways have a reduced local immunity to infections; they are also prone to disease flare-ups, with superimposed infections. If antimicrobials become ineffective in managing infective complications, illnesses such as pneumonia and complicated sinusitis could become life-threatening complications in atopic patients.

The WHO is actively working on global plans to increase awareness of antimicrobial resistance and encourages the prudent use of antibiotics across the relevant sectors.

CONCLUSION

In conclusion, the top five global health threats to be faced worldwide in the next few years have a direct effect on patients suffering from asthma and allergies. Healthcare providers should be acutely aware of these threats and the disease burden they could impose on their patients. In addition, they should have effective management plans in place for patients vulnerable to such threats.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

This article has been peer reviewed.

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