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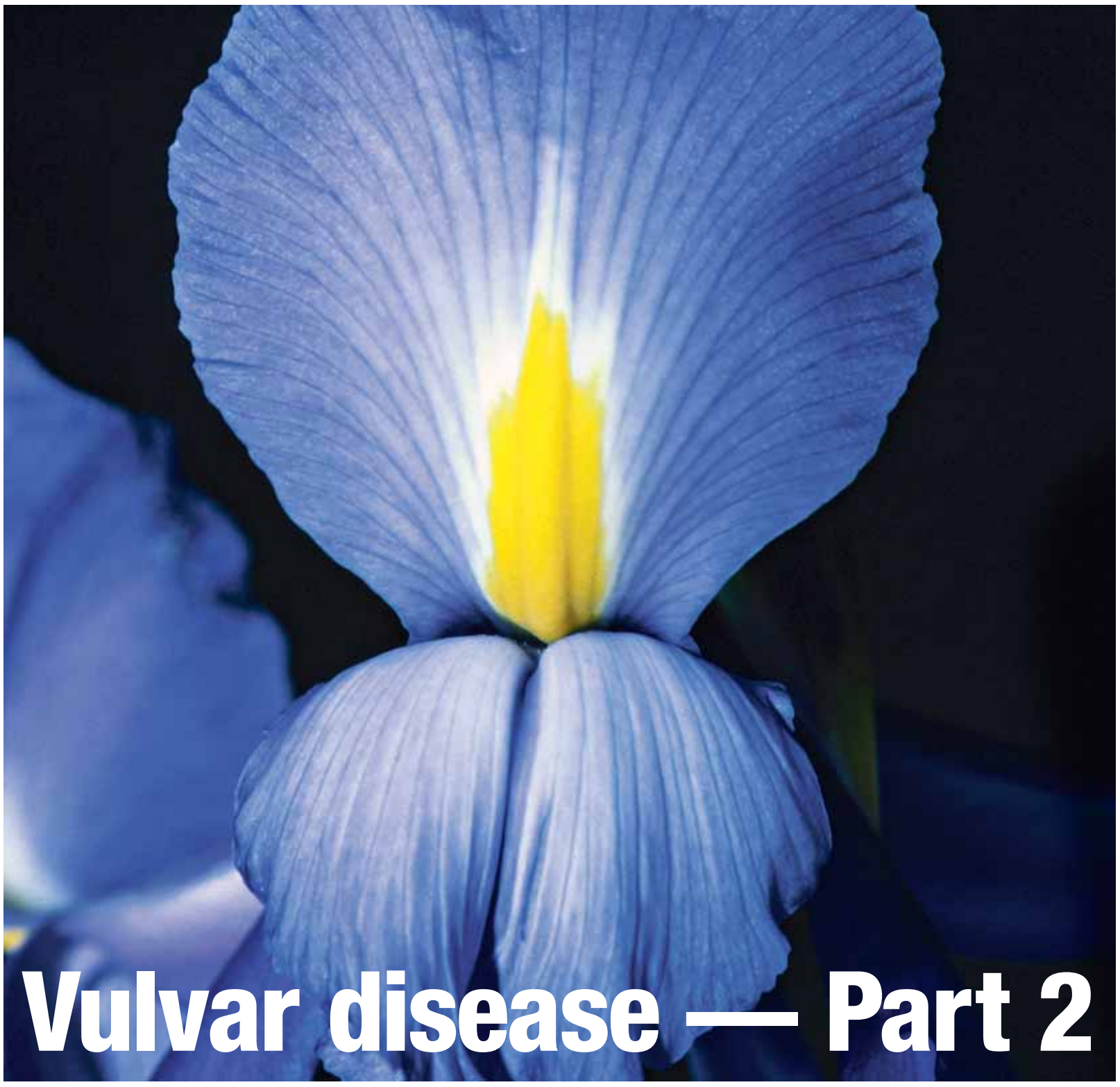

# Vulvar disease — Part 2

*Part 1 of this article described the anatomy of the vulva and provided a guide to clinical assessment for vulvar complaints. Vulvar injuries, lumps and bumps, and pigmented lesions were discussed. In Part 2 we discuss several vulval infections, autoimmune conditions, inflammations and carcinomas.*

## inside



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## The red, itchy or burning vulva

THE lower genital tract is basically self-cleansing. Adequate vulvar hygiene can be maintained with daily washing, which may include using a mild soap. Perfumes are discouraged, and underwear should not be washed in strong detergents or exposed to fabric softeners. Tight and impermeable underclothing that increases local humidity should also be avoided. However, from a lifetime of treating vulvovaginal disorders, we find that genuine disease processes are all too often overlooked, with the focus instead placed on advising women about hygiene practices.

Fungal infection is the most common cause of an itchy vulva. Infections of the central vulva are caused by yeasts (usually *Candida albicans*); infections of the labia majoral and inguinocrural folds are typically due to a dermatophyte (typically trichophyton and epidermophyton species). Dermatophyte fungi are unable to infect non-cornified skin or mucosae because these tissues do not have the keratin layer needed for dermatophyte growth.

### Candidal infections

A healthy vaginal flora is dominated by *Lactobacillus acidophilus*, which digests the abundant glycogen stored in the cytoplasm of desquamated vaginal cells. This process forms lactic acid and peroxidase molecules, creating an acidic milieu (pH <4.5), with high oxygen content. The resultant biochemical environment is conducive to normal flora and commensal yeast survival, but unfavourable to coliform or bacterial anaerobic overgrowth. Not surprisingly, the vaginal flora often contains a low number of saprophytic candida species, mainly in the non-filamentous (dormant) form. Colonisation is sufficient to produce a light fungal growth on culture, but direct microscopy of the vaginal secretions will be negative.

Transformation from a dormant commensal to an opportunistic pathogen is usually secondary to local changes that enhance yeast virulence (eg, increased glucose or haemolysing blood in the vaginal secretions) or impair host immune defences (eg, alterations in vaginal flora or increased pudendal warmth and humidity). Clinical correlates include:

- High oestrogen levels, which increase vaginal epithelial glycogen content. However, the widespread belief that candidiasis is increased by oral contraceptives is probably incorrect.
- Sugar bingeing in people with insulin resistance.
- Menstrual blood in the vagina (providing the iron needed for proliferation of virulent yeast types).
- Any disturbance of mucosal IgA production.
- Broad-spectrum antibiotic therapy.
- Humid weather or nylon underwear.

Interestingly, systemic steroids, immune suppressive and cytotoxic agents encourage systemic candidiasis, but have little effect on the behaviour of genital tract yeasts. Topical steroids can unmask clinically latent candidiasis but do not initiate candida infection per se.

Pathogenic yeast cells proliferate rapidly and sprout hyphae (filamentous outgrowths). They also secrete proteolytic and phospholipase enzymes that damage the epithelial cell membrane. Germinating infections are thus characterised by high numbers of filamentous yeasts that are actively invading the cytoplasm (rather than scant blastospores, passively adherent to the cell surface). Differentiation of colonisation

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**Figure 1: Acute sporadic candidal vulvovaginitis. ASCV is principally an intravaginal infection (as evidenced by the adherent flecks of cheese-like discharge) and the surrounding vestibular mucositis. There is also some mild inflammation of the labia majoral and anterior buttock skin.**

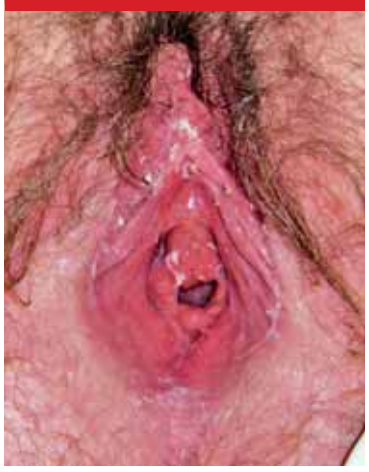


**Figure 2: Tinea cruris. Dermatophyte infections begin as inflammatory pustules that spread concentrically. Over time, the central area often heals, leaving a circinate line of tiny red blisters.**

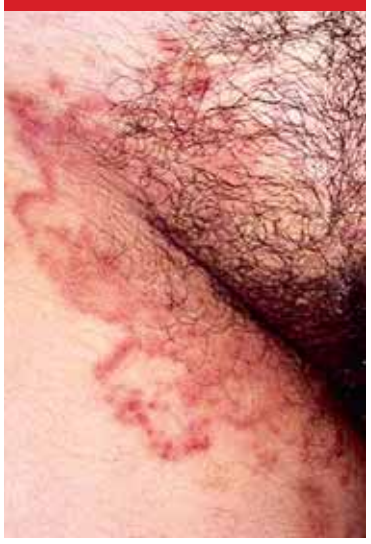


**Figure 3: Irritant contact dermatitis. This patient has suffered an acute chemical burn, with inflammation, marked oedema and blistering of the vulva and adjacent Intertriginous areas.**

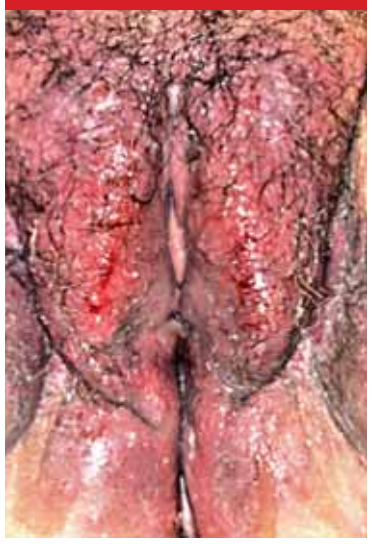
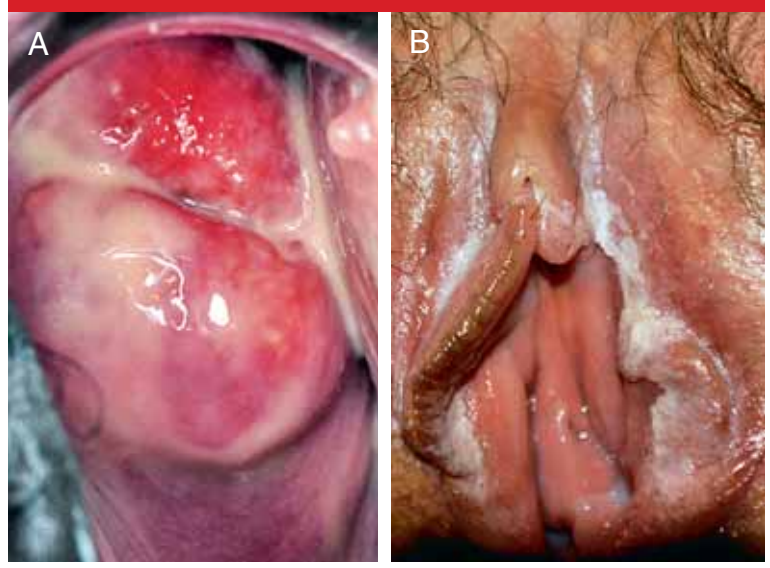


**Figure 4: Bacterial vaginitis is a common cause of chronic contact dermatitis. A. Speculum examination shows the typical thin, homogenous discharge caused by coliform and anaerobic bacteria overgrowth. B. Discharge tends to adhere to the glabrous skin, where exposure to noxious bacterial metabolites causes a contact irritation.**

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from active infection depends on direct microscopy of the vaginal discharge, using 10% hydroxide to dissolve the exfoliated cells, thus making any yeast budding more apparent. Microscopy should also look for clue cells in a saline wet mount in case concomitant bacterial vaginosis is present. A high vaginal swab can also be cultured in either Sabouraud's or Nickerson's medium, to help with speciation.

There are two clinical scenarios seen with candidiasis.

### Acute sporadic candidal vulvovaginitis

Acute candidal vulvovaginitis (ASCV) causes sudden severe itching and burning, superficial dyspareunia and external dysuria (figure 1). Speculum examination shows an odourless vaginal discharge, varying in consistency from thin and watery to curd-like with adherent white plaques. There can be substantial accompanying inflammation of the vulvar skin, manifesting as a glazed erythema of at least the central vulva. Severe episodes may encroach laterally, to inflame the hair-bearing skin (where satellite pustules are often seen).

ASCV infections are treated with topical polyenes (eg, nystatin) or topical imidazoles (eg, clotrimazole, miconazole, etc). A course of polyene therapy should last for at least 14 days; conversely, topical imidazoles are generally effective within 3-7 days (depending on drug concentration at each dosage application). However, symptom resolution does not equate to microbiological clearing; it may be helpful to give a follow-up course one week later. Oral fluconazole (Diflucan) has also become popular. This regimen is no more effective than a topical imidazole, but is often more convenient (eg, after genital tract surgery or when the local tissues are too sore for intravaginal applications). Table 1 lists the therapeutically equivalent regimens available in Australia for vaginal candidiasis.

There has been a rise in the incidence of vaginal infections due to non-albicans species, such as *C. tropicalis*, *C. krusei*, *C. parapsilosis* and *C. glabrata*. Such infections have a high relapse rate, are harder to eradicate and are more likely to cause a recurrent candidal vulvovaginitis. Boric acid 600mg pessaries, perhaps assisted by 8% boric acid ointment, may be more effective than topical imidazoles. Specialist referral is often helpful.

**Table 1: Therapeutic equivalents for treating vulvovaginal candiasis in Australia**

**TOPICAL AZOLES**

**Intravaginal medications**

*Topical imidazoles inhibit the transformation of colonising* Candida albicans *blastospores into invasive mycelial forms, and are therefore very effective against vaginitis caused by* Candida albicans*. They are less effective against vaginitis due to non-albicans species*

| *Drug* | *Dosage and duration of treatment* |
|---|---|
| Clotrimazole (Canesten) | Vaginal tablet (500mg): insert one tablet nocte as a single dose<br>10% 'Once cream': insert one 5g applicator dose nocte as a single dose |
| | Vaginal tablet (200mg): insert one tablet nocte on three consecutive nights<br>2% vaginal cream: insert a 5g applicator dose on three consecutive nights |
| | Vaginal tablet (100mg): insert one tablet nocte on six consecutive nights<br>1% vaginal cream: insert a 5g applicator dose on six consecutive nights |
| Miconazole (Resolve) | 2% vaginal cream: insert a 5 gm applicator dose on seven consecutive nights |

**External medications**

Candida albicans *vaginitis can also involve the vulvar, groin, perianal and buttock skin. Treating these sites needs either systemic therapy or the addition of a cream designed for external use*

| | |
|---|---|
| Clotrimazole 1% with hydrocortisone 1% (Hydrazole) | Rub into inflamed external skin 2-3 times daily; use for one week beyond resolution of clinical symptoms (because of the fungal reservoir within the hair follicles) |
| Ketoconazole 2% (Nizoral) | Rub into inflamed external skin 2-3 times daily. For stubborn yeast infections, use for two weeks and for tinea use for four weeks (at least one week beyond resolution of clinical symptoms because of the fungal reservoir within the hair follicles) |

**TOPICAL POLYENES**

| *Drug* | *Dosage and duration of treatment* |
|---|---|
| Nystatin | Vaginal cream, insert a 100,000 U/5g applicator doses on 14 consecutive nights |

**SYSTEMIC AZOLES**

**Triazoles**

*Systemic triazoles have good efficacy against* Candida albicans *species, with a very low risk of hepatic toxicity*

| *Drug* | *Dosage and duration of treatment* |
|---|---|
| Fluconazole (Diflucan) | 150mg as a single dose |

**Imidazoles**

*Systemic imidazole treatment has greater efficacy against non-albicans species, but this is counterbalanced by a higher risk of hepatic toxicity*

| | |
|---|---|
| Ketoconazole (Nizoral) | 200mg daily for 1-2 weeks |
| Itraconazole (Sporanox) | 200mg daily for 1-2 weeks |

### Recurrent vulvovaginal candidiasis

These patients tend to have an eczematoid mucositis and dermatitis rather than a burgeoning candidal infection. Clinical appearance is that of ill-defined erythema and oedema, similar to a contact dermatitis. Lichenoid change and fissuring is common. Speculum examination is usually unremarkable.

For many years the key event was thought to be repeated re-infection, either from the bowel or a sexual partner. Research has shown that relapses generally involve re-activation of infection with the same serotype, which had persisted as a subclinical vaginal colonisation. Recurrent vulvovaginal candidiasis (RVVC) is now known to be a candida-induced hypersensitivity state, mediated by increased production of histamine, prostaglandins E2 (PGE2) and IgE.

Control of RVVC is always a challenge. The key strategy is to block the yeast's ability to disrupt local cell-mediated immunity (by PGE2 suppression of T-cells) and humoral immunity (by blocking the interaction of candida-specific IgA with complement). This is most safely attempted in general practice with a course of Diflucan 150mg every four days for three months. Non-response warrants referral to a gynaecologist with a special interest in lower-tract pathology.

## Tinea cruris

Dermatophytes produce paragenital infections, usually limited to the intertriginous areas of groin and upper thighs. Mucous membranes are never affected because they lack a stratum corneum. Tinea cruris tends to appear in hot and humid summer months or in association with obesity and insulin resistance. The source is usually the moist skin in the lateral toe webs, activated by a change in local conditions. Infections manifest as an inflamed central zone with a bright-red peripheral margin (figure 2). Over time the centre of the lesion dries, leaving a pink scaly plaque; when it occurs in the skin folds, the central area of the lesion may be moist and weepy.

Diagnosis depends on identifying dermatophytes in the lesion — best done by submitting some of the scale for culture.

Treatment is usually with topical imidazole creams that must be applied twice daily for at least one week beyond the point of apparent healing. Shorter courses are notorious for leaving hyphae in the hair follicles, which allows re-emergence of infection.

## Contact dermatitis

Vulvar skin is more permeable than other cutaneous surfaces, creating a vulnerability to chemical irritation or immune sensitisation. Contact dermatitis now accounts for about 15% of referrals to tertiary vulvar clinics, and the prevalence is increasing. Common triggers include chronic vaginal discharge (eg, from bacterial vaginosis — figure 4) perfumed soaps, perfumed toilet paper, ammonia breakdown products in urine-soaked pads, latex, spermicides, tea tree oil, benzocaine, neomycin and preservatives in pharmacological creams.

### Irritant contact dermatitis

An irritant is any substance that causes direct dermal inflammation, erythema and induration on contact

with the epithelial surface. The resulting dermatitis occurs through an acute chemical compromise of the skin and mucosal barrier function. The associated inflammation has an immediate onset and is perceived as stinging or burning rather than itching. Severe cases often manifest as painful erosions and fissuring (figure 3).

### Allergic contact dermatitis

An allergen is any substance that stimulates a (type IV) delayed hypersensitivity reaction in sensitised people. The inflammatory reaction is cell mediated, and therefore takes 48-72 hours to develop. It is triggered by sensitisation to (rather than direct irritation by) a chemical. Symptoms tend to be more pruritic than painful. If the problem continues beyond a week or so, continued irritation and an itch–scratch cycle can lead to lichen simplex chronicus (see next section).

Physical findings in both forms range from mild erythema to weeping erythematous lesions. The geographic pattern of the rash often provides an excellent clue as to the causative agent. If the dermatitis spreads lateral to the pilosebaceous line, marked oedema is likely.

Treatment must eliminate exposure to the causative irritant or allergen. Symptom relief can be obtained by cool water rinses or a packet of frozen peas between the legs; bland emollients such as a vegetable oil are also helpful. Moderate potency topical steroids (eg, triamcinalone 0.2% ointment, applied twice daily) will reduce the inflammation. Antihistamines and/or tricyclic antidepressants can suppress involuntary scratching during sleep.

### Steroid rebound dermatitis

The modified skin of the central vulva is relatively resistant to steroid atrophy. However, overuse of fluorinated topical steroids can produce an inflammatory dermatitis not unlike a contact dermatitis, especially in periorificial skin. Potent steroids cause vasoconstriction. Rebound vasodilation as the vasoconstrictive effect wears off can result in an area of erythema associated with burning discomfort, leading to self-administration of additional topical medication.

Steroid-related thinning of the vulvar skin produces a fine-textured papular erythema (due to accentuation of the sebaceous glands) with telangiectasia (because the deep dermal capillaries become individually visible). Candida species colonisation is very common in these patients and may account for some of the symptoms. Treatment is by establishing an individualised weaning regimen — from high-, mid-, to low-potency steroid preparations.

## Specific dermatoses

VULVAR dermatoses present in a variety of ways ranging from asymptomatic lesions to chronically disabling itch, burning or pain. Women may be embarrassed by the disfiguring secondary changes, making them reluctant to continue sexual intimacy. Beyond such impact on quality of life, some of these dermatoses have a definite relationship with vulvar cancer. Not surprisingly, many clinicians find management of these conditions to be challenging, a problem that can result in suboptimal management.

### Psoriasis

Psoriasis is an incurable inflammatory dermatosis occurring in people with a genetic predisposition. The condition tends to flare and remit under the influence of environmental factors such as infection or stress. Favoured sites are the extensor surfaces and sacral areas. Classic appearance is that of bright-red plaques covered with a silvery scale. However, the moist lower genital environment tends to thin the overlying epidermal 'filter', making any vulvar lesions appear less scaly, less white and therefore redder to the naked eye. Diagnosis is often assisted by inspection of non-genital sites finding typical psoriatic lesions of extensor skin or pitting of the nails. In the absence of a firm clinical diagnosis, biopsy is definitive.

Treatment is with short-term topical fluorinated corticosteroids. Note that these agents need to be avoided over the long term because maceration and/or skin occlusion in intertriginous areas predisposes to skin atrophy.

### Seborrhoeic dermatitis

Seborrhoeic dermatitis is a red scaly rash occurring in areas of skin with a high density of sebaceous glands. Patients with seborrhoeic dermatitis tend to have dandruff, and lesions in the naso-labial folds, eyebrows and retro-aural area. Clinical appearance on the vulva is that of oily, whitish-yellow greasy looking plaques and reddish tinge to the underlying labia majoral and interlabial sulcus skin.

The disease itself is improved by good hygiene and restoration of natural skin oils (eg, with Bio-Oil). Topical steroids are helpful but are not curative. Medication is best applied after bathing, when the overlying keratin plaques have been softened. Because concomitant infection with pityrosporum fungal species is common, ketoconazole shampoos and topical creams may be helpful.

**Figure 5: Lichen simplex chronicus (LSC). Unlike lichen sclerosus, LSC may occur in any of the embryological areas of the vulvar skin. Here, the inflammation involves the vestibular mucosa (not shown), the glabrous skin of the labia minora and the hair-bearing skin of anterior buttock.**

### Lichen simplex chronicus

The word 'lichen' is merely a descriptive term, used originally to evoke a botanical image of a rough-surfaced lichen growing on a smooth-surfaced rock. Lichen simplex chronicus (LSC) is a neurodermatitis that begins with an itch–scratch cycle, in response to irritation from recurrent vulvovaginal candidiasis or a chronic contact dermatitis.

Clinical appearance is that of thick leathery plaques with enhanced skin markings, often accompanied by linear erosions from excoriation (figure 5). The appearance is not dissimilar to the other lichenoid dermatoses, but LSC is not restricted to any particular embryological skin area. In contrast, lichen sclerosus and lichen planus do not cross the pilosebaceous line into hair-bearing skin. LSC differs from psoriasis in having diffuse, ill-defined margins.

Histologically, LSC shows acanthosis (thickening of the stratum spinosum of the epithelium) with deep rete ridges.

Treatment consists of breaking the itch–scratch cycle and suppressing the deep dermal inflammation with a potent steroid ointment, followed by an adequate period of steroid maintenance therapy. It is essential that the trigger factor causing the itch does not remain as an ongoing irritant.

### Lichen sclerosus

Lichen sclerosus (LS) is a chronic autoimmune inflammatory disorder with a predilection for ano-genital skin. It affects about one in 70 women. Incidence of LS is bimodal, with a small peak in premenarchal girls and a large peak in perimenopausal women — related mainly to androgen (rather than oestrogen) decline. LS is strongly associated with other autoimmune disorders (especially Hashimoto's thyroiditis, vitiligo, pernicious anaemia and alopecia areata). There is a high prevalence of circulating autoantibodies. Histologically, the active inflammatory interface is located in the papillary and reticular dermis, reflecting an autoimmune attack on an as-yet unidentified vulvar antigen. The epidermis is usually atrophic, but with associated hyperkeratosis.

Most patients present with burning

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**Figure 6: Severe lichen sclerosus of medial labia minora, with some secondary lichenification of the anterior vestibule (caused by scratching).**

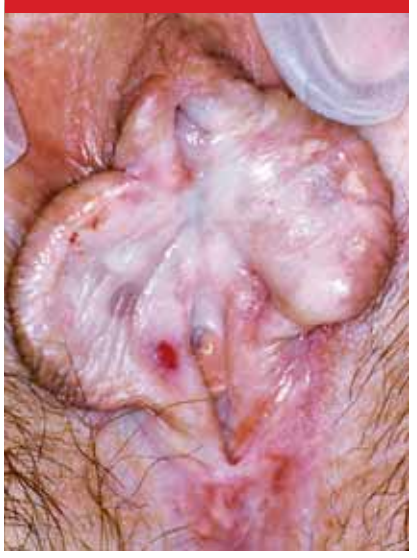
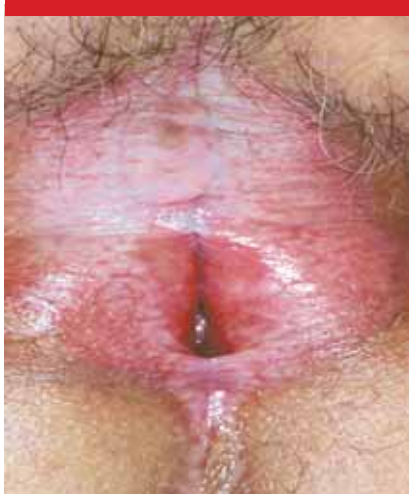


**Figure 7: Lichen sclerosus 'obliterans'. Autoimmune inflammation has destroyed the deep connective tissue folds of the vulva. This patient has clitoral obliteration, labial resorption and fourchette webbing.**



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and pruritus, which are typically worse at night. Dyspareunia is common (because of introital contracture). However, LS can also be asymptomatic. Affected skin takes on a wrinkled parchment-like appearance with depigmentation (figure 6, page 27). Concomitant ecchymoses are common because of atrophy of the rete ridges, such that the epidermis is easily sheared from the underlying dermis even with minimal trauma. Change is limited to the glabrous skin of ectodermal origin, often conferring a 'figure-of-eight' geographic pattern (widest in the peri-clitoral area, narrowing at the fourchette and flaring again in the perianal region). Over time, hyalinisation of the underlying dermis eventually destroys the vulvar anatomy, leading to clitoral obliteration, labial resorption and painful webbing of the posterior fourchette (figure 7, page 27).

Inflammation of LS that is allowed to persist for 10-15 years is associated with about 5% incidence of vulvar cancer (figure 8). This risk is reduced by effective treatment, comprising an initial intense pulse of an ultra-potent steroid, followed by lifetime maintenance with a potent or moderately-potent topical steroid. All LS patients need careful vulvar examination, at least annually. Women with poor symptom control or concomitant hyperkeratosis are at increased risk for malignancy. This group need six-monthly specialist visits, to look for emerging areas of differentiated vulvar intraepithelial neoplasia (VIN). Premalignant and early invasive lesions are subtle in appearance, and are easily overlooked by less experienced clinicians. Colposcopy can be invaluable.

**Figure 8: Malignant progression. Two separate squamous cell carcinomas (distinguished by a mosaic-like pattern of atypical vessels) can be seen arising within a background of poorly controlled lichen sclerosus.**

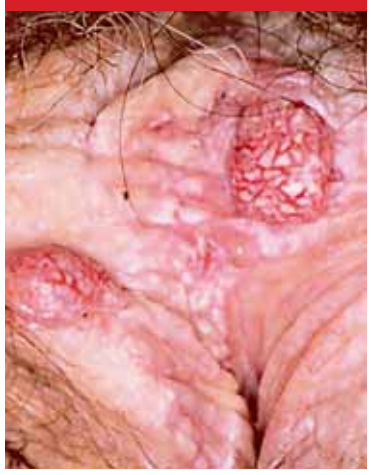
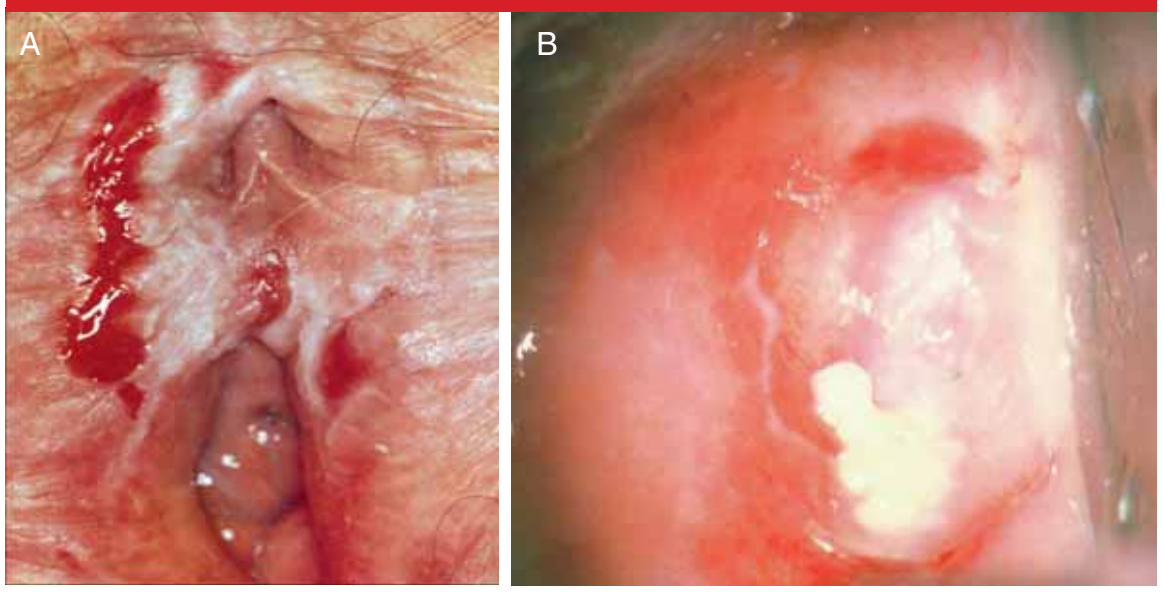


**Figure 9: Lichen planus. A: Erosive lichen planus of the anterior vestibule and adjacent glabrous skin of anterior commissure. B: Speculum examination shows severe desquamative inflammatory vaginitis, causing mucosal erosions and painful synechiae.**




### Lichen planus

Lichen planus is another autoimmune mucocutaneous disorder. About 1% of women have oral lichen planus, with 25% of affected women also developing genital tract disease.

Clinically, lichen planus can manifest in one of four patterns, all of which can coexist:

- Erosive lichen planus (ELP): a destructive disease associated with burning and pain rather than pruritus. Lesions are velvety red, exquisitely tender and bleed easily to touch. ELP often progresses to overt ulceration of the labia minora, with eventual contracture formation (figure 9A).
- Desquamative inflammatory vaginitis: many ELP patients also have a copious yellow discharge, caused by blistering of the inflamed vaginal parabasal cells. Desquamative inflammatory vaginitis (DIV) leads to eventual synechia formation, with obliteration of the vaginal lumen (figure 9B).
- Papulosquamous lichen planus: associated with violaceous papules affecting the keratinised skin of wrist, ankle and thigh, rather than mucous membranes. These non-erosive variants are intensely pruritic. Physical findings reflect the five Ps — pruritic, planar, purple, polygonal, papules. Papulosquamous lichen planus of the genital skin produces poorly demarcated, pink papules that are easily mistaken for genital warts or molluscum contagiosum.
- Hypertrophic lichen planus: hypertrophic variants present as rough keratotic patches that resemble leukoplakic VIN.

Vulvar and vaginal lichen planus is an extremely difficult disease to treat, and requires specialist referral. First-line treatment with super-potent steroids can be helpful. Topical calcineurin inhibitors (tacrolimus, pimecrolimus) have been used as immune suppressants with moderate success.

# Vulvar intraepithelial neoplasia

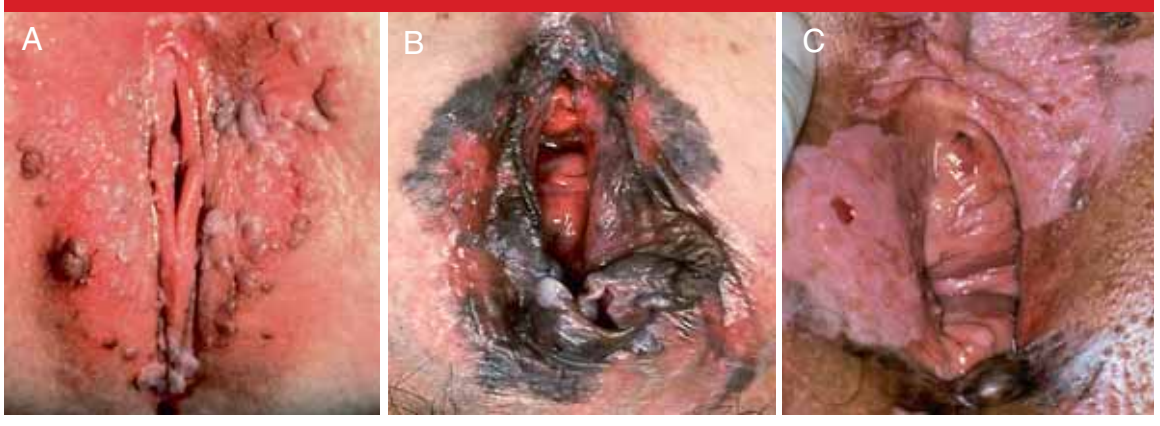
VULVAR intraepithelial neoplasia is the preinvasive phase of squamous carcinoma of vulva. It is important for GPs to appreciate that there are two forms — differentiated and undifferentiated. These two entities have essentially nothing in common with each other.

### Undifferentiated VIN

Undifferentiated VIN is the more common form. It is caused by high-risk HPV infection (particularly HPV 16 and related genotypes, rather than HPV 18). As such, undifferentiated VIN can be thought of as the vulvar equivalent of cervical intraepithelial neoplasia (CIN), but with some treacherous differences in natural history.

Histologically, HPV-associated premalignancy encompasses what was known in the older literature as VIN 2-3, Bowen's disease, bowenoid papulosis, or severe dysplasia and carcinoma in situ. The histological picture is nowadays subcategorised as warty (resembling condyloma), basaloid (resembling the carcinoma in situ of older literature) or a mixed pattern (figure 10). In essence, HPV-associated VIN reflects a field change in which oncogenic viral genes become integrated into the cellular genome in ways that impede homeostatic checking of chromosomal integrity before cellular division. This form of VIN tends to affect younger women, often has a multifocal distribution, and may follow or precede neoplastic disease elsewhere in the lower genital tract.

**Figure 10: The heterogeneous clinical features of undifferentiated VIN. A: Pigmented and leukoplakic papules, interspersed with some small keratotic plaques. B: Extensive VIN involving all three epithelial rings with an admixture of melanotic and erythematous lesions. C: Diffuse keratotic VIN 3 with two areas of ulceration, representing two foci of microinvasion.**




About 30% of women with undifferentiated VIN experience typical vulvar symptomatology — most commonly pruritus, burning, pain and external dysuria. At other times the patient herself will present reporting a localised lump, a thickening in the vulvar skin, or an area of discolouration. However, a significant proportion is diagnosed at routine examinations or in biopsies of refractory condylomas.

Physical appearance varies according to patient's age, complexion and disease location. Skin lesions (hair-bearing and glabrous) tend to be papular, while mucosal lesions are more typically macular (and therefore often subclinical, unless examined with a colposcope). The lesion may be red, whitish or brownish-grey.

Colposcopy is an essential tool for the diagnosis and assessment of preinvasive vulvar disease. The area of interest is first soaked with 5% acetic acid and then inspected under magnification. There are two key signs — areas of clearly demarcated aceto-whitening (caused by temporary opacification of the easily macerated keratins found in HPV-infected epithelium) or abnormal intra-epithelial vascular patterns (produced by neoplastic angiogenesis). Biopsy is needed but must be colposcopically directed.

The natural history of undifferentiated VIN 3 is well illustrated in a cohort of New Zealand women, some of whom were deliberately undertreated by a now discredited New Zealand gynaecologist between 1961 and 1993. Only four of 105 (3.8%) appropriately managed women developed invasive cancer over the succeeding 7-18 years. In contrast, seven out of of eight (87.5%) deliberately undertreated cases progressed to invasion in eight years. Such a high progression rate in so short a time highlights the fact that undifferentiated VIN is potentially a more treacherous disease than its cervical equivalent — especially in women with any form of compromised cellular immunity.

The past 30 years have seen a marked rise in the incidence of high-grade, preinvasive vulvar disease, as well as a decrease in the age at diagnosis. There has been no corresponding increase in vulvar cancer mortality, presumably because early detection is an effective preventive strategy. Hence, familiarity with the natural history and clinical features of pre-invasive squamous disease of the vulva and anus is important to the GP. Foci of invasive cancer commonly coexist with undifferentiated VIN, highlighting the risks of any diagnostic delay. Such invasion is often 'minimally invasive', meaning that treatment by wide local excision is an effective treatment. However, lesions with a depth of invasion of only 1mm have a 30% risk of lymph node metastasis and will require groin dissection.

Management of undifferentiated VIN involves the synchronous eradication of all existing neoplastic foci, and thereafter maintaining the patient in long-term follow-up as a safeguard against the real risk of new disease emergence. Lesion eradication can be approached from several viewpoints, depending on surgeon experience and the degree of concern about possible cancer. The first objective must always be to safely eradicate all areas of premalignancy, without missing a focus of occult invasion. This is most aesthetically done by $CO_2$ laser ablation (only suitable for expert colposcopists). More worrisome areas may need wide local excision with skin flap repair or skinning vulvectomy with a graft. Given that disease recurrence commonly reflects involved excision margins, adjuvant imiquimod (Aldara) treatment is helpful for controlling the viral reservoir.

### Differentiated VIN

This less common form of VIN occurs against a background of a poorly controlled vulvar dermatosis (particularly LS, but potentially LSC

and lichen planus) or longstanding inflammatory scars. Malignant risk relates to impaired function of p53, an important tumour suppressor protein that regulates the cell cycle (p53 prevents genome mutation, and has been described as 'the guardian of the genome'). Paradoxically, disruption of p53 genetic expression creates a differentiated histological picture, somewhat resembling VIN 1. However, the natural history of differentiated VIN is even less forgiving than that of undifferentiated VIN (previously known as VIN 2-3).

Differentiated VIN occurs in older women, is more likely to be a solitary lesion and has a predilection for the glabrous skin. Lesions are difficult to distinguish against the generally dystrophic background of the underlying dermatosis. A keratotic nodule or shallow ulcer may be the only clinical indicator.

# The ulcerated vulva

VULVAR skin is prone to a number of ulcerating diseases, reflecting a mixture of infectious, inflammatory and neoplastic processes. These conditions are chronic and painful, often progressing to the point of debilitation.

Erosions and ulcers generally begin as vesicles, bullae or pustules. Vulvar skin is so delicate and easily broken that these initial blistering changes are seldom seen. Patients present instead with erosions or ulcers. There are important distinctions to be made regarding the depth of ulcers.

- Shallow ulcers: sometimes the initial inflammation is a purely epidermal process, with fluid collecting between the squamous layers of the epidermis. Losing the roof of the blister will transform this vesicle or pustule into an erosion. Continued inflammation may also destroy the basal layer, creating a shallow ulcer.
- Deep ulcers: these extend through the basement membrane, involving both dermis and epidermis.

The most serious diagnostic error in general practice is to accept such lesions as aphthous or herpetic ulcers, without giving adequate thought to other diagnoses. Because ulcers do not have a keratinised layer, swabs are quite useful. It is good practice to culture every unexpected vulvar ulcer because 50% of HSV-positive lesions do not have typical herpetic morphology.

Evaluation of deep ulcerative vulvar disease requires either specialist consultation or biopsy. If a tissue sample is to be collected, the punch biopsy or wedge excision should target the edge of the lesion (where the active pathological process will generally be found), rather than the base (which is typically filled with necrotic debris and non-specific fibrosis). An exhaustive description of the various ulcerating conditions is beyond this review, but common causes are listed in table 2.

**Table 2: Common ulcerative conditions of the vulva***

| *Condition* | *Clinical features* | *Diagnostic steps* |
|---|---|---|
| **Erosions and shallow ulcers** | | |
| Contact dermatitis | Itchy blisters and erosions on an erythematous background | Clinical assessment |
| Herpes simplex virus (HSV) | Painful shallow ulcers with a fibrinous base, often occurring in groups. Recurrent | Viral culture or PCR for HSV DNA |
| Varicella-zoster virus | Shallow ulcers and/or umbilicated vesicles. Unilateral distribution | Viral culture or PCR for VZV DNA |
| Aphthous ulcer | Painful HSV -like ulcers on vestibular mucosa. Often recurrent. May be associated with oral canker sores | Exclusion of other causes |
| Candidiasis | Erosion of peripheral fungal pustules, generally limited to intertriginous areas | Potassium hydroxide wet mount, fungal culture |
| Impetigo | Primary staphylococcal infection of the vulva is uncommon, but other erosions may become secondarily infected | Clinical assessment, bacterial culture |
| Erosive lichen planus | Coalescent, exquisitely sensitive raw areas on vestibular or anal mucosa. May be associated with oral lesions and/or desquamative inflammatory vaginitis | Clinical assessment and biopsy |
| Excoriated lichen sclerosus | Haemorrhagic blisters, erosions and ecchymoses in a patient with poorly controlled lichen sclerosus | Clinical assessment |
| Extramammary Paget's disease | An itchy, erythematous plaque with white keratotic islands and oozing red erosions ('vin rouge') | Clinical assessment and biopsy |
| Erythema multiforme | Acute (often recurrent) haemorrhagic blisters and bright-red, very painful ulcers in a febrile patient. May be associated with 'target lesions' at other sites | Clinical assessment and biopsy |
| Bullous pemphigoid | Tense tough bullae that eventually erode. Seen in older women | Biopsy (subepithelial bullae) and direct immunofluorescence |
| Pemphigus | Flaccid, fragile bullae that rupture immediately, leaving large raw areas. Seen in older women | Biopsy (intra-epidermal bullae) and direct immunofluorescence |
| **Deep ulcers** | | |
| Behçet's disease | Persistent painful ulcers with a sloughing base. Predilection for labia minora | Clinical assessment (oral ulcers, posterior uveitis, synovitis and arthritis) |
| Fixed drug eruption | A blistered, pruritic patch that later ulcerates. Provoked by drug allergy and may affect any part of the skin. Healed ulcers often pigment, but will flare up on re-exposure to the causative drug | Clinical assessment |
| Pyoderma granulosum | Deep necrotic ulcers with dusky overhanging edges and a dirty base | Clinical assessment (rheumatoid arthritis, inflammatory bowel disease, lymphoproliferative disorders) |
| Crohn's disease | 'Knife-cut' ulcers with thickened edges, often occurring against a background of diffuse vulvar oedema. Sinus and fistula formation. May precede bowel manifestations by many years | Clinical assessment and biopsy |
| Hidradenitis suppurativa | Indolent, painful pustules or nodules. Associated comedones, skin bridges and sinuses. Limited to hair-bearing skin | Clinical assessment and biopsy |
| Lymphangectasia | Ulceration of verrucous-like papules, with drainage of clear or milky lymphatic fluid | Clinical assessment and biopsy |
| Squamous cell carcinoma | Erosive or nodular lesions, usually occurring against a background of undifferentiated vulvar intraepthelial neoplasia or a chronic dermatosis | Clinical assessment and biopsy |

*Ulcerations associated with sexually transmitted infections (primary and secondary syphilis, granuloma inguinale, lymphogranuloma venerum, chancroid) are not included in this table

# Extramammary Paget's disease

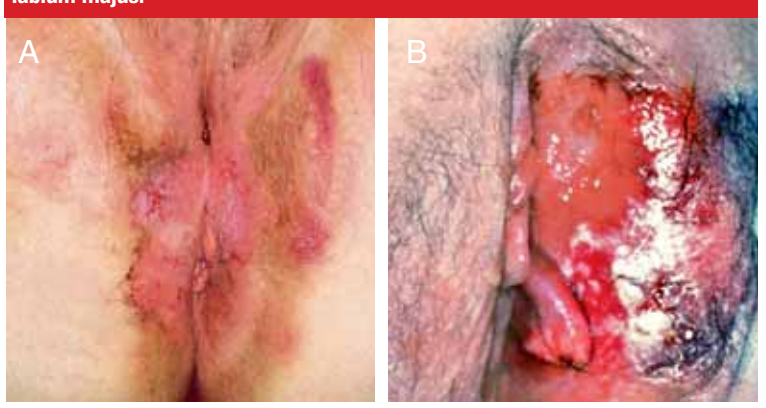
EXTRAMAMMARY Paget's disease is an adenocarcinoma affecting apocrine cells in hair-bearing skin. Labium majus and perineum are the most common sites, but disease may extend to the mons pubis, thighs and buttocks; rarely, the mucosa of rectum, vagina and urethra will be involved.

Histologically the disease is defined by the presence of distinctive malignant glandular cells in the vulvar epidermis and/or skin appendages. These cells closely resemble the malignant apocrine cells seen in the invasive adenocarcinoma affecting the mammary glands. However, Paget's disease of the vulva is usually an adenocarcinoma-in-situ, with only 10% of affected women having invasive disease. Vulvar Paget's disease also differs from its breast homologue in that it is not usually associated with underlying adenocarcinoma to be found elsewhere in the body. The one exception is in the 5-8% of cases that involve the anal mucosa. These women will usually have an underlying rectal adenocarcinoma.

Clinically, Paget's disease of the vulva presents as intensely pruritic, well-demarcated but multifocal papules. Lesions have a red, velvety appearance — and have been dubbed *vin rouge* by colposcopists (figure 11). Persistent weeping and soreness can be distressing features.

Treatment of primary Paget's disease of the vulva is notoriously difficult because malignant apocrine cells usually extend well beyond the area that is clinically abnormal. Wide excision is required, often with plastic reconstruction. Paget's disease of the vulva also tends to recur, often many years after excision. However, recurrent disease is rarely invasive, meaning that there can be a role for ablative procedures performed by expert colposcopists.

**Figure 11: Extramammary Paget's disease. A: Subtle perianal erythema with white keratotic islands, reflecting pre-invasive Paget's disease. B: A deeply invasive adenocarcinoma arising within diffuse Paget's disease of the left labium majus.**




# Conclusion

VULVAR disease can take many guises; some are confusing but become increasingly recognisable with experience. The plethora of possible clinical presentations is beyond the scope of this How to Treat two-part series, but we have endeavoured to cover the main conditions GPs are likely to encounter in their practice — and to help raise awareness of the pathology underlying each.

*cont'd next page*

## GP's contribution

**DR MATILDA METLEDGE**
Sydney, NSW

### Case study

MS W, 27, has had several sexual partners in the past few months. She presents with what appears to be recurrent monthly episodes of vaginal candidiasis, occurring roughly mid to late cycle each month.

She has intense itching and dysuria and has been self treating with over-the-counter once-only oral fluconazole tablets. This seems to have some effect, and her symptoms resolve completely when her period arrives. She is not on the contraceptive pill.

On examination she has some white plaques but minimal discharge. No ulcers are seen. She would like to know what to do to prevent further attacks. The oral regimen is also expensive and eating into her limited budget.

### Questions for the authors

**Other than general hygiene advice (assuming the diagnosis is correct), is there any advice you would give the patient for prevention, including dietary advice?**

In general, "minimal discharge" would not be an expected finding in someone with serial recurrence of simple thrush infections, and "white plaques" would not be expected in chronic candidosis. Acute yeast vaginitis responds well to all therapies; in contrast, RVVC is a refractory condition that has to be managed like a chronic disease. Success depends upon having an accurate diagnosis.

Workup must isolate and speciate the suspected yeast organism (because the non-albicans species are broadly resistant to imidazoles), and also exclude any amplifying factors (such as a concomitant bacterial vaginosis, which may produce a biofilm that will protect any candidal spores from destruction by Ms W's once-monthly fluconazole dose).

Assuming candidal vulvovaginitis is confirmed, the treatment imperative is to eradicate the subclinical candidal reservoir that disrupts local immune response and fuels her monthly recurrences. There are really only two lifestyle modifications that genuinely curtail recurrent vaginitis episodes:

- First, any factors that might be disturbing her glucose metabolism must be addressed. Is she insulin resistant? Does she 'sugar binge'? Restricting dietary intake of highly refined carbohydrates (eg, lollies, cakes, white bread, soft drinks or orange juice, and white rice) will help prevent sudden postprandial spikes in blood glucose. Although any absorbed glucose bolus will eventually be controlled by an insulin response, there can be considerable glucose diffusion into the vaginal fluids during the lag phase. Glucose-enriched vaginal fluids trigger yeast proliferation and enhance organism virulence.
- Second, the GP should ensure that choice of clothing does not unduly increase local heat and humidity.

Restrictive measures that generally prove ineffective include stopping birth-control pills and treating the male partner.

**You mention boric acid pessaries as a useful adjunct for some species of candida. Are these widely available from compounding chemists and what is the number and timing of capsules needed, and the cost? Is it used in conjunction or instead of imidazoles?**

Several epidemiological studies have shown non-albicans candida species to be relatively resistant to conventional azole antifungal treatment. Boric acid is a useful second-line agent in these circumstances; it inhibits the proliferation of both *C. albicans* (including fluconazole-resistant strains) and non-albicans candida species. The active ingredient is the trace metal boron.

Compounded boric acid suppositories deliver fungistatic boron levels within the vaginal fluid pool. Dosage ranges from 600mg twice daily, to 600mg on alternate nights. Treatment of external rashes can be augmented with an 8% boric acid ointment. Duration of treatment varies with the clinical circumstances.

Systemic toxicity in adults is low, but these capsules can produce an arsenic-like poisoning if ingested by children. Mild local irritation occurs in about 10% of women, especially at higher doses. Boric acid is known to be a powerful teratogen, so your patient would need to use a reliable birth-control method — preferably a low-dose oral contraceptive pill.

Boric acid suppositories can be used as either adjuvant or monotherapy. The cost of the boric acid powder and the empty gelatin capsules is minimal. However, filling the capsules is labour intensive, escalating retail price from a compounding pharmacy to about $1.00 per suppository.

### General questions for the authors

**Traditional teaching is that women with recurrent candidiasis often have been misdiagnosed and should be treated for herpes instead. Can you describe when you would treat for both when ulcers are not present?**

There is a widespread belief among GPs that the irritative symptoms of refractory candidosis reflect some form of herpetic neuralgia. This view is never the case, and the practice of diagnosing anything other than vulvar ulcers as being herpes-related is inappropriate.

**Is it expected that HPV vaccination will have a dramatic impact on the diagnosis of VIN?**

Placebo-controlled clinical trials have established that quadrivalent HPV vaccines (to HPV types 6, 11, 16 and 18) do indeed provide high-level protection against both benign condylomatous infections and neoplastic disease (both cervical and vulvovaginal) in subjects who were naive to the vaccine HPV types. There is also a degree of cross-protection against other non-vaccine high-risk HPV types. However, the vaccine is not therapeutic for a current HPV infection.

One caveat is that quadrivalent HPV vaccines will not prevent the development of the differentiated VIN that complicates poorly controlled vulvar dermatoses.

### Online resource

- Gallery of vulvar images: www.drrichardreid.info

# How to Treat Quiz

## Vulvar disease — Part 2
## 2 December 2011

**INSTRUCTIONS**

**Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points. We no longer accept quizzes by post or fax.**

**The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.**

**ONLINE ONLY**

www.australiandoctor.com.au/cpd/ for immediate feedback

**1. Which THREE factors predispose to vulvovaginal candidiasis?**
a) Low oestrogen levels
b) Sugar bingeing in insulin resistant individuals
c) Menstruation
d) Broad-spectrum antibiotics

**2. Which TWO statements are correct?**
a) The vagina normally has a slightly alkaline pH and is a low-oxygen environment
b) The normal vaginal flora does not contain candidal yeast species
c) A swab from a normal vagina will usually be negative for candida on microscopy, but produce a light candidal growth on culture
d) With a candidal infection there are large numbers of filamentous (active) yeasts

**3. Which TWO statements are correct?**
a) Identifying the particular candida species may be helpful in the management of acute sporadic and recurrent candidiasis
b) The vaginal discharge associated with candidiasis is usually odourless
c) Resolution of candidal symptoms and signs with topical treatment indicates microbiological clearing
d) Oral fluconazole is more effective than topical candida treatments

**4. Which TWO statements are correct?**
a) Infections with non-albicans candidal species have a high relapse rate after treatment and are harder to eradicate
b) Topical imidazoles are as effective for non-albicans as for albicans candidal infections
c) In recurrent vulvovaginal candidiasis there is ill-defined erythema and oedema, often with lichenoid change and fissuring
d) Recurrent candidiasis is usually caused by re-infection, either from the bowel or a sex partner

**5. Which TWO statements are correct?**
a) Tinea affects both skin and mucous membranes
b) Treatment of tinea cruris with imidazoles should be stopped when there is clinical resolution
c) Contact dermatitis of the vulva may be due to perfumed soaps or toilet paper, latex, spermicides, and preservatives within pharmacological creams
d) Irritant vulvar contact dermatitis has an immediate onset

**6. Which TWO statements are correct?**
a) Irritant vulvar contact dermatitis causes stinging or burning rather than itching
b) Allergic vulvar contact dermatitis is an immune reaction that takes 2-3 days to develop
c) Pruritus is unusual with allergic vulvar contact dermatitis
d) Lichen simplex chronicus is an autoimmune disorder

**7. Which THREE statements are correct?**
a) Lichen simplex chronicus can develop in association with recurrent vulvovaginal candidiasis or a chronic contact dermatitis
b) Lichen simplex chronicus appears as thick leathery plaques often with linear erosions from scratching
c) Lichen simplex chronicus does not extend into hair-bearing vulvar skin
d) Treatment of lichen simplex chronicus is with a potent topical steroid and removal/treatment of the trigger factor causing itch

**8. Which TWO statements are correct?**
a) Lichen sclerosus is an autoimmune disorder
b) Lichen sclerosus in postmenopausal women is associated with a decline oestrogen levels
c) Lichen sclerosus presents with burning and pruritus that is worse at night
d) Lichen sclerosus can affect all areas of vulvar skin

**9. Which THREE statements are correct?**
a) Longstanding lichen sclerosus is associated with an increased risk of vulvar cancer
b) Undifferentiated vulvar intraepithelial neoplasia (VIN) is caused by HPV infection, especially the HPV 16 subtype
c) Undifferentiated VIN tends to affect older women
d) Undifferentiated VIN is often multifocal and is associated with neoplastic disease elsewhere in the lower genital tract

**10. Which TWO statements are correct?**
a) Undifferentiated VIN is less likely to transform into invasive cancer than is cervical intraepithelial neoplasia
b) Foci of invasive cancer may coexist with undifferentiated VIN
c) Differentiated VIN tends to occur in association with poorly controlled lichen sclerosus
d) Differentiated VIN occurs in younger women and the lesions tend to be multiple (field effect)

### CPD QUIZ

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2011-13 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

**HOW TO TREAT** Editor: **Dr Giovanna Zingarelli**
Co-ordinator: **Julian McAllan**
Quiz: **Dr Giovanna Zingarelli**

**NEXT WEEK** The next How to Treat surveys a range of non-arthritic hip conditions. The author is **Associate Professor Peter J Papantoniou**, orthopaedic and spinal surgeon subspecialising in hip, knee and lumbar spine conditions; consultant in Sydney and on the NSW Central Coast; surgeon at Dalcross Adventist Hospital, St George Private Hospital, St Lukes Private Hospital and Berkeley Vale Private Hospital, NSW; Associate Professor at the San Seventh Day Adventist clinical school, The University of Sydney.