Itch: scratching more than the surface

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Summary

In origin, itch can be cutaneous (‘pruritoceptive’, e.g. dermatitis), neuropathic (e.g. multiple sclerosis), neurogenic (e.g. cholestasis), mixed (e.g. uraemia) or psychogenic. Although itch of cutaneous origin shares a common neural pathway with pain, the afferent C-fibres subserving this type of itch are a functionally distinct subset: they respond to histamine, acetylcholine and other pruritogens, but are insensitive to mechanical stimuli. Histamine is the main mediator for itch in insect bite reactions and in most forms of urticaria, and in these circumstances the itch responds well to H₁-antihistamines. However, in most dermatoses and in systemic disease, low-sedative H₁-antihistamines are ineffective. Opioid antagonists relieve itch caused by spinal opioids, cholestasis and, possibly, uraemia. Ondansetron relieves itch caused by spinal opioids (but not cholestasis and uraemia). Other drug treatments for itch include rifampicin, colestyramine and 17-α alkyl androgens (cholestasis), thalidomide (uraemia), cimetidine and corticosteroids (Hodgkin’s lymphoma), paroxetine (paraneoplastic itch), aspirin and paroxetine (polycythaemia vera) and indometacin (some HIV+ patients). If the remedies specified fail, paroxetine and mirtazapine should be considered. Ultraviolet B therapy, particularly narrow-band UVB, may be superior to drug treatment for itch in uraemia.

Introduction

Itch (pruritus) is ‘an unpleasant cutaneous sensation which provokes the desire to scratch’.¹ Like pain, acute itch serves a protective function, but chronic itch is mostly a nuisance. The prevalence of itch increases with age.²,³ It may be widespread or localized, and there may be no obvious cause. Itch is a dominant symptom of skin disease and also occurs in some systemic diseases. Itch can also occur in the squamous epithelium of the conjunctivae, mouth, nose, pharynx and anogenital area, and in the ciliated epithelium of the trachea.

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Neurophysiology

When stimulated by a pruritogen, a subset of specialized C-fibres, originating superficially in the skin, conveys impulses to the dorsal horn of the spinal cord and then via the spinothalamic tract to the thalamus, and on to the somatosensory cortex (Figure 1). These C-fibres are anatomically identical to those associated with the mediation of pain but functionally distinct. The most common type of C-fibre is the mechanical and heat nociceptor (polymodal nociceptor or CMH unit). These are either insensitive to histamine or only weakly activated by it.4 C-fibres which mediate itch comprise about 5% of the afferent C-fibres in human skin nerves; they respond to histamine and other pruritogens but are insensitive to mechanical stimuli.5 Itch-mediating C-fibres have conduction velocities (mean 0.5 m/s) about half those of CMH units, and receptor fields about three times greater (up to 85 mm diameter).6

Like pain, itch can be peripheral in origin (dermal or neuropathic) or central (neuropathic, neurogenic or psychogenic). Itch originating in the skin is ‘pruritoceptive’, i.e. induced by stimulation of the free nerve endings of the specialized C-fibres by one or more of a range of pruritogens. Many endogenous chemicals are locally pruritogenic when injected into the skin, e.g. amines, proteases, growth factors, neuropeptides, opioids, eicosanoids and cytokines.7,8 Some of these chemicals act by causing histamine release from local mast cells and/or by sensitizing the relevant C-fibres (Table 1).

![Figure 1. The neuroanatomy of pruritus of cutaneous origin.](image)

However, some stimulate the nerve endings directly, e.g. papain (a protease).9 As with pain, the effects of peripheral pruritogens are modified by neuromodulators in the central nervous system. Thus itch induced locally by the intradermal injection of histamine in healthy subjects is diminished by both a peripherally-acting low-sedative H1-receptor antagonist (H1-antihistamine, e.g. cetirizine) and a centrally-acting opioid antagonist (naloxone).10 Further, just as in certain pain states there is associated allodynia (pain evoked by a non-noxious stimulus), so with itch there may be alloskines, i.e. itch evoked by lightly touching the skin surrounding a histamine-induced weal and flare reaction.11,12

Neuropathic itch can originate at any point along the afferent pathway as a result of damage to the nervous system. Localized pruritus has been reported with peripheral nerve lesions in postherpetic neuralgia,13 notalgia paraesthetica (a sensory nerve entrapment syndrome involving the posterior rami of T2 -T6 nerve roots)14 and HIV infection.15 Paroxysmal pruritus has been reported in multiple sclerosis. Unilateral pruritus is occasionally seen with a cerebral tumour, abscess or thrombosis.16–18 Neurogenic itch (itch induced centrally but with no neural damage) is often associated with increased opioidergic tone caused by an accumulation of endogenous opioids, e.g. in cholestasis,19 or by the administration of exogenous opioids. In relation to morphine-induced itch, increased serotoninergic tone may also play a part.20

Itch is also associated with certain psychiatric disorders. The absence of any primary skin lesions

Table 1 Intradermal injection of inflammatory mediators, divided by mechanism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Itch response</th>
</tr>
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<tbody>
<tr>
<td><strong>Direct stimulation of itch-specific C-fibres</strong></td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>++ +</td>
</tr>
<tr>
<td>Papain (trypase)</td>
<td>++ +</td>
</tr>
<tr>
<td>Kallikrein</td>
<td>++ +</td>
</tr>
<tr>
<td>Interleukin-2 (cytokine)</td>
<td>++ +</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>+*</td>
</tr>
<tr>
<td><strong>Effect via histamine-release</strong></td>
<td></td>
</tr>
<tr>
<td>Chymase (trypase)</td>
<td>++ +</td>
</tr>
<tr>
<td>Trypsin (trypase)</td>
<td>++ +</td>
</tr>
<tr>
<td>VIP</td>
<td>++</td>
</tr>
<tr>
<td>Substance P</td>
<td>++</td>
</tr>
<tr>
<td>Serotonin</td>
<td>+</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Weak or no pruritogenic effect; potentiates histamine</strong></td>
<td></td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>(+)</td>
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</tbody>
</table>

*In atopy; causes pain in non-atopic subjects.
lends further support to the concept of itch of central origin. Psychological factors also influence itch in the absence of psychiatric disorder. With distraction, itch can be forgotten; with training, it can be suppressed.

### Histamine

Histamine directly stimulates histamine type 1 (H₁) receptors on itch-specific C-fibres. An intradermal injection or topical iontophoretic application of histamine causes: (i) an itch which begins after 30–45 s, peaks after about 2 min, then slowly declines over 10–15 min; (ii) a weal which develops over eight minutes; and (iii) a surrounding flare.

The weal is a response to H₁-receptor stimulation, whereas the flare is the result of the secondary release of vasoactive substances from collateral axons, particularly calcitonin gene-related peptide (CGRP) and, to a lesser extent, substance P. The weal and flare response is specific for histamine-mediated itch. Histamine is the mediator for itch in several conditions, including: (i) most forms of urticaria; (ii) insect bite reactions; (iii) cutaneous mastocytosis; and (iv) drug rashes, e.g. antibiotics. The involvement of histamine is confirmed by the antipruritic effect of low-sedative H₁-antihistamines in these conditions. However, in other situations histamine plays little or no part in the mediation of itch.

The main source of histamine in the skin is the dermal mast cell from which it is released by mast cell degranulation. Both H₁- and H₂-receptors are responsible for the vasodilation and increased vascular permeability caused by histamine. Cimetidine, an H₂-receptor antagonist, does not alone reduce itching caused by histamine, but enhances the impact of H₁-antihistamines in these conditions. However, in other situations histamine plays little or no part in the mediation of itch.

### Acetylcholine

Acetylcholine stimulates histamine-sensitive and histamine-insensitive C-fibres. The flare response to intradermal acetylcholine is smaller than that induced by intradermal histamine. Patients with atopic dermatitis are less sensitive to histamine but more sensitive to acetylcholine than normal subjects. Whereas intradermal acetylcholine causes pain in normal subjects, it causes itch in atopy.

### Serotonin

Serotonin (5-hydroxytryptamine, 5HT) can cause itch by both peripheral and central mechanisms. Peripherally, it acts indirectly through the release of histamine from dermal mast cells. The central mechanism probably involves the opioid neurotransmitter system. The specific 5HT₃-receptor antagonist ondansetron relieves itch associated exogenous opioids. As no 5HT₃-receptors have been identified in the skin, this action is almost certainly central.

### Prostaglandins

Prostaglandins are not themselves pruritogenic, but potentiate itching caused by histamine and probably other mediators. Paradoxically, in one study, aspirin (a prostaglandin synthase inhibitor) made skin more sensitive to histamine injection. However, apart from a subset of HIV + patients and polycythaemia vera, non-steroidal anti-inflammatory drugs (NSAIDs) generally have no effect on itching. The benefit of NSAIDs in HIV + patients with itch may relate to blocking cytokine-induced PGE₂ production.

### Cytokines

Several hours after interleukin-2 (IL-2) is injected intradermally in both atopic and non-atopic subjects, itch and erythema occur and last 2–3 days. When given intravenously with cytotoxic drugs in the treatment of malignant melanoma, IL-2 causes intense itch. Cyclosporin, which down-regulates the production of IL-2 by activated CD-4⁺ T-lymphocytes, rapidly eases itch in atopic dermatitis. Dry skin is a major contributory factor to itch, particularly in the elderly and debilitated. This may relate to the local production of cytokines. Immune dysregulation with an altered pattern of cytokine production may be responsible for itch in some HIV + patients. Interferon γ, IL-2 and IL-12
concentrations are decreased, and IL-4, IL-5, IL-6 and IL-10 concentrations are increased in HIV+ patients.43

Neuropeptides

The release of neuropeptides that mediate neurogenic inflammation involves type-2 proteinase-activated receptors (PAR-2) in sensory nerves.48,49 Tryptase from mast cells and neutrophils cleaves PAR-2, and this may lead to histamine release. PAR-2 also releases CGRP and substance P (neurokinin 1) from nociceptive C-fibres.48,49 Both CGRP and substance P appear to potentiate itch. However, whereas substance P causes itching when injected intradermally, CGRP does not.50–52 On the other hand, there is no evidence that the concentration of substance P reached after its release from nerve fibres is high enough to release histamine from dermal mast cells. Indeed, substance P applied via a microdialysis probe does not result in a weal, only a flare, and no itch.23 Further, mast cell tryptase and chymase have been shown to degrade substance P, presumably following its release from C-fibres.53 Topical capsaicin (0.075%) depletes substance P from cutaneous nerve terminals. It also destroys about 80% of C-fibres in the superficial layers of the skin and sometimes relieves localized chronic itch.54–56 Neither topical nor intradermal capsaicin causes histamine release, or local oedema.57

Evaluation

Diagnosis of the likely cause of itch in patients without skin lesions is based on history-taking, examination and laboratory investigations (Box 1). Pattern recognition often suggests the cause.

Itch is a subjective perception and cannot be quantified objectively. The use of a visual analogue or other scale to record itch intensity provides only subjective data.46,58–60 On the other hand, scratching activity (the behavioural consequence of itch) can be quantified. The measurement of scratching activity, independent of arm or hand movements, is currently the only reliable objective

<table>
<thead>
<tr>
<th>History</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodicity</td>
<td>Full blood count and if anaemic:</td>
</tr>
<tr>
<td>day or night</td>
<td>plasma iron</td>
</tr>
<tr>
<td>intermittent or continuous</td>
<td>total iron binding capacity (transferrin)</td>
</tr>
<tr>
<td>Nature</td>
<td>plasma ferritin concentration</td>
</tr>
<tr>
<td>burning</td>
<td>Sedimentation Rate (ESR)</td>
</tr>
<tr>
<td>pricking</td>
<td>Plasma creatinine</td>
</tr>
<tr>
<td>insects crawling</td>
<td>Biochemical liver tests</td>
</tr>
<tr>
<td>Location</td>
<td>total and direct bilirubin</td>
</tr>
<tr>
<td>scapula/subscapula (notalgia paraesthetica)</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>palms of hand and soles of feet (cholestasis)</td>
<td>gamma-glutamyl transpeptidase</td>
</tr>
<tr>
<td>Provoking factors</td>
<td>aspartate and alanine transferases</td>
</tr>
<tr>
<td>activity/exercise</td>
<td>fasting total plasma bile acids</td>
</tr>
<tr>
<td>cold</td>
<td>Thyroid function (T₄, TSH)</td>
</tr>
<tr>
<td>sunlight</td>
<td>Plasma glucose (fasting)</td>
</tr>
<tr>
<td>water</td>
<td>Faecal analysis for parasitic ova</td>
</tr>
<tr>
<td>Medications</td>
<td>Other investigations</td>
</tr>
<tr>
<td>opioids</td>
<td>Chest radiograph</td>
</tr>
<tr>
<td>hypersensitivity reactions</td>
<td>Abdominal ultrasound (?lymphoma)</td>
</tr>
<tr>
<td>Atopic history</td>
<td>Skin biopsy</td>
</tr>
<tr>
<td>subclinical eczema</td>
<td></td>
</tr>
<tr>
<td>Travel history</td>
<td></td>
</tr>
<tr>
<td>parasitic infections</td>
<td></td>
</tr>
</tbody>
</table>

Box 1 Evaluation of itch without obvious cause

<table>
<thead>
<tr>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry skin?</td>
</tr>
<tr>
<td>Scabies?</td>
</tr>
<tr>
<td>Icteric conjunctivae?</td>
</tr>
<tr>
<td>Loss of weight?</td>
</tr>
<tr>
<td>Mental status?</td>
</tr>
</tbody>
</table>
efficacy end-point for use in controlled trials of new therapies for itch.\textsuperscript{61–63}

**Clinical syndromes**

**Senile itch**

Itch without an obvious cause occurs in more than half of the population aged \( > 70 \) years (Box 2). The elderly often have increased skin sensitivity to histamine. Aged skin has a lower water content than younger skin,\textsuperscript{64} and dryness of the skin may induce the local production of pruritogenic cytokines.\textsuperscript{47}

**Cholestasis**

Cholestasis is often but not always associated with itch. Typically itching starts on the soles of the feet and the palms of the hands and subsequently becomes more generalized. A central mechanism associated with increased opioidergic tone and involving activation of itch centres in the brain has been postulated.\textsuperscript{19,65} Findings consistent with such a concept include: (i) the plasma and dermal interstitial fluid concentrations of bile acids do not correlate with the subjective severity of the itch;\textsuperscript{66} (ii) in cholestasis, plasma enkephalin concentrations are increased;\textsuperscript{67,68} (iii) in cholestasis, the liver produces endogenous opioid peptides;\textsuperscript{69} (iv) plasma extracts from cholestatic patients with itch, but not from those without itch, induce naloxone-reversible scratching behaviour in animals when administered centrally;\textsuperscript{70} (v) the opioid antagonists naloxone and nalremfene substantially reduce scratching activity in most patients with cholestasis;\textsuperscript{61,71–73} (vi) the opioid antagonists nalbuphine and naltrexone administered orally induce an opioid withdrawal-like reaction in patients with cholestasis even though they have not been receiving exogenous opioids.\textsuperscript{67,74,75}

Dermal mast cells are increased in patients with cholestasis and itch, and there is evidence of degranulation with histamine release.\textsuperscript{76} However, the fact that low-sedative \( \mathrm{H}_2 \)-antihistamines do not relieve itch in cholestasis indicates that, at most, histamine plays only a minor role in its genesis.

**Uraemia**

Itch in uraemia (chronic renal failure) may be generalized or may be limited to the back and to the forearm in which the haemodialysis arteriovenous shunt is sited.\textsuperscript{77,78} Older studies reported itch in up to 85% of patients receiving dialysis.\textsuperscript{79} It occurred before dialysis in about one third of patients, and after dialysis in most.\textsuperscript{77,76,80–82} However, recent data indicate that nowadays only about 25% of patients are severely affected.\textsuperscript{83,84} Improvements in dialysis technology and technique may be the explanation for this. For example, the incidence is lower in patients using a more permeable membrane (polysulphone) than in those using a less permeable dialysis membrane (cuprophane). This suggests that more pruritogens accumulate when less permeable membranes are used.

However, many factors appear to be involved (Box 1).\textsuperscript{85} For example, the skin of patients with chronic renal failure becomes atrophic and dry.\textsuperscript{79} Pruritogenic cytokines may be produced in the dermis by various activated cells close to itch receptors.\textsuperscript{46,77,86,87} Although interleukin–1 is not itself pruritogenic, it may cause the release of pruritogens. Involvement of immunological mechanisms is further suggested by the finding that after kidney transplantation, even when there is substantial loss of transplant function, itch is rare as long as immunosuppressive therapy is continued.\textsuperscript{88}

In contrast to normal individuals and uraemic patients without itch, mast cells in itching uraemic patients are more numerous,\textsuperscript{80,82,89} possibly related to the raised parathyroid hormone plasma

<table>
<thead>
<tr>
<th>Old age</th>
<th>Renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry skin</td>
<td>Dry skin</td>
</tr>
<tr>
<td>Increased mast cell degranulation</td>
<td>Cytokines</td>
</tr>
<tr>
<td>Increased skin sensitivity to histamine</td>
<td>Mast cell proliferation</td>
</tr>
</tbody>
</table>

**Box 2** Some known or postulated causal factors in itch

<table>
<thead>
<tr>
<th>Cholestasis</th>
<th>Increased endogenous opioid peptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraneoplastic</td>
<td>Histamine release from basophils</td>
</tr>
<tr>
<td></td>
<td>Eosinophilia</td>
</tr>
<tr>
<td></td>
<td>Immune reaction</td>
</tr>
</tbody>
</table>

| | Increased skin vitamin A |
| | Secondary hyperparathyroidism |
| | Increased release of substance P |
| | Increased skin divalent ions (\( \text{Ca}^{2+}, \text{Mg}^{2+}, \text{PO}_{4}^{3-} \)) |

<table>
<thead>
<tr>
<th>Paraneoplastic</th>
<th>Increased release of substance P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increased skin divalent ions (( \text{Ca}^{2+}, \text{Mg}^{2+}, \text{PO}_{4}^{3-} ))</td>
</tr>
</tbody>
</table>
concentration that occurs in uraemic patients with secondary hyperparathyroidism. The mast cells are diffusely spread throughout the dermis and are mostly degranulated. However, these changes could be the response to skin damage from scratching.

The skin of chronic dialysis patients with itch consistently contains increased concentrations of calcium, magnesium and phosphate. An increased skin divalent ion concentration may lead to microprecipitation of calcium or magnesium phosphate, which may cause itch. Magnesium itself may be involved in the modulation of nerve conduction and the release of histamine from mast cells. It is also postulated that calcium influences itching by modifying degranulation of mast cells. Marked improvement of uraemic itch with low dialysate calcium and magnesium has been reported. Plasma histamine concentrations are much higher in uraemic patients with itch than in non-uraemic or non-itching patients, but there is no correlation between the severity of the itch and the plasma histamine concentration. Even so, an intradermal injection of histamine in itching uraemic patients causes more intense local itch than in either non-itching uraemic patients or healthy subjects, indicating an increased sensitivity to histamine. However, the importance of histamine in itch in uraemia remains uncertain; tachyphylaxis occurs with repeated intradermal injections and H₁-antihistamines are ineffective.

In uraemia, there are changes in the relative expression of mu- and kappa-opioid receptors on lymphocytes. It is possible that the imbalance in the expression of the opioid receptor subtypes may contribute to the pathogenesis of uraemic itch. However, the results from two randomized placebo-controlled crossover trials are conflicting. In the first trial, long-term haemodialysis patients rated their itch much less 1–2 days after starting naltrexone. In the second trial, also in dialysis patients, the effect of naltrexone was indistinguishable from that of placebo throughout a 4-week period.

**Solid tumours**

Generalized itch may be the presenting symptom of a solid tumour, and may be present for several years before the diagnosis is made. Specific tumours are sometimes associated with localized itch. For example: (i) scrotal itch with prostate cancer; (ii) itch in the nostrils with brain tumours which infiltrate the floor of the fourth ventricle; (iii) vulval itch with cervical cancer; (iv) peri-anal itch with cancers of the sigmoid colon and rectum. Cutaneous metastases, particularly in en cuirass breast cancer, are sometimes both painful and itchy and, interestingly, the itch appears to benefit from NSAIDs.

Neuropathic itch may complicate chemotherapy. This may be generalized or segmental and often persists after the cancer has been successfully treated.

**Haematological disorders**

Itch frequently occurs in blood disorders, e.g. polycythaemia vera, Hodgkin’s lymphoma, Sezary’s syndrome (T-cell lymphoma), leukaemia, multiple myeloma, Waldenström’s macroglobulinaemia, mycosis fungoides, benign gammopathy and systemic mastocytosis. It may be the presenting symptom.

Generalized itch occurs in nearly 50% of patients with polycythaemia vera. It also occurs in about 30% of patients with Hodgkin’s lymphoma, and may persist after disease remission.

About 5–10% of patients with Hodgkin’s lymphoma become clinically jaundiced; occasionally this is caused by vanishing bile duct syndrome. At autopsy, the incidence of hepatic involvement is over 50%. How much of the itch of Hodgkin’s lymphoma relates to hepatic infiltration and cholestasis is unclear. Itch is rare in non-Hodgkin’s lymphoma, although in Sezary’s syndrome (T-cell lymphoma) the incidence is almost 100%.

The association between iron deficiency and itch is unexplained. Itch affects only a minority of iron-deficient patients and it does not correlate with the severity of the anaemia.

**HIV/AIDS**

Itch is sometimes the first symptom of HIV-related disease, even in the absence of associated skin disease or scabies. Many HIV+ patients have dry skin and have increased plasma cytokines. However, itch develops in some HIV+ patients with no demonstrable skin lesions, and increases as the disease progresses. The itch is probably partly related to cytokine-induced PGE₂ synthesis. A subset of HIV+ patients with intractable itch also have hypereosinophilia.

Localized itch is sometimes associated with peripheral neuropathy in HIV+ patients.
Opioid-induced itch

When injected intradermally, some opioid agonists cause local itching and a typical histamine weal and flare response, e.g., morphine and methadone. In contrast, intradermal fentanyl and oxymorphone do not. Further, although H1-antihistamines relieve the local itch of intradermal morphine injection, naloxone does not when morphine 5 μg or more is administered. Nor does naloxone prevent the release of histamine from mast cells incubated for 45 min in solutions containing various concentrations of morphine sulphate. This indicates that histamine release by intradermally injected opioids is not opioid receptor-mediated.

Generalized itch occurs in about 1% of those who receive an opioid agonist by mouth or by subcutaneous or intravenous injection, and in 10–90% of patients who receive spinal opioids for labour pain or peri-operatively. The incidence depends on which opioid is used and whether the patient is opioid-naive. After spinal injection, itch spreads rostrally through the thorax from the level of the injection, and is characteristically maximal in the face. In some patients it is limited just to the nose. (This may explain why patients given opioid premedication before endoscopy are often observed scratching their nose.)

In contrast to itch induced by opioids injected intradermally, histamine release from dermal mast cells is not responsible for itch induced by clinical doses of opioids administered spinally or systemically. In these circumstances, the itch is relieved by naloxone but not by H1-antihistamines. Indeed, the dose of morphine or methadone needed to release histamine from rat peritoneal mast cells is some 10 000 times greater than the dose needed to inhibit evoked contractions of the guinea pig ileum (a model for mu-opioid receptor activation). It is therefore necessary to postulate a central opioid receptor-mediated mechanism for generalized itch associated with spinal or systemic opioids. Interestingly, plasma concentrations of histamine increase after intravenous morphine but not after spinal morphine.

Other neurotransmitter systems interact with the opioid system in relation to the mediation of itch, notably the serotonin system. For example, ondansetron, a specific 5HT3-receptor antagonist, relieves itch caused by spinal morphine and prevents recurrence of itch for 24 h. Ondansetron is also effective prophylactically.

In animals, intracisternal administration of small amounts of morphine causes intense scratching activity. Facial scratching is triggered by injecting morphine into certain areas of the medullary dorsal horn, but subsequent intramuscular morphine reduces the facial scratching. The effect of morphine, therefore, seems to depend both on the site of action of morphine in the CNS and on relative changes in opioidergic tone. In other words, the dose-response curve for opioid-induced itch appears to be bell-shaped. This would be analogous to the emetic effect of morphine. Small doses generally do not cause nausea and vomiting; middle of the range doses commonly do; large doses may not.

On the other hand, it has recently been suggested that the mu-opioid receptors mediate itch, whereas the kappa-opioid receptors may suppress itch. In keeping with this hypothesis is the observation that a kappa-opioid receptor agonist, TRK-820, reduces scratching in a mouse model. Further, in haemodialysis patients with itch, the expression of all opioid receptors on lymphocytes is lower than that in healthy volunteers, with mu-opioid receptors being less affected than kappa-opioid receptors. This imbalance in the expression of mu- and kappa-opioid receptors could contribute to the pathogenesis of uraemic itch.

Management of itch

Correct the correctable

Because pruritus is often associated with dry skin, an emollient (moisturizer) should be tried first. Many proprietary emollients are available, but aqueous cream BP is usually adequate when applied once or twice a day. In patients with malignant obstruction of the common bile duct, it is often possible to overcome the obstruction by stenting or, if the obstruction is caused by a gall stone, by endoscopic ensnaring and removal.

Non-drug treatment

Patients troubled by itch generally benefit from keeping cool. For example: (i) wearing light cool clothes; (ii) maintaining a cool ambient environment that is not too dry; (iii) having tepid showers or baths; (iv) avoiding alcohol and hot or spicy foods and drinks. Patients should be advised to keep their nails short and to rub itching skin gently so as to prevent skin damage by scratching. Ultraviolet B therapy has been used successfully for itch associated with uraemia, malignant skin infiltration, and with AIDS. In uraemia, remissions of up to 18 months have been reported.
B therapy: (i) decreases the number of dermal mast cells by accelerating apoptosis (programmed cell death);\textsuperscript{137} (ii) causes nerve degeneration;\textsuperscript{138} (iii) reduces divalent ion concentrations in the skin.\textsuperscript{91}

Liver transplantation may be considered an option for intractable itch associated with cholestasis due to non-malignant disease, but only after failure of an adequate trial of an opioid antagonist.\textsuperscript{139}

**Drug treatment**

No ‘broad-spectrum’ antipruritic drug exists. Several topical or systemic agents are available that suppress itching in certain clinical settings. Attempts to develop specific drugs for itch have been unsuccessful, possibly because the target population is too small to warrant a major drug development programme and because it is not known if there is a final common pathway for itch. Low-sedative H\textsubscript{1}-antihistamines relieve itch only when it is histamine-mediated.

**Topical drugs**

Topical antipruritic agents are often of benefit with itchy skin rashes and insect bites.

**Menthol and phenol**

Menthol and phenol are time-honoured topical antipruritic agents. Either can be added to aqueous cream to make a 1–2\% compound cream, and applied topically several times a day.

**Calamine**

Calamine is a lotion (cutaneous suspension) containing phenol 0.5\%. Its effect can be enhanced by the addition of a further 0.5\%. However, as the water evaporates, a lotion has a drying effect, which is counterproductive. Alternative calamine preparations are an oily lotion and an aqueous cream. The former contains arachis (peanut) oil and lanolin (wool fat) and the latter liquid paraffin; these additives circumvent the problem of drying. However, the pink colour of calamine is cosmetically unacceptable to most people.

**Crotamiton**

Crotamiton is marketed as a 10\% cream (e.g. Eurax). It has a mild antiscabetic effect and it is probably this effect that is responsible for its reputation as an antipruritic. However, in a controlled trial, crotamiton was no more effective than plain aqueous cream,\textsuperscript{140} and therefore cannot be recommended.

**Antihistamines**

Several topical H\textsubscript{1}-antihistamines are available, notably mepyramine and diphenhydramine. Mepyramine can cause contact dermatitis and its use is best limited to a period of a few days.

**Local anaesthetics**

Several preparations containing a local anaesthetic are available. Benzocaine and lidocaine (lignocaine) are the commonest but some preparations contain tetracaine (amethocaine). Apart from lidocaine, local anaesthetics can cause contact dermatitis. They are also absorbed to a variable extent and, if large amounts are applied, could cause cardiac arrhythmias. Use is best restricted to a few days.

Polidocanol (mixed lauromacrogols) is a non-ionic surfactant with local anaesthetic properties. In uraemia, the regular use of an emollient bath additive comprising soya oil and polidocanol improves dry skin and reduces itch and sleep disturbance.\textsuperscript{141} A cream containing 5\% urea and 3\% polidocanol has been used in dermatitis (atopic and non-atopic) and psoriasis with 90\% of patients reporting improvement in the condition of their skin and 50\% becoming itch-free.\textsuperscript{142–144}

**Capsaicin**

Capsaicin, isolated from pepper plants of the genus *Capsicum*, depletes substance P from C-fibres when applied repeatedly and reduces both pain and itch. Capsaicin cream 0.025\% or 0.075\% is applied 3–5 times daily. For the first few days it causes a local burning sensation that is poorly tolerated. It has been shown to be effective in itch caused by notalgia paraesthetica and localized itch in uraemia.\textsuperscript{145}

**Strontium nitrate**

Topical 10–20\% strontium nitrate possesses potent antipruritic properties and is effective in reducing the itch of facial peels.\textsuperscript{146–148} It may act by selectively blocking neuronal transmission in C-fibres.

**Systemic drugs**

**H\textsubscript{1}-receptor antagonists**

These are the drugs of choice for histamine-mediated itch. Chlorphenamine 4 mg t.d.s. (sedative) or cetirizine 5 mg b.d. or 10 mg o.d. (low-sedative) are commonly used. After relief is obtained, a lower maintenance dose may suffice.
Any benefit in non-histamine-mediated itch is associated with the sedative effect of the first-generation H1-antihistamines; second- and third-generation low-sedative drugs have no effect.27 Not surprisingly therefore, in some studies, benzodiazepines were as beneficial as sedative H1-antihistamines.149 However, in one study, diazepam was no better than placebo.9 In a study of itch associated with various dermatoses, amylobarbital was as effective as trimiprazine, an H1-antihistamine.150 However, another study demonstrated no benefit with barbiturates.149

**H2-receptor antagonists**

Cimetidine, an H2-receptor antagonist, enhances the effect of H1-antihistamines in urticaria.25,151 In Hodgkin’s lymphoma, case reports suggest that cimetidine, an H2-receptor antagonist, 1g daily in divided dosage may be beneficial.152 It may also be of benefit in polycythæmia vera.153 In these latter conditions, the antipruritic effect is possibly related to inhibition of hepatic cytochrome CYP2D6.154

**Doxepin**

Doxepin, marketed primarily as a tricyclic antidepressant, is a potent H1- and H2-receptor antagonist. Its affinity for H2 receptors is six times that of cimetidine.155 It also blocks muscarinic receptors.156 Amitryptiline is similar in potency to doxepin as an H1-antihistamine, but other tricyclic antidepressants much less so.157 Patients with chronic urticaria who do not respond to conventional H1-antihistamines may well benefit from doxepin 10–75 mg o.n.156

Doxepin is available as a 5% cream.158 It is of benefit in some patients with atopic dermatitis159–161 but is not generally suitable for use in children. It is applied t.d.s. or q.d.s. to no more than 10% of the body surface. Thus the maximum topical dose is 3 g per application. Absorption is variable and plasma concentrations range from undetectable to the same as the peak concentrations seen after doxepin 75 mg by mouth. On average, the intensity of the itch is reduced by about half, sometimes with initial benefit apparent after 15 minutes and typically with increasing benefit during the first week. About 15% of patients complain initially of localized stinging or burning, and a similar number of drowsiness. These symptoms generally decrease in time. Dry mouth can be a problem. Doxepin cream is not as effective as systemic treatment.162 It is also very expensive compared with doxepin tablets plus aqueous cream.

As with all tricyclic antidepressants, monoamine oxidase inhibitors should be discontinued at least two weeks before starting treatment with either topical or systemic doxepin. Patients prescribed doxepin by either route should also avoid the concurrent use of drugs that inhibit cytochrome P450, e.g. cimetidine, imidazoles, antifungals and macrolide antibiotics.

**Ondansetron**

In patients with itch induced by spinal opioids, a randomized placebo-controlled trial of intravenous ondansetron 8 mg demonstrated benefit in 70% of patients within 1 h.20 Excellent results have also been reported in case reports and from open-label studies of either single or multiple doses of intravenous and/or oral ondansetron in chronic cholestasis and uraemia.163–166 However, in randomized controlled trials, ondansetron was either of no benefit (cholestasis,167 uraemia168) or of minimal benefit (cholestasis169).

**Paroxetine**

Paroxetine, a serotonin selective reuptake inhibitor (SSRI), relieves itch in some patients. Originally, a beneficial effect was noted in a patient with lung cancer and bullous pemphigoid who was given paroxetine for depression precipitated by intense itch.170 Similar benefit was seen in two patients in whom the cause of the itch was paraneoplastic (cancers of the colon and prostate) and in two patients with morphine-induced itch. In a subsequent randomized controlled trial mainly in cancer patients, using a numerical analogue scale (0–10), nearly 40% of the patients reported at least 50% improvement with paroxetine 10–30 mg o.d. (Krajnik M, Zylicz Z, Vijverberg H, van Sorge A, unpublished observations) Relief occurred within a few days, i.e. too soon for the benefit to be secondary to the relief of depression. Of the responders, half to two-thirds experienced sedation or nausea; the latter responding to low doses of cisapride, e.g. 5 mg b.d.171 Non-responders had significantly fewer adverse effects. Doses of paroxetine as low as 5–10 mg o.d. are now being used; such doses appear to be equally effective and reduce undesirable effects. Unfortunately, the antipruritic effect of paroxetine tends to wear off after 4–6 weeks.172 Because benefit has not been observed with other SSIRIs, it is possible that paroxetine exerts its effect by a non-serotonergic mechanism.

**Mirtazapine**

Mirtazapine, a noradrenaline and specific serotonin antidepressant with H1-antihistamine properties173,174 has been used successfully to...
relieve itch in patients with malignant cholestasis, lymphoma and uraemia. Doses of 15–30 mg o.n. were used but success with a dose of 7.5 mg has been reported (Zylicz Z, Krajnik M, unpublished observations). It is possible, of course, that the antipruritic effect of mirtazapine is at least partly a consequence of non-specific sedation. However, mirtazapine is a 5HT2- and 5HT3-receptor antagonist as well as an H1-antihistamine and a specific effect via serotonin-related mechanisms is possible. Unlike paroxetine, its use is not associated with initial nausea and vomiting.

Opioid antagonists
The use of opioid antagonists is discussed in the next section under cholestasis, uraemia and the spinal administration of opioids. In an open-label uncontrolled study in various dermatological and systemic disorders, a good result was obtained in about 70% of the patients. However, the results should be interpreted cautiously in the absence of controlled data.

Cause-specific treatments
The next section is summarised in Box 3. However, weight of evidence is not the only criterion which determines a treatment of choice; absence of hard evidence (e.g. from a controlled trial) is not proof of lack of efficacy. Guidance for the clinician has been summarized in a series of treatment ladders (see below), but these too should not be regarded as immutable.

**Box 3 Management of itch in non-skin diseases**

<table>
<thead>
<tr>
<th>Non-drug treatment</th>
<th>Specific drug treatment and weight of evidence</th>
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<tbody>
<tr>
<td>Dry skin</td>
<td>Corticosteroids ± palliative chemotherapy&lt;sup&gt;C&lt;/sup&gt;</td>
</tr>
<tr>
<td>Malignant extrahepatic cholestasis</td>
<td>Naltrexone&lt;sup&gt;A&lt;/sup&gt;</td>
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<tr>
<td>Uraemia</td>
<td>Rifampicin&lt;sup&gt;A&lt;/sup&gt;</td>
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<td>Hodgkin’s lymphoma</td>
<td>Nalidixic acid&lt;sup&gt;AB&lt;/sup&gt;</td>
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<tr>
<td>UVB phototherapy&lt;sup&gt;A&lt;/sup&gt;</td>
<td>Thalidomide&lt;sup&gt;U&lt;/sup&gt;</td>
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<tr>
<td>Modify dialysis regimen&lt;sup&gt;C&lt;/sup&gt;</td>
<td>Methyltestosterone&lt;sup&gt;C&lt;/sup&gt;</td>
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<tr>
<td>Stenting of common bile duct</td>
<td>Danazol&lt;sup&gt;U&lt;/sup&gt;</td>
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<tr>
<td>UVB phototherapy&lt;sup&gt;A&lt;/sup&gt;</td>
<td>Fluoxymesterone&lt;sup&gt;U&lt;/sup&gt;</td>
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<tr>
<td>Curative radiotherapy and/or chemotherapy</td>
<td>Fluoxymesterone&lt;sup&gt;U&lt;/sup&gt;</td>
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**Non-specific drug treatment**

- Paroxetine<sup>U</sup>
- Add mirtazapine to paroxetine if latter begins to lose its effect<sup>***</sup>
- Mirtazapine<sup>U</sup>

For references, see main text. Weight of evidence based on the system used by the Agency for Healthcare Policy and Research, USA: A, 1+ randomized controlled trial; B, non-randomized studies; C, based on expert opinion, including ‘respected authorities’ and consensus reports; U, unclassified, based on single case reports or small series. *Not of value in complete large duct biliary obstruction. **Controlled trials give diametrically opposite results (much benefit v. no benefit). ***Krajnik M & Zylicz Z, unpublished observations.
Cholestasis (Figure 2)

**Opioid antagonists**

In controlled studies, both naloxone infusions and oral nalmefene have been shown to decrease scratching activity by patients with itch associated with cholestasis. Naloxone infusions have a potential place in the emergency treatment of acute exacerbations of the itch of cholestasis. Naltrexone and nalmefene, which are both bioavailable by mouth, can be used for long-term management. However, orally administered opioid antagonists can precipitate a transient opioid withdrawal-like reaction in patients with cholestasis, including hallucinations and dysphoria. To avoid or minimize such a reaction, treatment is best started with a cautious infusion of naloxone, e.g. 0.002 mg/kg/min (about 160–200 mg/24 h). The rate of infusion can be doubled every 3–4 h provided no withdrawal-like symptoms occur. After 18–24 h, when a rate known to be associated with opioid antagonistic effects is reached (0.2 µg/kg/min), the infusion is stopped and naltrexone 12.5 mg (1/4 of a 50 mg tablet) t.d.s. or 25 mg (1/2 of a 50 mg tablet) b.d. is started. The dose is escalated steadily over a few days until a satisfactory clinical response is obtained. At this stage the effective dose should be consolidated into a single daily maintenance dose. Nalmefene is an alternative orally bio-available potent opioid antagonist, but it is not licensed in the UK. The effective dose of nalmefene ranges from 25–250 mg o.d. that of nalmefene is 20–120 mg b.d. Naltrexone is sometimes associated with hepatotoxicity.

Curiously, one patient with itch associated with cholestasis obtained relief from morphine (a single injection) and from regular oral codeine. Because of severe constipation, she stopped taking codeine and the itch returned. Buprenorphine has also been reported as beneficial in two out of five patients with itch associated with cholestasis. These observations also suggest that there could be a specific range of increased opioidergic tone associated with itch.

**Rifampicin**

Rifampicin is widely used for itch associated with intrahepatic cholestasis. Rifampicin is not only a hepatic enzyme inducer but also inhibits bile acid re-uptake by hepatocytes, and thereby increases plasma bile acid concentrations. However, by interrupting the enterohepatic circulation of bile acids, rifampicin may reduce the impact of increased bile acids on the metabolic processes of the liver. Rifampicin causes hepatic dysfunction in some patients, but the risk of this is reduced by starting with a low dose, e.g. 75 mg o.d. If this is not effective after a week, the dose should be increased to 150 mg o.d., and then to 150 mg b.d. Phenobarbital, another hepatic enzyme inducer, is also of benefit in a dose of 2–5 mg/kg/24 h. However, any benefit is probably the result of non-specific sedation, and it is now seldom used.

**Colestyramine**

Colestyramine is an intestinally active anion exchange resin primarily licensed for the management of hypercholesterolaemia. However, by chelating bile acids in the intestines, it interrupts the enterohepatic circulation of bile acids. It has been used for many years to relieve itch in cholestatic disorders such as primary biliary cirrhosis. Benefit has been claimed only in an open-label non-randomized long-term study of 27 patients. Colestyramine is not effective in itch associated with complete large-duct biliary obstruction.
When used, one 4 g sachet is given before and one after breakfast so that the arrival of the resin in the duodenum co-incides with gall bladder contraction. If necessary, a further dose can be taken before the midday and evening meals. The maintenance dose is generally 12 g per day. However, many patients find it unpalatable and nauseating, and it commonly causes bloating and constipation. If used long-term, it can cause malabsorption of fat-soluble vitamins.

Androgens
The use of androgens to relieve pruritus in cholestasis stems from the serendipitous observation some 60 years ago in a patient with primary biliary cirrhosis whose itching cleared up when given an androgen for an unrelated reason. Benefit is largely limited to 17α-alkyl androgens, e.g. norethandrolone, methyltestosterone, stanozolol, possibly because of their greater bioavailability. Typical doses are: methyltestosterone 25 mg o.d. (sublingual); norethandrolone 10 mg b.d.-t.d.s.; or stanozolol 5–10 mg o.d.

The manufacture in the UK of the first two drugs was discontinued many years ago, and stanozolol was withdrawn worldwide in early 2002. However, the antipruritic effect appears to be a class property, and benefit should be obtained with an alternative 17α-alkyl androgen, e.g. danazol, fluoxymesterone or oxandrolone. In women with a normal or long life expectancy, masculinization (amenorrhoea, hirsutism and deepening of the voice) is a problem, but can be contained by reducing the dose of the androgen from daily to thrice weekly or even less.

17α-alkyl androgens are directly toxic to hepatocytes. It is possible that the effect of androgens such as methyltestosterone and stanozolol is mediated via focal hepatocellular damage, thereby limiting the ability of the cholestatic liver to produce enkephalins. Certainly, androgens themselves can cause cholestatic jaundice and have occasionally caused serious liver impairment. This is clearly a potential problem for patients with a prognosis measured in years, e.g. those with primary biliary cirrhosis. However, now that orally administered opioid antagonists are available, the use of androgens has been superseded, except in patients taking opioid analgesics for pain relief in advanced cancer. In such patients, a trial of a 17α-alkyl androgen for 7–10 days is warranted.

Uraemia
Enhancing the dialysis regimen is the standard response when dialysis patients experience itch (Figure 3). Parathyroidectomy may result in a remission of itch in patients with secondary hyperparathyroidism. (In other circumstances hypercalcaemia is not associated with itch.) Ultraviolet B therapy, particularly narrow-band UVB, is effective in many patients, and may be superior to drug therapy. Thalidomide is effective in >50% of patients but because it can cause serious foetal malformations, in women who could become pregnant it should be used only when other measures have failed and in conjunction with reliable contraception.

Opioid antagonists
The conflicting trial results with naltrexone are confusing. Both trials were randomized placebo-controlled double-blind studies of naltrexone 50 mg once daily, and both used VAS as a subjective measure of itch. One also used a modified Duo ‘detailed score’ that gave results
which paralleled the VAS scores. 84 Although both studies involved small numbers (15 and 23, respectively), the results were consistently distinct. However, in the positive outcome trial, the patients had initial VAS scores of 9–10 out of 10, whereas in the negative outcome trial the mean initial VAS score was about 6/10 before the first 4 week period and about 5/10 before the second period. It is possible, therefore, that naltrexone is of benefit only in very severe uraemic itch, when a disturbance in the balance of mu- and kappa-opioid receptors could become a prominent causal or exacerbating factor. Thus, until further data is available, it seems reasonable to offer a trial of naltrexone to uraemic patients with severe uncontrolled itch, possibly increasing the dose progressively to 250 mg/day (as in cholestasis) if 50 mg/day does not suffice. Alternatively, mirtazapine should be considered.175

### Haematological diseases

The use of interferon-α as a cytoreductive agent in polycythaemic vera is associated with amelioration of itch.197 Itch in polycythaemia vera responds poorly to H1-antihistamines but often responds well to paroxetine.198 However, the drug of choice is low-dose aspirin: 300 mg is generally effective within 30 min, with a duration of action of 12–24 h.41 Because platelet degranulation is increased in polycythaemia (releasing serotonin and prostanoids) and is known to be decreased by aspirin, the antipruritic effect of aspirin could be related to its impact on platelet dynamics.199

Curative radiotherapy and/or chemotherapy is obviously the best approach in Hodgkin’s lymphoma (Figure 4). Corticosteroids (generally given in conjunction with palliative chemotherapy, such as intermittent vinblastine) often relieve itch in late-stage Hodgkin’s lymphoma, although the mechanism of this effect is unknown. In the past some patients obtained benefit with γ-interferon,200 but this treatment is no longer used.

### Solid tumours

Paraneoplastic itch associated with solid tumours is not eased by corticosteroids or cimetidine. However, paroxetine is almost always beneficial,
often within 24 hs (Zylicz Z, unpublished observations; Figure 5).

**HIV/AIDS**

There are many causes of itch in HIV+ patients. Treatment depends on the cause but, when not associated with skin disease or infestation, it is largely empirical. Some patients obtain benefit from indometacin 25 mg t.d.s.

**Opioid-induced itch**

H$_1$-antihistamines are ineffective for generalised opioid-induced itch. Bupivacaine added to spinal opioids tends to restrict itch to just the face. 5HT$_3$-receptor antagonists, e.g. ondansetron 4–8 mg intravenously, may also be beneficial. Relief is generally complete and is achieved within 30 min, often in 3–5 min.

Naloxone abolishes itch induced by spinal morphine but sometimes also reverses analgesia. Itch associated with systemic morphine is similarly abolished, but always with loss of analgesia. Naltrexone is also effective. However, nalbuphine, a mixed μ-receptor antagonist and κ-receptor agonist, is more effective than naloxone and does not reverse analgesia.

Intranasal and epidural butorphanol reduces spinal opioid-induced itch, although when given alone it can induce itch. Butorphanol, a potent κ$_1$- and μ$_1$-receptor agonist and a weak μ$_2$-receptor agonist, may act as a competitive antagonist at μ$_2$-receptors when given with other opioids.

In one trial, intravenous propofol relieved itch induced by spinal morphine in over 80% of patients (compared to 16% in the placebo group), but several other studies have produced negative results.

Pretreatment with a non-steroidal anti-inflammatory drug (NSAID), either rectal diclofenac 100 mg or intravenous tenoxicam 20 mg, has been shown to reduce the incidence, intensity and duration of itch in surgical patients receiving spinal opioids. These patients also had significantly less pain than control patients and needed significantly less postoperative opioid analgesia. It is possible that the difference in opioid dosage may explain the difference between the two groups.

Opioid-induced itch is rare in palliative care; few patients receive spinal opioids and those who do are not opioid-naïve. Further, such patients almost always receive bupivacaine concurrently. When itch is induced by a systemic opioid, switching to an alternative may help, e.g. from morphine to hydromorphone.

**Conclusions**

Intractable itch deserves the same degree of attention as pain. The pathogenesis of itch varies, ranging from a lack of moisture in the skin to a complex array of factors in uraemia. Even though much is still unknown, when topical emollients fail to provide relief and low-sedative H$_1$-antihistamines are not indicated, other options with specific rationales are generally available. When conventional options are ineffective, mirtazapine and paroxetine should be considered. Ultraviolet B therapy is not widely used at present but appears promising, particularly in uraemia.

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**References**


