

# Underlying systemic causes of itch\*

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**ABSTRACT** The evaluation of the pruritic patient can appear daunting at first glance. Itching can be a manifestation of an underlying disease, making a systematic approach to the itchy patient necessary. A general history and physical, along with key laboratory tests as guided by the history and physical, can yield clues to the diagnosis. Hepatobiliary, renal, endocrine and lymphoproliferative diseases are some of the most common underlying systemic causes of itch. Treatment should be guided by the diagnosis, and may include topical steroids, oral antihistamines, opioid antagonists and phototherapy. In this review we outline the steps to take when evaluating a patient with pruritus. In addition, we highlight some of the more common systemic causes of itch and discuss treatment options.

**KEYWORDS** Endocrine, haematologic, hepatobiliary, itch, malignancy, pruritus, pruritus of undetermined origin, renal, screening test, systemic itch

**LIST OF ABBREVIATIONS** Computerized tomography (CT), human immunodeficiency virus (HIV)

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## INTRODUCTION

Itching is a common complaint that may reflect underlying systemic disease. General practitioners are equipped to identify the more common cutaneous and non-cutaneous causes of itching. Dermatology consultation may be warranted if the diagnosis is unclear or the condition does not respond to treatment.

The first step in evaluation of a patient complaining of itch is to determine if it is caused by a skin condition or a systemic disease (see Tables 1 and 2). The physician should attempt to identify primary skin lesions or any evidence of infestation. It is common to miss the diagnosis of scabies. The skin exam may reveal burrows in scabies; papules and plaques in eczema, contact dermatitis and psoriasis; and vesicles in dermatitis herpetiformis and bullous pemphigoid. A biopsy of the skin may be helpful if primary skin lesions are found, and is sometimes helpful even if they are not.

The second step is to proceed to a general history and physical, with particular stress placed on the review of systems and a search for adenopathy, organomegaly and icterus. A complete medication list is especially important, as medications must be ruled out as a possible cause of itching with or without a rash. Medications that bring on itching by causing cholestasis include phenothiazines, tolbutamide, erythromycin, oestrogen, progestin and testosterone. Other drugs that can cause itching include morphine, cocaine, butophanol, aspirin, quinidine and

vitamin B complex. Even if the patient has been taking the medication for years it may still cause itch.

An attempt should be made to characterise the quality of the itch. Itching of internal disease tends to be fairly generalised and not associated with primary lesions. Some exceptions exist, including the localised anogenital itching of diabetes mellitus. Secondary changes from rubbing and scratching may be present: it is important not to mistake them for primary skin disease and make a misdiagnosis of, for example, 'dermatitis'. Aquagenic pruritus (itching provoked by bathing) may occur with xerosis, polycythaemia vera, Hodgkin's disease or mastocytosis.

If no cause is identified after a thorough history and physical, the third step in evaluation includes a search for occult disease (see Table 3). Laboratory testing is guided by the patient's history and physical findings. Often the evaluation will begin with simple and inexpensive blood tests including a complete blood count with differential, serum glucose, liver function tests, renal function tests, thyroid function tests and stool for occult blood. A chest X-ray is important to exclude Hodgkin's disease. Further testing should pursue any localising signs or symptoms. Additional tests may include serum protein electrophoresis, erythrocyte sedimentation rate, anti-mitochondrial antibodies (if the clinical context is suggestive of primary biliary cirrhosis), stool exam for ova and parasites, HIV testing, Papanicolaou smear and imaging studies – including mammography, ultrasonography and CT scans. If no underlying

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**TABLE 1** Ten major dermatological causes of pruritus

Scabies
Dermatitis herpetiformis
Atopic dermatitis
Lichen simplex chronicus
Bullous pemphigoid
Drug hypersensitivity
Urticaria
Xerosis (winter itch)
Mycosis fungoides
Psoriasis

abnormality can be identified, the patient should continue to be followed periodically because itch may precede the onset of some diseases by months to more than a year. If, after careful examination, no cause is found, the patient should be referred to dermatology.

### HEPATOBIILIARY DISORDERS

The pathophysiology of itch in hepatobiliary disorders is not clear. Endogenous opioids may play a causative role, and indeed this type of pruritus often improves with opiate antagonists. Itching may be the presenting complaint of drug-induced hepatic cholestasis (e.g. oral contraceptives) or malignancy that causes biliary obstruction. There may be a predilection for the hands and feet. Pruritus is the most common symptom of primary biliary cirrhosis. It may precede the development of jaundice by months, and is the presenting symptom in half of the patients.

### RENAL DISEASE

Itching is rarely the presenting complaint in renal disease. Often the diagnosis of renal insufficiency is established before itching develops. Associated skin changes include the discoloration common to uraemia and atrophy of sebaceous glands and eccrine sweat glands. The precise aetiology of uraemic pruritus remains undetermined. Ultraviolet B phototherapy is a major treatment option.

### ENDOCRINE DISORDERS

Hyperthyroidism, hypothyroidism, diabetes mellitus and carcinoid syndrome may each be associated with pruritus. Both hyper- and hypothyroidism can present with itch. If hyperthyroidism is discovered, treating it results in clearance of itch, while use of emollients for dry skin in hypothyroidism leads to improvement. Localised anogenital pruritus occurs in diabetic patients and may be caused by mucocutaneous candidiasis.

**TABLE 2** Five important systemic causes of itching

#### Hepatobiliary

Primary biliary cirrhosis  
Biliary obstruction  
Cholestasis during pregnancy

#### Renal

Chronic renal failure (even on dialysis)

#### Endocrine

Hyperthyroidism

#### Malignancies

Lymphoma  
Central nervous system tumours  
Multiple myeloma

#### Haematological

Polycythaemia vera  
Iron deficiency  
Paraproteinaemia

### HAEMATOLOGICAL DISORDERS

Polycythaemia vera often presents with aquagenic pruritus. The itch begins after emerging from a bath or shower and lasts for 15–60 minutes. No visible skin changes are present. Patients with aquagenic pruritus should be followed periodically for development of polycythaemia vera because the symptoms may precede diagnosis by months. Pruritus and iron deficiency may occur in patients with polycythaemia vera, and correction of the iron deficiency may result in improvement. Other myeloproliferative disorders, as well as iron deficiency that is unassociated with polycythaemia vera, may be associated with pruritus.

### MALIGNANT NEOPLASMS

The association of malignancy and generalised itching is quite rare. Of all malignancies, Hodgkin's disease more frequently presents with pruritus, which may precede the diagnosis by months. The severe, often burning, itch of Hodgkin's disease responds only to treatment of the underlying lymphoma. Itch is also very common in cutaneous T-cell lymphoma (e.g. mycosis fungoides). Visceral cancers (adenocarcinoma and squamous cell cancers of various organs), central nervous system tumours and multiple myeloma have been reported in association with pruritus.

### INFECTION

Patients with infectious diseases, most notably parasitic and HIV infection, can present with pruritus without easily recognised primary skin lesions. The itch of HIV may be

**TABLE 3** Laboratory investigation of the pruritic patient who does not have a primary dermatological disease**Routine screening tests**

Serum glucose  
 Complete blood count with differential  
 Liver function tests  
 Renal function tests (blood urea nitrogen, creatinine, urinalysis)  
 Thyroid function tests  
 Iron studies  
 Stool for occult blood  
 Chest X-ray

**Additional testing**

Serum protein electrophoresis  
 Erythrocyte sedimentation rate (ESR)  
 Antimitochondrial antibodies  
 Stool for ova and parasites  
 Papanicolaou smear  
 HIV testing  
 Imaging studies (CT scan, ultrasonography, mammography)

secondary to co-morbid conditions such as scabies, seborrhoea, candidiasis, folliculitis and lymphoma, but it may also result from the direct effects of the virus.

**PSYCHOGENIC ITCHING**

Psychogenic pruritus is a diagnosis of exclusion. It is especially important to consider and exclude scabies and pediculosis. Some patients may have delusions of parasitosis or neurotic excoriations. Patients with delusions of parasitosis complain of the sensation of insects crawling across or emerging from the skin. Delusions of parasitosis may respond to pimozide, a neuroleptic agent.

**TREATMENT**

There are many ways to treat itch symptomatically – regrettably there is no single best treatment unless a specific treatable cause can be identified. Factors known to make itching worse should be reduced. Dry skin may be improved by changing to milder soap, minimising exposure to soap, limiting bathing, avoiding hot water when bathing, applying emollients and humidifying dry environments. Stress can reduce the itch threshold and an effort should be made to address it. The sensation of itching is increased if the skin is warm, and measures to keep the skin cool can be undertaken. Topical preparations for itch should begin with moisturising emollients and menthol preparations. Topical pramoxine creams or lotions may help. Topical antihistamines are generally not recommended as they may result in contact dermatitis. Once a diagnosis is established, topical steroids may be used to treat steroid-sensitive conditions.

Systemic corticosteroids, however, have no role in pruritus of undetermined origin.

The next level of treatment includes oral medications. Antihistamines are often effective in histamine-related disorders (such as hives). Antihistamines also have sedating/soporific properties that may offer some relief. H1 receptor antagonists, alone, in combination or along with H2 receptor blockers may be required to suppress chronic urticaria. Certain antidepressants, namely doxepin, have strong antihistaminic properties as well and may have potent antipruritic potential. Paroxetine, a selective serotonin reuptake inhibitor, has been prescribed for itch associated with malignancy. Opioid antagonists, including naloxone and naltrexone, have been used successfully to treat cholestatic and uraemic pruritus, but they should not be given to patients treated with opioid analgesics. Rifampin may relieve cholestatic pruritus to some extent. Ultraviolet B phototherapy is often effective against pruritus of renal or hepatic origin, but may also be helpful in pruritus of unknown origin. Treatments are typically given 2–3 times a week for one month or so, with remissions of weeks to months being obtained.

**KEYPOINTS**

- Generalised and occasionally localised pruritus without primary cutaneous findings may be a symptom of underlying systemic disease.
- A multi-tiered evaluation of the pruritic patient should include an initial thorough history and physical with a careful skin exam, review of systems, medication history and, if necessary, laboratory investigation and psychiatric assessment. Medications and cutaneous causes should be ruled out before a search for systemic cause is begun.
- Non-cutaneous diseases that may cause pruritus include hepatobiliary, renal, endocrine, haematological, malignant and psychogenic disorders.
- Itching may be the presenting complaint of a disease that may not otherwise manifest itself for months.
- Management is multimodal, with major emphasis on avoiding factors that may exacerbate itching. Topical preparations, oral medications and phototherapy are the major components of symptomatic treatment.

**FURTHER READING**

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