Dermatology
Collection

PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS

Reprints in Dermatology

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A MEDICINE TODAY PUBLICATION

Dermatology Collection

PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS

FOREWORD FROM THE EDITOR-IN-CHIEF, DERMATOLOGY COLLECTION

Dermatology consultations make up 10 to 20% of the average GP's workload and GPs are called on to diagnose and treat skin diseases on a regular basis. *Medicine Today* is keen to provide regular updates and quizzes on the topic.

In this third issue of *Dermatology Collection* you will find more of the articles that we feel have been among the most important published in *Medicine Today* on skin diseases in recent years.

Acne is the most common skin condition seen in adolescents but it occurs in adults and children as well. Although advanced treatment with isotretinoin requires the input of a dermatologist, patients with mild to moderate acne can be treated in general practice. Another common skin condition is psoriasis, affecting at least 2% of the population. Since the advent of new biologic agents, which have necessitated extensive screening, it has been appreciated that patients with this condition are more likely to suffer from comorbidities.

Vulval conditions are often a mystery to doctors, particularly when they are chronic or recurrent. Many dermatological conditions affect the vulva and too many of them are dismissed as thrush. Ironically, however, when thrush becomes chronic and disabling, it is not recognised as such. Chronic vulvovaginal candidiasis has been recently characterised and is easy to treat.

In an ageing population, skin problems of elderly people present unique challenges and solutions. At the other end of the age scale, children with red scaly rashes are also common.

I hope you will enjoy this informative collection of dermatology articles.

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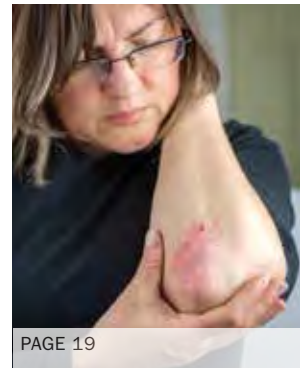

PAGE 2

PAGE 19

PAGE 25

PAGE 38

FEATURE ARTICLES PEER REVIEWED

A GP's guide to treating acne

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The many different treatments available for patients with acne range from over-the-counter preparations to highly teratogenic isotretinoin. GPs are in the ideal position to assess the patient with acne and offer an individualised treatment regimen.

In a world full of Internet experts and seemingly endless treatment choices, patients are confused as to how to choose the correct treatment options for their acne. GPs are on the 'front line' of acne management, and need to be able to offer their patients safe and effective treatment, as well as address concerns about acne management.

Epidemiology and patient concerns

Typically, acne vulgaris occurs during the teenage years; however, prepubertal acne and postadolescent acne also occur and GPs should be competent in managing these patients.[1] Recent studies have shown that an earlier onset of acne seems to coincide with an earlier onset of puberty.[2,3]

Acne is often considered to be a chronic disease as it can persist continuously for years or be episodic over months or years. Some patients become disillusioned with their doctors and acne treatment because they feel the condition is not getting better or they may have a relapse of acne after clearance. The type of acne (i.e. mild, moderate or severe) a patient has therefore needs to be recognised to determine the treatment options that will work best. It is most important that treatment be individualised for each patient.

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KEY POINTS

- Consider acne as a diagnosis in children and adults, as well as in adolescents.
- Individualise treatment according to the clinical presentation and psychological needs of the patient.
- Review patients every three to six months so management can be assessed and changed if ineffective.
- Treat patients with acne early and effectively to avoid acne scarring.

Many patients are worried about acne scarring (Figure). Early effective management can lessen the risk of permanent scarring and therefore it is vital that effective treatment is prescribed.[4] Patients are also often concerned about the side effect profile of acne medications, and this may decrease patient adherence to treatment.

Because of global concern about the increasing antibiotic resistance of bacteria, topical or oral antibiotics should not be prescribed as monotherapy for patients with acne.[5] The risk of antimicrobial resistance is minimised by adding benzoyl peroxide to either topical or oral antibiotic therapy. Antibiotic courses should be limited to three to six months, and topical and oral antibiotics should not be prescribed simultaneously.

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beneficial effect is seen. Other patients are prescribed antibiotics indefinitely; these patients should be reviewed and the treatment changed if not effective. Side effects can occur with prolonged use of antibiotics, such as minocycline hyperpigmentation. It is important to address questions about side effects as some patients may not be willing to adhere to treatment if they are worried about drug side effects and safety.

Time should also be taken to find out how acne affects a patient psychologically. Issues of self-esteem may prevent patients from socialising or affect their functioning at work or school. It is important to note that quality of life improves with effective management and clearing of acne. Although consultation time may be limited, it may be worthwhile asking the patient why they think they have acne or what they think the cause is. The four main factors contributing to the cause of acne are:

- high sebum production
- hyperkeratinisation of the pilosebaceous duct
- colonisation of the ducts by *Propionibacterium acnes*
- inflammation.

Many myths surround the factors that influence acne and these should be dispelled. Diet is a controversial topic; however, the most recent Cochrane review of acne suggested that a diet comprising foods with a low glycaemic load may be useful in reducing total skin lesions in acne vulgaris.[7]

The physical examination

GPs can quickly assess acne severity by looking at the patient's face and torso and asking about its psychological impact. Acne severity can be classified as mild (noninflammatory or inflammatory comedones), moderate (with inflammatory papules and pustules) or severe (with deep inflammatory nodules and cysts). Patients, especially those with darker skin (Fitzpatrick III or higher), may have postinflammatory redness or hyperpigmentation as their inflammatory lesions resolve. These lesions are often mistaken as being active acne lesions.

Severe but uncommon forms of acne such as acne conglobata and acne fulminans may require urgent referral to a dermatologist for prescription of oral or intralesional corticosteroids or oral isotretinoin.

Postadolescent acne may be a continuation of acne from adolescence into adulthood or may appear later in life. Both rosacea and perioral dermatitis can occur in the presence of adult acne, but lack comedones which are the clinical hallmark of acne. Acne in adults may be clinically indistinguishable from teenage acne, yet may be refractory to conventional treatment.

Investigations

Most patients with acne do not have abnormal laboratory test results but further investigations may be warranted if the patient has a sudden onset of severe acne with symptoms of

The GP consultation

A diagnosis of acne is made clinically by taking a full patient history and an examination to establish the type and severity of the acne and the underlying psychological impact. Laboratory investigations may be needed if underlying hormonal factors are being considered or as a baseline for some oral medications such as isotretinoin.

A key question to ask is how long the patient has had acne. A long period of acne may increase the risk of scarring and may also be a clue that the patient may be resistant to previous treatments. It is important to enquire about any family history of acne and whether the patient is taking any medications or supplements. Recently, there has been concern that certain bodybuilding supplements may contribute to acne.[6]

It is important to determine which treatments have been used and, in particular, the duration of use because many patients do not persevere with a treatment for long enough for it to be effective. Many patients take oral antibiotics for acne for a short time and expect them to be effective immediately, so it is important to explain that it can take up to four to six weeks before a

Figure. Acne scars.

hyperandrogenism. Screening tests should be performed in the luteal phase of the menstrual cycle after the patient has stopped taking the oral contraceptive pill for at least one month. Tests include measurement of serum dehydroepiandrosterone sulfate, total testosterone, free testosterone and sex hormone binding globulin levels, and the luteinising hormone/follicle-stimulating hormone ratio. Patients with sudden-onset severe acne with symptoms of hyperandrogenism may exhibit insulin resistance and they are at risk of developing diabetes and cardiovascular disease in later life.

Treatment options

Acne treatments are tailored to patients according to the severity of the acne, as shown in the Table.[8]

Before a prescription is written, the patient should be offered advice regarding skin care, particularly skin cleansing, because this can improve the condition, especially in mild cases. Even in cases of more severe types of acne, an appropriate cleanser and moisturiser can help minimise the side effects of irritant topical treatments or oral isotretinoin use. As mentioned earlier, acne myths such as the role of hygiene and diet should be dispelled. Many resources are available for both the practitioner and the patient, including the All About Acne website (www.acne.org.au) and *Fast Facts: Acne, 2nd ed.*[9,10]

Mild acne

An acne cleanser is a good starting point for patients with mild acne and many brands are available over the counter. These products usually contain salicylic acid, glycolic acid or benzoyl peroxide; benzoyl peroxide is the stronger active ingredient, but the patient can start using products containing any of them.

Improvement may be seen within six weeks of starting use. A leave-on acne treatment, which may contain benzoyl peroxide, glycolic acid or azelaic acid, can also be added to the patient's skin care regimen.

Benzoyl peroxide works by reducing the bacterial colonisation by *P. acnes* of the pilosebaceous follicle and decreases follicular hyperkeratosis and microcomedone formation. It can be potentially irritating, so gradual introduction is recommended, starting at a low concentration. It may be used as the active ingredient in a facial wash or a leave-on cream with or without concomitant use of oral antibiotics or it can be incorporated into combination products with a topical antibiotic (e.g. clindamycin phosphate 1% and benzoyl peroxide 5%) or topical retinoid (e.g. adapalene 0.1% and benzoyl peroxide 2.5%).

Glycolic acid and other α-hydroxy acids decrease altered follicular keratinisation and improve the appearance of the skin by promoting desquamation of the stratum corneum.

Azelaic acid as a topical cream inhibits *P. acnes* growth and improves abnormal pilosebaceous follicular keratinisation. It is tolerated well and has fewer irritant side effects than benzoyl peroxide.

By the time the patient presents to their GP, they may often need a prescription for a topical acne treatment. The newer combination topical treatments, such as clindamycin phosphate plus benzoyl peroxide and adapalene plus benzoyl peroxide, aim to work faster than previous topical monotherapies as they target more areas of acne pathogenesis. Ideally, patients should be assessed eight to 12 weeks after starting treatment, and if no significant improvement is seen then treatment should be changed. It is important to confirm that the treatment regimen has actually been adhered to by the patient. A new topical antiinflammatory cream has just been approved for use in Australia. Dapsone 7.5% gel used once a day is well tolerated with few irritant side effects.

Moderate acne

In patients with moderate acne (i.e. more lesions or more inflammatory lesions than in mild acne), oral treatment is often needed. Both patient and physician should be aware that acne can increase in severity.

For patients with moderate acne, it may be necessary to:
- consider use of an oral instead of a topical antibiotic and add benzoyl peroxide
- consider prescribing the oral contraceptive pill in women with unresponsive acne.

Oral antibiotics

The primary mechanism of action of oral antibiotics is the suppression of *P. acnes* growth, but they also have antiinflammatory properties. Recent research suggests that inflammation may be the key causative factor for acne. Doxycycline is considered

TABLE. ACNE TREATMENT CHOICES[8]

	Mild		Moderate		Severe
	Comedonal	Papular/pustular	Papular/pustular	Nodular[†]	Nodular/conglobate
First choice*[†]	Topical retinoid	Topical retinoid plus topical antimicrobial	Oral antibiotic plus topical retinoid with or without benzoyl peroxide	Oral antibiotic plus topical retinoid and benzoyl peroxide	Oral isotretinoin[§]
Alternative[‖]	Alternative topical retinoid or azelaic acid or salicylic acid or topical dapsone	Alternative topical antimicrobial agent plus alternative topical retinoid or azelaic acid or topical dapsone	Alternative oral antibiotic plus alternative topical retinoid with or without benzoyl peroxide or topical dapsone	Oral isotretinoin or alternative oral antibiotic plus alternative topical retinoid with or without benzoyl peroxide or azelaic acid	High-dose oral antibiotic plus topical retinoid and benzoyl peroxide
Maintenance therapy	Topical retinoid with or without benzoyl peroxide	Topical retinoid with or without benzoyl peroxide	Topical retinoid with or without benzoyl peroxide	Topical retinoid with or without benzoyl peroxide	Topical retinoid with or without benzoyl peroxide

* Consider removal of comedones.
[†] Treatment options for pregnant women include topical antibiotics, azelaic acid, nicotinamide and glycolic acid.
[‡] With small nodules (0.5 to 1 cm).
[§] Second course in case of relapse.
[‖] Oral antiandrogen therapies, such as the combined oral contraceptive pill, are an alternative treatment for women.

first-line therapy and the most frequently prescribed dosage to treat patients with acne is 100 mg/day, but this dosage can range up to 200 mg/day. The capsules should be taken with a full glass of water and should not be taken just before lying down or at bedtime due to the risk of dysphagia and oesophageal irritation. Doxycycline is not recommended for use in children under 12 years of age, because of the risk of tooth discolouration, or in women who are pregnant or breastfeeding.

Minocycline is also used at a dosage of 100 mg/day. However, there are more safety concerns with minocycline than with doxycycline, including possible hepatitis, lupus-like hypersensitivity syndrome and minocycline hyperpigmentation with long-term use.

Oral erythromycin at a dosage of 500 mg twice daily is effective to treat acne but *P. acnes* resistance to erythromycin is much more common than with other antibiotics, as are gastrointestinal side effects. Its use is reserved for children and pregnant women, in whom tetracyclines are contraindicated.

Trimethoprim can be used as third-line therapy at a dosage of 200 to 300 mg twice daily.

Hormonal therapy
Hormonal therapy can be a very effective treatment for women with acne, even if their serum androgen levels are normal. Treatment decreases androgen production by the ovaries and adrenal glands as well as inhibiting the local activity of androgen nuclear receptors on sebocytes and keratinocytes. The most commonly prescribed antiandrogen therapies are the combined oral contraceptive pill, cyproterone acetate and spironolactone.

A recent Cochrane review found that all combined oral contraceptive pills had similar efficacy in acne improvement.[11] Women with acne must be patient because they may only start to see an improvement in their symptoms after three months of taking the combined oral contraceptive pill and the full effect may not be seen until after six to nine months of treatment. Acne improved in 50 to 90% of cases.[11]

Cyproterone acetate reduces sebum production and may also decrease comedone formation. It is usually given in combination with the pill at a dosage of 12.5 to 50 mg/day during the first 10 to 15 days of the menstrual cycle. It can also be prescribed on its own at a dosage of 50 to 100 mg/day from day one or five of the menstrual cycle and stopped before ovulation on day 14. An improvement is usually seen within three months.

Spironolactone acts both as an androgen-receptor blocker and inhibitor of 5α-reductase, which decreases sebum flow. It is recommended that treatment starts with a low dose such as 25 to 50 mg twice daily and is then increased if the patient has no significant breast tenderness or headache. Improvement in acne may take up to three months. Spironolactone is contraindicated in pregnancy because of the potential for feminisation of the male fetus. Used in combination with an oral contraceptive to minimise menstrual irregularity, it is a safe, inexpensive and effective long-term treatment and is often used for years.

Severe acne

A new, stronger, topical fixed combination of adapalene 0.03% and benzoyl peroxide 2.5% gel has recently been approved for patients with moderate to severe acne. This may be used in combination with oral antibiotics or other oral medications before considering oral isotretinoin.

Oral antibiotics are the first-line treatment prescribed by GPs for patients with acne. Some patients may require referral to a dermatologist for prescription of oral isotretinoin, such as in the following situations:

- patients with severe acne
- patients who are unresponsive to oral antibiotics
- patients at risk of scarring
- patients with psychological impairment.

The daily dose and duration of treatment of oral isotretinoin depends on the patient's weight, response to treatment and the side effects that occur. Many dermatologists are now tending to prescribe lower daily doses and then increase the dose as the patient tolerates the treatment, so it is important to note that there is no standard dose.[12] It has been suggested that before referral of the patient for isotretinoin prescription some baseline investigations, such as liver function tests, measurement of fasting cholesterol and triglyceride levels and in women of childbearing age beta human chorionic gonadotrophin, may be helpful. As there are reports of mood change in patients taking isotretinoin, any concerns should be addressed by the dermatologist and GP, and referral to a psychiatrist may be needed. Despite potential side effects, oral isotretinoin remains an effective treatment for severe or unresponsive acne.

A new biophotonic treatment called Kleresca has just become available for patients with moderate to severe acne. It relies on a gel being applied to the face and LED illumination for 12 treatments. This technology is only available in a limited number of clinics.

Acne medication and pregnancy

A challenge for any practitioner is the patient with acne who wants to conceive or who is pregnant. These patients should not be prescribed topical or oral retinoids because of the risk of birth defects. Tetracycline antibiotics should not be given to pregnant women because this will lead to deposition in and staining of the infant's teeth. The limited treatment options include topical antibiotics, azelaic acid, nicotinamide and glycolic acid. Chemical peels, lasers and light treatments have some benefit but are not discussed in this article.

Conclusion

Acne management is a partnership between patient and doctor. Good communication is vital to hear patients' concerns, deliver effective treatment and modify treatment if no improvement is seen or if acne severity increases. The existence of many so-called experts selling products or treatments may be a reflection of the needs of patients to get better and get better faster. The GP, with a medical scientific background and understanding of pathophysiology, is the perfect person to advise and manage the many complexities with which patients with acne present. MT

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A guide to skin conditions in older people

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The dermatoses associated with ageing can, at times, be severely debilitating and it is important to be aware of common presentations so that early intervention can be commenced.

KEY POINTS

- Skin ageing occurs via two pathways: intrinsic ageing and photoageing.
- The skin conditions most commonly seen in the elderly are xerosis, onychomycosis, dermatitis and skin cancer.
- Regular skin checks are recommended in elderly patients who have had excessive cumulative sun exposure, whether or not they have a history of skin cancer.
- Scabies spreads rapidly within nursing homes. However, it is relatively underdiagnosed because the lesions may be atypical. Burrows should be looked for in the web spaces between fingers, in the creases of the wrists and elbows, and on the palms and soles.
- Adverse drug reactions are common in older patients, and are due in part to polypharmacy and comorbidities. Prompt identification and withdrawal of the drug can limit toxic effects.

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Australia's population is ageing as a result of increasing life expectancy and sustained low fertility. Over the past two decades, the number of people aged 85 years and over in this country has increased by 170.6%, compared with a total population growth of 30.9% over the same period.[1]

Ageing is accompanied by changes in all organs, including the skin. This naturally occurring atrophy and fragility of the skin is accelerated by chronic environmental insults, such as ultraviolet (UV) irradiation. A survey of skin conditions in nursing home patients in Australia found that more than half of the patients (54.4%) had at least one skin disease, the most common problems being xerosis (29.5%), onychomycosis (22.5%), dermatitis (8.9%) and skin cancer (4.9%).[2]

This article describes the more common skin conditions that occur in the ageing population of Australia and provides advice regarding management.

Skin ageing

Ageing of the skin occurs via two major pathways: intrinsic ageing and photoageing. Intrinsic ageing is an inevitable change over the passage of time, whereas photoageing is the result of chronic sun exposure and is superimposed on intrinsic ageing.

Intrinsic skin ageing

Major age-related changes in the skin's appearance include dryness, wrinkling, laxity and a variety of benign neoplasms. Aged skin is relatively inelastic and has a slower recovery time after injury. Examples of the functions of human skin that decline with age include barrier function, cell replacement, DNA repair, epidermal hydration, mechanical protection and wound healing.[3]

There are several theories about the mechanism of intrinsic skin ageing. One is that intrinsic skin ageing is secondary to cumulative damage to biomolecules by free radicals, which results in increased cellular weakness and eventually senescence or apoptosis of skin cells.[4]

Photoageing

Photoageing is related to the effects of chronic UV-induced damage, and is superimposed on intrinsic ageing. It accounts for most age-associated changes in skin appearance.[5] Features of photoaged skin include dryness, (senile) purpura, telangiectasia, solar keratoses, wrinkling, coarseness and irregular pigmentation (lentigines).

Senile xerosis and asteatotic dermatitis

Xerosis is a dry, rough quality of the skin that is present in most elderly patients (Figure 1). Although water loss is not increased in aged skin, the water content of the epidermis, particularly the stratum corneum, appears to be reduced.[6] There is no explanation for the pruritus that often accompanies xerosis. Hypotheses include frequent penetration of irritants through an abnormal stratum corneum and an altered sensory threshold due to subtle neuropathy.[7]

Asteatotic eczema/dermatitis is superimposed on dry skin and is frequently found in the elderly, especially during winter. It is often caused by low humidity in a heated environment, and presents as dry, fissured skin with fine scale, mostly over the lower legs. This condition may be extremely itchy. It usually responds to the liberal application of moisturisers, which create an inert barrier over the skin surface, trapping moisture underneath, and/or to medium potency topical corticosteroids (ointments or creams) to settle inflammation.[8] Weak topical corticosteroid ointments may be used for application to face or flexures. Conservative measures, such as reducing the frequency and duration of showers and baths and the water temperature, will also help.

Pruritus

Pruritus is thought to be the most common skin-related complaint of the elderly. In most cases, xerosis is the only cause. Pruritus is often exacerbated by low humidity, frequent bathing or application of irritants to the skin; however, in as many as half of patients, pruritus may have other aetiologies, including metabolic or endocrine disorders such as diabetes mellitus, renal failure, thyroid disease and liver disease. Pruritus can also be a manifestation of a malignant neoplasm, such as lymphoma or leukaemia, or the result of a haematological disease such as polycythaemia rubra vera. Adverse drug reactions can manifest predominantly or exclusively as pruritus, and thus should always be excluded in older patients.[7]

In some cases, the diagnosis is apparent from the history and/or physical examination. When the diagnosis is not apparent, laboratory studies may be indicated. The appropriate initial laboratory investigations for generalised pruritus are:[9]

- full blood count with differential
- electrolytes, urea and creatinine
- liver function tests
- hepatitis C antibodies

Figure 1. Xerotic skin on the legs of an elderly patient.

- thyroid-stimulating hormone levels
- chest x-ray.

Identification and treatment of the causes of pruritus usually helps resolve the condition. In those individuals with no obvious cause, treatment can be difficult and often unsatisfactory. The use of emollients, soothing preparations such as menthol in calamine and topical corticosteroids may be helpful, as may ultraviolet (UV) B phototherapy. However, most patients with intolerable pruritus are unable to manage topical therapy themselves, and it often becomes necessary to resort to mildly sedating systemic drugs such as phenothiazine-type antihistamines (promethazine, trimeprazine). Doxepin, a dibenzoxepin tricyclic antidepressant, has been found to have a useful psychotherapeutic effect in pruritic patients, achieved by its depression of cutaneous sensory receptors. The starting dose is 25 to 50 mg daily, taken at bedtime. There is anecdotal evidence that low-dose oral corticosteroids may be effective in the treatment of some patients with pruritus, but this should be considered a last resort as the treatment may need to be prolonged.[10]

Skin cancers

The age-specific incidence of skin cancer, including melanoma, increases exponentially with age.[11] This is presumably due in part to cumulative exposure to carcinogens over a lifetime causing cell damage and the associated risk of mutation when these damaged cells divide. Nonmelanoma skin cancer (NMSC) is the most common form of cancer in Australia, and skin cancers account for 80% of all newly diagnosed cancers.[12]

Basal cell carcinoma

Basal cell carcinoma (BCC) is the most common form of skin cancer in all age groups, including the elderly, in Australia. They are slow-growing, locally invasive skin tumours that have a diverse

Figure 2. Nodular basal cell carcinoma on the right nasal bridge.

range of clinical appearances and morphology. Examples include nodular, cystic, superficial, morphoeic and pigmented variants, with a higher risk of recurrence associated with infiltrative, micronodular, morphoeic and giant tumour subtypes (Figure 2). Although metastasis is very rare, morbidity results from local tissue invasion and destruction.

Diagnostic accuracy is increased with good lighting and magnification, and a dermatoscope may be helpful in some cases, especially pigmented BCC. Surgical excision is an effective treatment for patients with primary BCC, with a recurrence rate of less than 2% in the five years following complete excision. In difficult areas (e.g. central face, around the eyes, nose, lips and ears) or with large or recurrent lesions, referral for more extensive surgery may often be indicated. In appropriate cases (low-risk small nodular and superficial BCCs), curettage and cautery and/or cryotherapy can be good treatment options. Topical therapy with imiquimod or photodynamic therapy can also be considered in the treatment of patients with superficial BCCs.[13]

Solar keratosis and squamous cell carcinoma

UV irradiation is the major aetiological factor for skin cancer. Habitual sun exposure in fair-skinned individuals induces both actinic keratosis (AK) and squamous cell carcinoma (SCC).

Actinic keratoses (also called solar keratoses) are hyperkeratotic lesions that are commonly seen in the elderly population in Australia. The great majority of these occur in fair-skinned people who have had excessive exposure to solar UV radiation. There is a low risk of AK transforming into SCC (about 0.1%); however, the presence of AK is an important biomarker of excessive UV exposure and NMSC risk.[14] If lesions are symptomatic, or there is concern regarding the risk of malignant transformation (large size, multiple lesions, tenderness), treatment may be required. Treatment options for AK include cryotherapy, curettage and cautery, shave biopsy and topical preparations such as 5-fluorouracil, imiquimod and diclofenac gel.[3]

The aim of therapy for confirmed cutaneous SCC is complete removal to prevent recurrence, extension or metastasis. The favoured method of removal is excision with a 3 to 4 mm clinical margin. This can be difficult, depending on the location of the tumour, and referral to a dermatologic or plastic surgeon may be required.

Melanoma

The elderly, especially men, present with melanomas that are thicker than those of young adults, probably due in part to delayed diagnosis because of failure to examine their skin properly, poor vision and other medical problems, and the fact that these melanomas often occur on a background of multiple benign skin lesions. This delayed diagnosis is the reason that men older than age 50 years have an increased mortality risk from melanoma compared with women or younger men.[15]

Melanomas are described according to their appearance and behaviour. Those that start off as flat patches (i.e. have a horizontal growth phase) include:
- superficial spreading melanoma
- lentigo maligna melanoma
- acral lentiginous melanoma (on soles of feet, palms of hands or under nails).

These superficial forms of melanoma tend to grow slowly but, at any time, may progress to a more rapid vertical growth phase.

Melanomas that quickly involve deeper tissues include:
- nodular melanoma (presenting as a rapidly enlarging lump)
- mucosal melanoma (arising on lips, eyelids, vulva, penis, anus)
- neurotropic and desmoplastic melanoma (fibrous tumour with a tendency to infiltrate nerves).

Lentigo maligna (Hutchinson's melanotic freckle) is an early form of melanoma (melanoma in situ) in which the malignant cells are confined to the tissue of origin, the epidermis of sun-damaged skin. Lentigo maligna melanoma is diagnosed when the malignant melanoma cells have invaded the dermis and deeper layers of the skin. Although all types of melanoma have increased age-specific incidences, lentigo maligna melanoma overwhelmingly develops in people aged over 60 years, in areas of habitually sun-exposed skin.

Patient education is imperative when it comes to skin cancer, and older patients should be advised to cover up with a hat and protective clothing, as well as to wear an SPF30+ sunblock. Patients who have a history of excessive sun exposure, with or without a past history of melanoma or NMSC, may benefit from having regular skin checks. Taking baseline photographs helps in monitoring any suspicious lesions.

The American Cancer Society's 'ABCDE criteria' provide a useful clinical prediction rule for malignant melanoma with a sensitivity and specificity of 93% and 37%, respectively. The test is considered positive if a lesion exhibits one or more of the five criteria: [16]
- Asymmetry – one half of the lesion is not identical to the other
- Border irregularity – lesion has an uneven or ragged border
- Colour variegation – lesion has more

Figures 3a and b. Scabies.
a (left). Scabetic nodule on the right nipple of a nursing home patient.
b (right). Crusted (Norwegian) scabies. Note the burrow on the middle finger (arrow).

than one colour (i.e. black, blue, pink, red or white)
- Diameter – lesion has a diameter greater than 6 mm
- Elevation or Enlargement – elevation of lesion above skin surface or enlargement by patient report.

Another potentially useful diagnostic test is the revised seven-point checklist developed in the UK. This, too, has a high sensitivity (90%) and low specificity (34%).[16,17] In this test,
- melanoma should be suspected if there are one or more of the major signs:
  - change in size
  - change in shape
  - change in colour
- the presence of three or four minor signs without a major sign can also indicate a need to biopsy suspicious lesions:
  - inflammation
  - crusting or bleeding
  - sensory change
  - diameter (7 mm or more).

Suspected melanomas should be surgically excised with a narrow margin. If the initial excision is positive then a wider excision (10 mm) is usually undertaken. Again, referral to a plastic or dermatologic surgeon may be required. If the melanoma is thicker than 1 mm, sentinel node biopsy may be recommended to assist in staging; however, it does not offer any survival advantage.

Infectious processes
Bacterial infections
The elderly are often predisposed to cellulitis and erysipelas because of dry skin, oedema, diabetes and poor circulation. Gram-positive bacteria cause most cases (group A streptococci for both and *Staphylococcus aureus* also for cellulitis).

Cellulitis should be clinically distinguished from erysipelas, to guide antibiotic choice. Erysipelas involves the dermis, occurs mainly on the legs and tends to be sharply demarcated, as opposed to cellulitis, which involves the skin and subcutaneous fat and is less well demarcated.[18]

Areas of cellulitis and erysipelas need to be swabbed for culture and treated aggressively with appropriate antibiotics in elderly patients because comorbidities can increase the already high risk of complications associated with these conditions. These complications include septicaemia, thrombophlebitis, septic arthritis, osteomyelitis and endocarditis. Methicillin-resistant *S. aureus* (MRSA) has become an increasingly important pathogen in hospital and community acquired infections, and age over 80 years is significantly associated with MRSA carriage.[19]

Parasitic infections (including scabies)
Scabies, a skin infestation with the mite *Sarcoptes scabiei*, can occur in people of any age. However, nursing homes provide a fertile ground for rapid spread of the infestation. In the elderly, partly because of their decreased immunity, lesions may be atypical and, for this reason, scabies is relatively underdiagnosed. In addition, older people often have xerosis, and pruritus at times may be attributed to this aetiology.

Scabies mites burrow into the skin, where they live and reproduce. Eggs laid in the burrows hatch, and the larvae crawl out onto the skin, make new burrows and mature into adult mites. The skin infestation commonly involves the genital areas, buttocks, lower abdomen, wrists, forearms and webs between the fingers. Burrows can be difficult to see but are most often seen on the webs between the fingers, around the waist, in the creases of the wrists and elbows, and on the palms and soles of the feet.[20] The itchy rash on the limbs and trunk is due to an allergy to the mites and their products. Itchy nodules are often seen on the penis in men, on the nipples in women and around major flexures in children (Figure 3a).[21] Diagnosis may be confirmed by microscopy of a skin scraping.

The topical treatment of choice for scabies is permethrin 5% cream, which should be applied topically to dry skin from the neck down, paying particular attention to the hands and genitalia, and under the nails (using a nailbrush). The

Figure 4. Onychomycosis.

Figure 5. Herpes zoster involving the left mandibular branch of the facial nerve, with dissemination.

cream should be left on the skin for a minimum of eight hours (usually overnight) and reapplied to hands if they are washed. The time may be increased to 24 hours if there has been a treatment failure. There is a better success rate if permethrin is used on two occasions, one week apart. Benzyl benzoate and crotamiton are other treatments used.

Crusted (Norwegian) scabies is a very contagious but less itchy form of scabies in which the mite population on the patient is very high due to poor host response (Figure 3b). It is often confused with eczema. Oral treatment with ivermectin (200 μg/kg, two to five single doses several days to a week apart, depending on severity) may be required.[21] The patient should be quarantined, and bedding, clothes and towels should be laundered. If the patient resides in a nursing home, all patients, medical and nursing staff and their families should be treated; if staff from the affected ward have worked elsewhere, that area should also be treated.

Dermatophyte and yeast infections

Onychomycosis (tinea unguium) is present in about 35% of people aged over 60 years, and tinea pedis is also present in about 25% of this patient population (Figure 4).[22] Onchomycosis is most commonly caused by the dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes* var. *interdigitale*. Although tinea pedis (most commonly caused by *T. rubrum*,

T. mentagrophytes and *Epidermophyton floccosum*) will usually have been present for decades, it may worsen with age. In elderly people with diabetes, interdigital tinea pedis may ulcerate and predispose to bacterial cellulitis. Culture-proven dermatophyte infection of the nails may not respond as well to oral terbinafine in the elderly as it does in younger patients.

Cutaneous infections due to *Candida albicans* are also common in the elderly, especially those with diabetes and other forms of immunosuppression. Intertrigo is a mechanical, frictional problem in the flexures, with frequent secondary infection by *Candida*. Inflammation should be treated with topical corticosteroids, and the use of moisture-absorbing powders can reduce maceration. The *Candida* component should be treated with topical azoles or nystatin.

Viral infections

Viral infections of note in the elderly include herpes zoster, which is the most common, and also herpes simplex and molluscum contagiosum. Elderly immuno-compromised patients are most at risk of such infections.

Herpes zoster (shingles), a reactivation of the chickenpox virus (varicella–zoster virus), is primarily seen in older patients, with an incidence of about 1500 cases per 100,000 persons annually at age 75 years.[23] The initial symptom is pain and burning, which is followed by the appearance of

grouped vesicles on an erythematous base and in a dermatomal distribution (Figure 5). Herpes zoster can be complicated by eye involvement, which can result in serious conjunctivitis, iritis or uveitis. Postherpetic neuralgia is often debilitating in the elderly.

Systemic therapy with oral famciclovir, valaciclovir or aciclovir can shorten the course of herpes zoster and potentially prevent postherpetic neuralgia. This treatment is particularly effective if administered within 72 hours of the onset of vesicles. Amitriptyline and pregabalin are commonly used for the treatment of patients with postherpetic neuralgia.[21]

Herpes zoster can be effectively prevented with appropriate vaccination of individuals over the age of 60 years. The Shingles Prevention Study demonstrated vaccine efficiency in trial participants with a significant reduction in the incidence of herpes zoster, postherpetic neuralgia and the burden of illness associated with the infection.[24] Overall, compared with placebo, vaccination reduced the incidence of herpes zoster by 51.3% and the incidence of postherpetic neuralgia by 66.5% over a median follow up of more than three years.

Ulcers

Chronic ulcers of all aetiologies are more common in the elderly than in younger people, most likely because of a combination of impaired wound healing and higher

MEDICATIONS ASSOCIATED WITH DRUG-INDUCED SKIN REACTIONS*[27]

Common causes of exanthematous reactions
- Allopurinol
- Antimicrobials
- Barbiturates
- Captopril
- Carbamazepine
- Frusemide
- Lithium
- Phenytoin
- Thiazides

Common causes of fixed drug eruptions
- ACE inhibitors
- Allopurinol
- Antimicrobials
- Barbiturates
- Benzodiazepines
- Calcium channel blockers
- Carbamazepine
- Diltiazem
- Fluconazole
- NSAIDs, including aspirin
- Paracetamol

Drugs often associated with photosensitivity reactions
- Amiodarone
- NSAIDs
- Phenothiazines
- Retinoids
- Sulfonamides

- Tetracyclines
- Thiazines

Possible causes of cutaneous vasculitic reactions
- Allopurinol
- Aspirin
- Beta-lactam antibiotics
- Carbamazepine
- Carbimazole
- Diltiazem
- Erythromycin
- Frusemide
- Hydralazine
- Interferons
- Methotrexate
- Minocycline
- NSAIDs
- Retinoids
- Sulfamethoxazole–trimethoprim
- Sulfasalazine
- Sulfonamides
- Thiazides
- Thrombolytic agents

Possible causes of erythema multiforme or Stevens–Johnson syndrome
- Barbiturates
- Beta-lactam antibiotics
- Carbamazepine
- Chlorpropamide
- Gold

- Histamine H_2-antagonists
- Lamotrigine
- Leflunomide
- Macrolides
- Mefloquine
- NSAIDs
- Phenothiazines
- Phenytoin
- Rifampicin
- Sulfamethoxazole–trimethoprim
- Sulfonamides
- Tetracyclines
- Thiazides

Possible causes of toxic epidermal necrolysis
- Allopurinol
- Antituberculous drugs
- Barbiturates
- Carbamazepine
- Gold
- Griseofulvin
- Lamotrigine
- Leflunomide
- Nitrofurantoin
- NSAIDs
- Penicillins
- Phenytoin
- Salicylates
- Sulfonamides
- Tetracyclines

* Not a comprehensive list.
Adapted from: Lee A, Thomson J. Drug-induced skin reactions. In: Lee A, ed. Adverse drug reactions, 2nd ed. London: Pharmaceutical Press; 2006. p. 125-156.[27]

prevalence of underlying diseases. The most common are leg ulcers, usually in the setting of chronic venous insufficiency leading to venous hypertension.

Treatment of ulcers depends on the cause, as indicated below.
- Venous ulcers are caused by venous reflux through valves, obstruction of veins and/or impaired calf-pumping action. They are usually relatively painless and associated with aching, swollen lower legs that feel more comfortable when elevated. Treatment of these ulcers requires compression, elevation and exercise, which help reduce oedema.
- Arterial ulcers are most often due to atherosclerosis, and are often painful and have 'punched out' borders. Re-establishment of adequate arterial blood supply is required.
- Diabetic foot ulcers are caused by the combination of arterial blockage and nerve damage resulting in repetitive trauma. They are notably located over pressure points, such as heels and the tips of toes. Education and prevention are the key to management.

Decubitus ulcers, or pressure sores, are far more common in elderly hospitalised patients than in younger patients, as the former tend to be less mobile, needing help turning in bed, and have additional aggravating disorders such as dry skin over bony prominences, incontinence and/

Figure 6. Cutaneous drug eruption with mucosal involvement.

or poor nutritional state. Regular turning and use of pressure-relieving support surfaces aid in prevention. Pressure ulcers are also often infected so any associated infection must be treated.[25]

It is important to consider a diagnosis of skin cancer, most commonly basal cell carcinoma, in the case of nonhealing bleeding ulcers.

Miliaria

Miliaria (sweat rash) arises from obstruction of the sweat ducts. Miliaria rubra (prickly heat) is the most common form of miliaria in the elderly, and results when obstructed sweat migrates into the epidermis as well as the upper dermis, causing itchy inflamed papules around the sweat pores. In contrast to acne and other forms of folliculitis, miliaria lesions do not arise around hair follicles. Miliaria typically occurs on the backs of people who lie in bed for prolonged periods, but also commonly occurs during humid summer weather or in winter when people wear multiple layers of clothing.

Conservative management of miliaria revolves around avoiding further sweating and irritants (for example, avoiding excessive clothing, friction from clothing and excessive use of soap, and by wearing breathable fabrics). A useful topical therapy is the combination of 2% salicylic acid and 1% chlorhexidine (in 70% ethanol) used over the areas sparingly until resolution.

Grover disease is a skin condition affecting the chest and back that is also seen frequently in overheated, bed-bound people. The cause is unknown, and most cases last six to 12 months. It often starts suddenly and is more common in winter than in summer in the elderly population. Erythematous blistered, crusted or eroded papules are seen on the central back, mid-chest and occasionally elsewhere. The condition is often itchy but can be asymptomatic. Occasionally it may be complicated by the development of dermatitis, usually in a nummular pattern.

There is no curative treatment but possibly helpful options include keeping cool and applying emollients, antipruritic lotions or mild corticosteroid creams. Calcipotriol cream has been reported to be of benefit for some patients, as has a course of tetracycline or an oral antifungal agent (e.g. itraconazole).

Bullous pemphigoid

Bullous pemphigoid is more common in people aged over 60 years and is the most often seen of the autoantibody-mediated blistering disorders in the elderly. The blisters are large and tense and most commonly seen in the flexures, trunk and limbs. They may arise from urticarial papules or plaques. Although it is a self-limited condition that frequently resolves within six to 12 months, elderly patients may experience increased morbidity and mortality because of debilitated general

health or as a side effect of treatment.[26]

Occasionally, potent topical corticosteroids can control localised forms of bullous pemphigoid but most cases require oral prednisolone, with doses varying depending on severity of disease. Less extensive disease may require only 0.3 to 0.5 mg/kg of prednisolone, whereas more extensive and severe forms may require up to 1 mg/kg. If high-dose oral corticosteroids are contraindicated, doxycycline may be used, either alone or as a corticosteroid-sparing agent.[21] Healing with scarring is rare but there may be hyper- or hypopigmentation.

Drug eruptions

Adverse drug reactions of all kinds are much more common in older patients, partly because the elderly consume more medications than younger people and partly because of medical conditions (e.g. impaired renal, hepatic or cardiac function) that affect drug metabolism or excretion. The most frequently observed adverse cutaneous drug reactions are pruritus, exanthems and urticaria, but the most severe are, of course, Stevens–Johnson syndrome and toxic epidermal necrolysis (Figure 6).

Diagnosis of a drug eruption requires taking a careful history of all prescription medications as well as those purchased over the counter. Drugs that are well known for causing cutaneous reactions include antimicrobial agents, NSAIDs, chemotherapeutic agents, anticonvulsants and psychotropic agents (see the Box).[27] Prompt identification and withdrawal of the offending agent can help to limit its toxic effects.

Conclusion

Ageing of skin and cumulative UV damage makes older patients more susceptible to a wide variety of skin conditions, many of which can be severely debilitating. It is important to be aware of the more common presentations of these dermatoses so that early intervention and treatment can be commenced.　　　　　　　　MT

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Psoriasis
Don't miss the comorbidities

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Psoriasis has a complex aetiology that includes genetic and immunological components. Accepted comorbidities of psoriasis include psoriatic arthritis, cardiovascular disease, metabolic syndrome and depression. Psoriasis and its comorbidities have a significant impact on a patient's quality of life.

KEY POINTS

- Psoriasis is a common condition characterised by erythematous, scaly patches and plaques.
- The aetiology and pathogenesis is complex and not fully understood; however, genetic and immune-related components play a key part.
- Accepted comorbidities of psoriasis include psoriatic arthritis, cardiovascular disease, the metabolic syndrome and depression.
- Timely diagnosis and effective management of comorbidities are vital to limit morbidity and mortality. The role of the GP is central in co-ordinating care of patients with this complex condition.
- Comorbidities change over time, are associated with increased psoriasis severity and can occur secondary to treatments used.
- Psoriasis and its comorbidities have a huge impact on a patient's quality of life. Modifiable comorbidities should be treated aggressively.
- Referral of the patient to a dermatologist is recommended when the patient does not respond to conventional therapy.

P soriasis is a common, chronic, noncontagious, multisystem autoinflammatory disease.[1] It is complex in its aetiology and pathogenesis and appears to be influenced by genetic and immune-related components.[2,3] Psoriasis affects between 2 and 3% of the population worldwide; it is seen less commonly in the tropics and in dark-skinned populations. The onset of disease can occur at any age; however, there is a probable bimodal distribution at 16 to 22 years and 57 to 60 years, with early-age onset being associated with more severe disease and an affected first-degree relative. Men and women are equally affected, with children less than 10 years of age contributing to more than 20% of all new cases.[4]

The characteristic form of psoriasis, psoriasis vulgaris, presents with erythematous, scaly papules and plaques (Figures 1a to c). Morphological variants include guttate (Figures 2a and b), palmoplantar (Figures 3a and b), erythrodermic (Figures 4a and b) and pustular (Figures 5a and b) psoriasis.[5] Disease severity is classified according to percentage of body surface involved combined with plaque thickness and scaling (Psoriasis Area and Severity Index [PASI] score), with moderate-to-severe disease being defined as more than 10% body surface area affected.
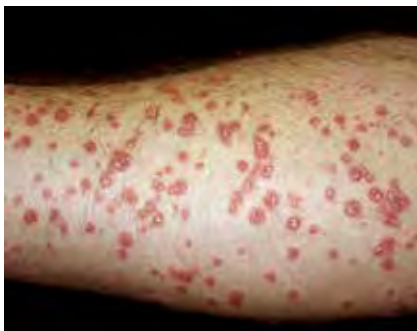
Figures 1a to c. Psoriasis vulgaris.

Figures 2a and b. Guttate psoriasis.

Figures 3a and b. Palmoplantar psoriasis.

Pathophysiology

Psoriasis is a complex disease that has a strong genetic background. The genetic basis of psoriasis has long been evident from high concordance rates in twin studies.[3] Major insights through genetic sequencing of patients with familial psoriasis have provided evidence that mutations in the *CARD14* and *IL36RN* genes are disease inducing. Further studies have identified numerous psoriasis susceptibility loci, implicating the human leucocyte antigen Cw6 (*HLA-Cw6*) gene with psoriasis heritability and early onset.[2] Genetic sequencing has also validated the importance of T lymphocytes, with the central importance of interleukin (IL) 17 and tumour necrosis factor (TNF) alpha now recognised in the pathogenesis of psoriasis.[3] Such information has led to the identification of treatment targets for effective biological therapies.

The underlying pathological mechanisms of triggers and initiators of psoriasis remain incompletely understood. However, a correlation between streptococcal throat infection and guttate psoriasis has been identified in patients with *HLA-Cw6* expression.[6] Furthermore, studies suggest that psychological stress may play a role in the exacerbation of psoriasis.[7]

Comorbidities associated with psoriasis

Psoriasis is a systemic autoinflammatory disorder associated with a number of comorbidities.[8] Autoinflammation is the dysregulation of the innate immune system, leading to propagation of inflammatory pathways. Autoinflammatory disorders are distinct from autoimmune diseases, which result from the proliferation of T lymphocytes and/or antibodies directed against self antigens.

The exact mechanisms behind the associations between psoriasis and its comorbidities are unclear; however, a common genetic background and acquired risk factors appear to link psoriasis to its comorbidities. Epidemiological studies have shown that more severe disease accompanies

a higher risk of significant comorbidities. The systemic inflammation in psoriasis contributes to continuation of the disease, as well as the development of comorbidities.[1] Accepted comorbidities of psoriasis include psoriatic arthritis, cardiovascular disease, metabolic syndrome, inflammatory bowel disease and depression.

Psoriatic arthritis

Up to 35% of patients with chronic plaque psoriasis have an associated spondylo-arthropathy, the most common being dactylitis (Figure 6) and enthesitis – that is, inflammation at the site of insertion of tendon into bone (Figure 7).[9] Individuals with psoriatic arthritis (PsA) have more severe skin symptoms and a lower quality of life than patients with psoriasis but not arthritis.[10] PsA commonly develops after the onset of skin changes (in 6 to 18% of patients), but may also develop before.[11] PsA has a variable but chronic clinical course, and causes severe disability from destructive lesions in 20% of affected individuals. The skin manifestations of PsA may be mild and in some cases poorly recognised, with nail dystrophies often misinterpreted as fungal infections especially when affecting toes (Figures 8a and b).

Screening for PsA in patients with psoriasis is recommended, with involvement of a rheumatologist for definitive diagnosis. To meet the CASPAR (Classification Criteria for Psoriatic Arthritis) criteria for PsA, a patient needs to have inflammatory articular disease and score three or more points from the categories of psoriasis, nail dystrophy, a negative rheumatoid factor, dactylitis (Figure 6) and radiological evidence of juxta-articular new bone formation.[12]

Cardiovascular disease

Psoriasis is strongly related to an increased risk of cardiovascular disease, including ischaemic heart disease, myocardial infarction (MI) and arterial/venous thrombosis.[13] Psoriasis is an independent risk factor for the development of an MI, especially in young people.[14] Both patients with mild and with severe psoriasis have been shown to have an increased risk of MI when compared with matched controls.[15] Underlying mechanisms include common genetic factors and risk factors for both conditions, specifically metabolic syndrome, obesity, a sedentary lifestyle, depression or anxiety and smoking. Control of these modifiable cardiovascular risk factors is essential in the management of patients with psoriasis, through guidance by the GP with a holistic approach to patient care. Recent evidence suggests that systemic therapy, particularly biological agents such as infliximab and etanercept, reduces mortality and morbidity.[9,16]

Metabolic syndrome

Psoriasis is associated with a higher prevalence and incidence of insulin resistance and diabetes. In particular, young patients with psoriasis and those with severe disease have a greater risk of developing diabetes.[16] It is thought that systemic inflammation in psoriasis promotes insulin resistance, which is an independent risk factor for type 2 diabetes.[17] Insulin resistance is also related to endothelial dysfunction, an important component in

Figures 4a and b. Erythrodermic psoriasis.

Figures 5a and b. Pustular psoriasis.

Figure 6. Dactylitis.

Figure 7. Enthesitis.

the pathogenesis of atherosclerosis and coronary artery disease. In the authors' clinic more than 50% of patients with moderate-to-severe psoriasis are affected by the metabolic syndrome and more than 65% are obese according to body mass index (BMI). Obesity seems to be particularly treatment resistant in this cohort.

As part of the metabolic syndrome, psoriasis has a significant association with dyslipidaemia, a known risk factor for cardiovascular disease. Greater psoriasis disease severity is linked to a higher prevalence of dyslipidaemia.[18] Control and monitoring of blood lipid levels by dietary

Figures 8a and b. Nail dystrophies: pitting and oil spotting.

and medical means is important to reduce morbidity and mortality rates.

Obesity has long been associated with psoriasis in adult and now paediatric populations, with an increased BMI contributing to increased risk for disease development.[4,19] BMI and other measurements of adiposity are independent risk factors for the development of psoriasis and PsA.[20] Patients with psoriasis have a more than 50% increased odds of being obese compared with the general population.[21] Also, obese patients have been found to have a higher risk of developing more severe forms of psoriasis. Recent literature suggests that adipocytes and inflammatory macrophages play key roles in the disease processes of both obesity and psoriasis.[21] Activated macrophages stimulate adipocytes to secrete inflammatory mediators called adipokines that establish and maintain an inflammatory state in patients with obesity.[4] The increased visceral adipose tissue compartments in obese patients appear to be central in adipokine dysfunction.[20]

Depression

Psoriasis has a significant impact on quality of life and is associated with an increased prevalence of depression, anxiety, suicidal ideation and substance misuse.[22] Up to 60% of patients with psoriasis have depression, which is comparable with the prevalence in patients with cancer, chronic obstructive pulmonary disease, ischaemic heart disease and diabetes.[10,22] Patients with psoriasis have

increased rates of smoking and alcohol misuse, contributing to the worsening of psoriasis and cardiometabolic comorbidities.[8] Smoking has been shown to increase the likelihood of psoriasis onset and chronicity of the disease when it is established and to negatively affect treatment outcomes.[22] Recognition and treatment of psychological distress is important in patient management.

Other comorbidities

Other comorbidities associated with psoriasis include inflammatory bowel disease, particularly Crohn's disease (CD), uveitis and skin cancer. The exact relation between psoriasis and inflammatory bowel disease is uncertain and is currently being investigated.[23] Patients with psoriasis have a 2.9 times higher risk of developing CD, and patients with CD are seven times more likely than the normal population to develop psoriasis.[24,25] Noninfectious uveitis has been reported to occur in 7 to 10% of patients with psoriasis, and as many as 7 to 25% of those with psoriatic arthritis. Biological therapy with adalimumab is effective in patients with both uveitis and psoriasis.[26] The association of psoriasis with nonmelanoma skin cancer is related to previous treatment with phototherapy.

Investigations

A diagnosis of psoriasis is usually based on a clinical history and examination. Patients with psoriasis should be screened for PsA by taking a thorough history of any early morning stiffness and joint symptoms, with review of inflammatory markers (i.e. C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor). The Early Arthritis for Psoriatic Patients (EARP) questionnaire is a simple and fast tool that can help to identify PsA in the clinic setting (Box).[27]

On examination, the extent of body surface involvement should be noted. Measurements of adiposity (i.e. BMI, waist circumference, weight) are essential at each patient review and provide a good

opportunity to introduce the patient to the possibility of lifestyle changes that may reduce cardiovascular morbidity. Components of the metabolic syndrome and cardiovascular disease risk factors should be identified and investigated at the first consultation and monitored at subsequent reviews. Any bowel symptoms should be investigated if present. Baseline blood test results, including full blood count and renal and liver function, should be obtained before systemic therapy is used.

Treatment options

Treatment options for psoriasis include the following and are listed in order of increasing specificity.

- **Topical therapies:** corticosteroids alone or in combination with vitamin D analogues
- **Narrow band** ultraviolet B phototherapy
- **Systemic therapies:** acitretin, methotrexate, cyclosporin
- **Biological agents:** etanercept, infliximab, adalimumab, ustekinumab
- **Newer agents:** oral apremilast (phosphodiesterase-4 inhibitor), secukinumab (biological agent), brodalumab (biological agent).

Considerations for management

Consideration of comorbidities associated with psoriasis is vital when reviewing each patient. Comorbidities change over time, are associated with increased psoriasis severity and can occur secondary to treatments used for psoriasis. Psoriasis and its comorbidities have a huge impact on a patient's quality of life. Modifiable comorbidities should be treated aggressively. Close patient monitoring, potentially with the involvement of a multidisciplinary team, is essential for those with moderate-to-severe disease and those with significant comorbid disease.

Entry on a national registry (Australian Psoriasis Registry at www.psoriasis.asn.au) for all patients on systemic therapies (including biological agents) is now available and encouraged. Data are entered by centres providing such treatment.

Numerous support groups for patients with psoriasis exist within Australia and internationally. Engagement of patients with support groups has shown to improve patient satisfaction, education, treatment compliance and overall psychological wellbeing.[28,29] The chronicity and recalcitrance of this condition makes patients vulnerable to the variously marketed over-the-counter products, many of which are ineffective and cause unnecessary harmful side effects. Support groups may have the additional potential to assist by providing realistic advice, orientating towards education and encouraging necessary lifestyle changes. Psoriasis Australia (www.psoriasisaustralia.org.au) is one such organisation.

Resources for rural GPs

Tele-Derm offers an invaluable opportunity for rural GPs to engage in holistic care through a co-operative approach that transcends barriers between rural, remote, regional and tertiary centres. The service provides support, advice and valuable rapid information about new and emerging therapies. It is available online at www.acrrm.org.au/tele-medicine.

Conclusion

Psoriasis is a common yet complex multisystem autoinflammatory disease. Accepted comorbidities of psoriasis include PsA, cardiovascular disease, metabolic syndrome and depression. The role of the GP is central in co-ordinating care of patients with this complex condition. Psoriasis and its comorbidities have a huge impact on a patient's quality of life. Modifiable comorbidities should be treated aggressively.   MT

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Scaly red plaques in children

Differential diagnoses and treatment

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Scaly red plaques are a common presentation in children and an accurate diagnosis is often sufficient on history and examination alone. The main differential diagnoses include discoid eczema, psoriasis, tinea corporis and pityriasis rosea. This article focuses on how to diagnose and treat each of these conditions.

KEY POINTS

- The most common differential diagnoses of a presentation of red scaly plaques are discoid eczema, psoriasis, tinea corporis and pityriasis rosea.
- Discoid eczema is common and tends to be very pruritic.
- Psoriasis is well-demarcated, is a salmon-pink colour and has a silvery scale.
- There is usually a history of expansion of circular lesions with tinea corporis.
- Pityriasis rosea patches tend to have an internal scale.
- A biopsy can be helpful to aid with the diagnosis of children with red scaly plaques in difficult clinical situations.

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Scaly red plaques are a common presentation in childhood and the main differential diagnoses include discoid (nummular) eczema, psoriasis, tinea corporis and pityriasis rosea.

This article focuses on the presentation of scaly red plaques, which refers to the clinical situation where there are multiple lesions on the skin, usually circle to oval in shape with a rough or scaly surface. The differential diagnoses of red scaly plaques (see Table) and therapy for each of these common conditions are discussed in this article.

Discoid eczema
History
Discoid eczema, also known as nummular dermatitis, falls within the eczema category, although there are differences from the typical atopic eczema presentation. It can be seen in individuals who are not particularly atopic and/or without a significant past history of severe eczema. A biopsy of the lesions shows changes similar to any other form of eczema; however, the behaviour is different.

Discoid eczema appears to begin at one part of the body, triggered by any number of reasons. Particularly if the eczema is reasonably intense or becomes infected, it is then as if the entire skin becomes 'supercharged' and distant coin-sized patches of eczema start to break out over the body. It is often extremely itchy and the more the eczema is scratched the more it seems to feed the process and a significant vicious cycle is created.

TABLE. DIFFERENCES BETWEEN THE MAIN DIFFERENTIAL DIAGNOSES OF SCALY RED PLAQUES

Plaques	Itch	Symmetry	Expansion of plaques	Morphology
Discoid eczema	+++	Usually	No	Mostly intense in centre, may be weeping Ill-defined edge
Psoriasis	0 to +	Usually	No	Salmon-pink and evenly coloured Silvery scale and well-demarcated
Tinea corporis	+ to ++	No	Yes	Clearing in centre with active 'serpiginous' edge
Pityriasis rosea	0 to ++	Usually	No	Oval plaques with long axis along ribline Scale on inside of outer annulus

Morphology

The lesions of discoid eczema tend to be more intense and oedematous in the central component of the plaque, fading out to an ill-defined edge. Examples of discoid eczema are shown in Figures 1a and b. If intense enough, the eczema can become weepy and a secondary bacterial infection is possible. As a rule it tends to be symmetrically distributed on the body.

Therapy

The basic premise for treating all eczema is to address the underlying triggers and then settle the eczema with use of anti-inflammatory therapy. There are multiple triggers for eczema and most often the triggers are multifactorial, including dryness, irritation, overheating, food (allergy or intolerance), environmental allergies and infection. It is important to be thorough in addressing all of these potential factors in any child presenting with eczema. However, the major emphasis is using aggressive therapy in an attempt to break the vicious cycle that is present with discoid eczema.

Potent topical corticosteroids, such as mometasone or methylprednisolone ointments, should be used liberally and persistently in children presenting with discoid eczema. Notoriously, if therapy is used for only a short time, the condition will then immediately worsen. It is expected that corticosteroid creams will be needed for many weeks, and it is important that they be used until each particular lesion is totally clear rather than just improved. Side effects from prolonged use of topical corticosteroids are extremely rare, and the only areas where one would have any potential concern would be on the face (perioral dermatitis), around the eyes (ocular absorption of steroids) and in the areas prone to stretch marks in teenagers.[1] However, for most areas on the skin there is no risk of side effects from use of topical corticosteroids, even with prolonged use.

At times other therapy is required for discoid eczema and short bursts of oral corticosteroids, ultraviolet (UV) B therapy and wet dressings (for more details see: www.rch.org.au/emplibrary/derm/Wet_dressings_eczema.pdf) are needed. Very occasionally stronger, longer-term immunosuppressive therapy with methotrexate, cyclosporin or azathioprine is warranted.

Psoriasis
History

The history of onset of psoriasis is extremely variable but for most cases the first patch will occur during childhood. It can occur essentially anywhere on the body and may be mildly pruritic but not to the same degree as eczema. There is a family history of psoriasis in at least 25% of cases. The distribution in children is often different from that of adults. The typical sites in adults of the scalp, knees and elbows are less common in childhood. Facial and flexural psoriasis are more frequent in children as are genital involvement and napkin area involvement in babies (see Figure 2a). Certain sites are very suspicious for psoriasis as a diagnosis and these include the concha of the ear (see Figure 2b), umbilicus, genitals, nails and natal cleft. It is possible for psoriasis to co-exist with atopic dermatitis.

Figures 1a and b. Discoid (nummular) eczema.

Figures 2a to d. Psoriasis. a (top left). Napkin involvement in a baby with psoriasis. b (top right). Psoriasis in the concha of the ear. c (bottom left). Well-demarcated salmon-pink plaque in the axilla. d (bottom right). Widespread raindrop-sized patches in a guttate form of psoriasis.

Morphology

Psoriasis can be more difficult to diagnose in children than in adults because the features are less conspicuous. A typical patch of psoriasis will be well-demarcated and even in colour and thickness throughout the plaque. It tends to be more of a salmon-pink colour than eczema and the scale tends to be more silvery in nature and have larger flakes than that of the powdery scale in eczema. Particularly in the flexural areas, the scale is often absent, making the assessment difficult (see Figure 2c).

Psoriasis can occur in a guttate form where there is sudden onset, widespread, raindrop-sized patches (see Figure 2d). Each individual patch tends to have the typical colour and scale of psoriasis and does not tend to be very pruritic.

Therapy

Unfortunately in most cases of psoriasis no particular cause or trigger is discovered.

In children, psoriasis can be triggered by streptococcal infection and it is always worth questioning patients and/or their parents regarding a history of pharyngitis along with perianal soreness as potential sources for streptococcal infection. This is particularly relevant if there is a guttate flare.

Therapy for children with psoriasis is essentially suppressive therapy and is individualised depending on the severity and cosmetic impact for the child involved. A list of therapies for psoriasis is shown in the Box.

Tinea corporis

History

The most common cause for widespread tinea in a child is contact with infected animals. These animals are normally kittens, puppies, pet mice or guinea pigs but other farm animal contact should be considered. Tinea is usually localised to a particular site rather than being widespread and symmetrical. Each particular lesion should have a history of expansion, which is unlike the patches of discoid eczema and psoriasis, which tend to be static.

Morphology

Tinea will often have evidence of a scaly outer edge with a tendency to clear centrally. Particularly if longstanding, the outline is often serpiginous. The degree of inflammation with tinea can be highly variable and primarily depends on the species of tinea – as a rule the animal-based tineas will cause more inflammatory reactions than the anthropophilic varieties. Examples of tinea corporis are shown in Figures 3a and b. Treatment with topical corticosteroids will cause a reduction in inflammation and apparent improvement; however, topical corticosteroids will generally accelerate the spread of the outline with a tendency to cause secondary folliculitis.

Therapy

It is always prudent to take a skin scraping for microscopy and culture when considering tinea as a diagnosis. Even though it can take up to four weeks to receive a culture result, it is helpful to have the

Figures 3a and b. Tinea corporis.

diagnosis confirmed, particularly if therapy has only been partially successful.

The topical therapy of choice for tinea is terbinafine and a daily application until the tinea has cleared is usually all that is required for children with localised infection. At times there may be an increase in the inflammatory nature following the commencement of tinea creams, which can give the patient the false impression that treatment is ineffective

If more widespread, there is involvement of hair-bearing areas or topical corticosteroids have been inadvertently used, oral therapy is justified. Oral griseofulvin at the dosage of 20 mg/kg/day in divided doses is required and often used for up to four to six weeks. If this is not tolerated or contraindicated, other oral agents include oral terbinafine or itraconazole.

Pityriasis rosea
History
The typical history for pityriasis rosea is that of a herald patch or patches that arise spontaneously as a red scaly plaque, often near the shoulder or hip. After a number of hours or days a more widespread eruption occurs over the trunk and usually this is symmetrical. Itch is highly variable and pityriasis rosea can be asymptomatic through to extremely pruritic.

Morphology
The individual morphology of a plaque of pityriasis rosea is described as having a 'trailing' scale around the edge. Compared with tinea, where the scale will be on the outer edge of the annulus, in pityriasis rosea it will be on the internal aspect. Examples of pityriasis rosea are shown in Figures 4a to c. There is a tendency for the plaques of pityriasis rosea to be oval and the long axis of the oval to line up along the riblines.

Therapy
Treatment with topical corticosteroids tends to be disappointing for patients with pityriasis rosea; however, the eruption is self-limiting, usually over six weeks. Sunlight and UVB therapy tend to be helpful and there is some controversy as to whether oral erythromycin can be beneficial for patients who are pruritic.

Other differential diagnoses
There are other potential differential diagnoses for children with red scaly plaques in children, including systemic lupus erythematosus, pityriasis versicolor, drug eruptions, lichen planus and congenital syphilis. A biopsy may sometimes be required if the presentation is unusual.

Conclusion
The presentation of children with scaly red plaques is common and usually there is sufficient information on history and examination to make an accurate clinical diagnosis. There are distinguishing

Figures 4a to c. Pityriasis rosea.

features between the most common differential diagnoses of red scaly plaques; the main changes are summarised in the Table. MT

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Coping with
chronic vulvovaginal candidiasis

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Acute vulvovaginal candidiasis (VVC) is common and usually easily treated but some women develop chronic symptoms that do not respond to conventional anti-*Candida* treatment. Current diagnostic criteria may help clinicians identify women with chronic VVC. Evidence is mounting that it represents a hypersensitivity response to commensal *Candida* spp. Chronic VVC usually responds to long-term antifungal treatment.

Acute vulvovaginal candidiasis (VVC) is a common condition that affects 70 to 75% of women at least once in their lives.[1] It is usually easy to diagnose and treat in general practice. However, about 5% of women have very frequent recurrences of VVC.[2,3] Four or more episodes of microscopically proven candidiasis per year has been defined as 'recurrent vulvovaginal candidiasis'.[4] However there is also a group of women who do not have recurrent symptoms but have disease that is chronic, continuous and unremitting. Women such as these are common patients in practices that specialise in vulval diseases. Their symptom complex includes itch, pain and dyspareunia that worsen premenstrually, remit during menstruation and are associated with an erythematous vulvovaginal eruption.

There is no international consensus on a name for this form of candidiasis and until now it has come under the umbrella of recurrent VVC. However, a set of diagnostic criteria have been proposed for what is termed 'chronic vulvovaginal candidiasis' (Box 1).[5]

Recent research suggests that chronic VVC is not due to opportunistic infection or host immunodeficiency but is likely to be a hypersensitivity response to a commensal organism. This response may be genetically determined. Furthermore, chronic VVC, like acute VVC, does not occur before menarche or after menopause in healthy individuals unless the patient is taking hormone replacement therapy and, although it may commence at any stage of reproductive life, it is most common in young adults.[6,7] It therefore appears

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KEY POINTS

- **Vulvovaginal candidiasis (VVC) covers a disease spectrum, from a single episode to chronic disease with unremitting symptoms.**
- **The concept of chronic VVC has been described; it is a common cause of chronic nonerosive vulvovaginitis in women presenting at vulval disease clinics.**
- **Evidence suggests chronic VVC is a hypersensitivity response to commensal *Candida* spp.**
- **In healthy nondiabetic patients, chronic VVC, like acute VVC, occurs only in the presence of oestrogen.**
- **Chronic VVC may be diagnosed based on clinical features and a history that satisfies specific criteria; diagnosis is supported by, but does not require, a positive swab result for *Candida* spp. at presentation.**
- **Patients with chronic VVC respond well to oral antifungal therapy, which may be needed long term.**

Clinical features

The typical clinical features of recurrent VVC are well described in the medical literature as itch, variable discharge, soreness, irritation, burning, dyspareunia and dysuria with a premenstrual exacerbation.[1] These are also features of chronic VVC (Box 1). Most patients report that their male partner has no symptoms, but postcoital penile erythema and irritation occurs in about 10% of men with a partner with untreated vaginal candidiasis.[1] Examination reveals vaginal erythema, a nonoffensive mucoid discharge and erythema of the labia minora and majora, perineum and sometimes perianal skin, which may be complicated by oedema and painful fissuring (Figures 1 to 3). During pregnancy and lactation, symptoms usually improve. During lactation, low oestrogen levels are implicated. The reason for improvement in pregnancy is unknown.

Patients with chronic VVC are typically systemically well. They show no evidence of immunosuppression, and oral and oesophageal involvement is the exception. The latter do occur in individuals with VVC who are immunosuppressed or have diabetes, but this group appears distinct from the otherwise healthy women who have chronic VVC.

It is not uncommon for patients with chronic VVC to have a negative vaginal swab for *Candida* at presentation.[5] There are several possible causes of false negatives. They are most likely the result of self-medication with over-the-counter antifungals, but sampling errors and the limitations of current detection methods may also be implicated. Patients with this condition find that antifungals afford some relief, even if temporary or partial, and use them frequently. There are no data on how long after antifungal treatment one should wait before trying to

that oestrogen plays an essential permissive role and that in healthy nondiabetic patients, no forms of VVC occur in the absence of oestrogen, whether endogenous or exogenous. The nature of this relationship with oestrogen has not been established.

VVC, including chronic VVC, imposes a significant burden on health resources and, like any chronic disease, has a large impact on quality of life, particularly as it occurs in an area of the body that many are too embarrassed to present to their doctor. Self-diagnosis and the availability of over-the-counter medication make it difficult to estimate this burden accurately; however, VVC has been estimated to cost one billion dollars per year in the USA.[4]

A typical case of chronic VVC is described in Box 2.

1. DIAGNOSTIC CRITERIA FOR CHRONIC VULVOVAGINAL CANDIDIASIS[5]

A patient presenting with chronic nonerosive erythematous vulvovaginitis with any five of the following characteristics is likely to have chronic VVC.

- Previous response, even if brief, to antifungal treatment
- History of a positive vaginal swab for *Candida* spp. at any time while symptomatic
- Cyclical symptoms: build-up before menses, improvement during menses
- Discharge: usually nonoffensive, mucoid
- Exacerbation with antibiotics
- Dyspareunia
- Soreness
- Vulval oedema, including after coitus

isolate *Candida* from the vagina of a patient with chronic VVC. In my experience, swab results may still be negative several months after the last treatment. A positive culture result for group B streptococci should be ignored, as in any other nonpregnant patient.

Despite negative culture results for *Candida*, patients with a typical history and examination results for chronic VVC usually respond to oral antifungal therapy. Although short-term management of patients with recurrent VVC with oral fluconazole is well described, data on the long-term outcome of this treatment have been lacking, with the longest follow-up period being 12 months. Recent Australian research has provided the first indication of the need for long-term treatment.[8,9]

How common is chronic VVC?

Chronic VVC is common but we do not know precisely how common or what proportion of women have acute versus recurrent or chronic disease. All attempts to define the prevalence of chronic VVC have been hampered by the lack of definition of the condition, diagnostic

2. A TYPICAL CASE OF CHRONIC VULVOVAGINAL CANDIDIASIS

Jenna is a healthy 22-year-old woman who presents with vulvovaginitis. Her first attack occurred soon after she started taking the oral contraceptive pill (OCP) and concurrently became sexually active at the age of 18 years. She was too embarrassed to visit her family GP, who had known her all her life, but went instead to a pharmacist who provided her with a course of antifungal suppositories. Her symptoms improved rapidly but she had frequent recurrences, responsive to topical therapy.

At the age of 21 years, Jenna had an appendectomy and was treated with intravenous antibiotics. While in hospital, she developed severe vulvovaginitis. She again self-medicated with topical antifungals but this time without a response. At this point she consulted her GP. A vaginal swab was negative for *Candida* spp. but showed group B streptococci. At a loss to explain her problem, her GP prescribed a course of amoxicillin. Her symptoms of itch, dyspareunia and discharge worsened and she was then empirically treated with two single doses of fluconazole 150 mg. After each dose, her symptoms remitted but rapidly returned.

Each month Jenna noted a premenstrual flare of symptoms, and the only time she felt well was while menstruating. Stopping the OCP made no difference to her symptoms and extensive investigations for sexually transmitted infections, iron deficiency and impaired glucose tolerance gave negative results. A referral to an immunologist did not reveal anything to suggest immunodeficiency.

Examination revealed nonspecific vulvovaginal erythema extending to the labia minora and the sulcus between the labia minora and majora, accompanied by a nonoffensive mucoid discharge. A repeat vaginal swab revealed no abnormality.

Jenna was referred to a vulval disease clinic, where she was diagnosed with chronic VVC. She gradually became asymptomatic over a three-month course of continuous treatment with oral fluconazole.

Commentary

This young woman's story is typical of the history and evolution of chronic VVC over time. Many similar patients present at vulval dermatology clinics. Patients are usually aged in their late teens to early 20s and at symptom onset have recently become sexually active. They are otherwise healthy with no factors to suggest immunodeficiency. Because sexual activity often coincides with commencing the OCP, the latter is usually implicated, but patients find no change in symptom severity whether they are taking or not taking the OCP.

Attacks are initially sporadic and readily treated with antifungal medication. With time, they become progressively more frequent, treatment resistant and finally chronic with a premenstrual flare. The typical appearance of acute candidiasis is replaced by a low-grade chronic erythema involving the vagina, introitus and vulva. The dominant symptoms are pain, dyspareunia and itch with a definite but not cheesy discharge. Oral antibiotics are frequently associated with flares, and patients learn to avoid them. Single-dose antifungals bring only brief relief.

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inaccuracy, variability of clinical presentation and self-diagnosis and self-treatment with antifungals.[1,10]

Differential diagnoses

The differential diagnoses of VVC include a range of conditions that cause persistent erythematous vulvovaginitis (Box 3). Of these many conditions, VVC is the only one that is causally related to *Candida albicans* or *Candida glabrata* and the only one that responds to antifungal medication alone. It is an important practice point that common skin conditions causing vulvitis such as dermatitis and psoriasis are not associated with a vaginitis but may resemble VVC externally and may coexist with it.[11] Patients with psoriasis or dermatitis may have signs of these conditions on other parts of their skin and it is always worth taking a history for these conditions and scanning patients for such evidence on first examination. Patients who have a dermatosis, rather than chronic VVC, generally give a very different history that does not include a previous good response to antifungal treatment, discharge, dyspareunia or a premenstrual flare.

Although burning and pain as symptoms are certainly seen in patients with chronic VVC, they are rarely the only symptoms. Nevertheless, chronic pain syndromes that can cause burning can occur concurrently, and if a patient has not responded to antifungal therapy then these should be considered.

How can GPs confidently diagnose chronic VVC?

Acute VVC appears to be overdiagnosed, particularly by patients themselves who frequently assume that most vulvovaginal complaints are due to 'thrush'. However, chronic VVC appears to be significantly underdiagnosed owing to its lack of definition and the insistence of previous definitions of recurrent VVC that the diagnosis cannot be made in the absence of a positive culture result at presentation.

The difficulty with this concept is that even a positive culture result for *Candida* does not always confirm the diagnosis. About 10 to 15% of asymptomatic women are colonised by *Candida*, and conversely many women with significant chronic symptoms have negative cultures at presentation.[5] In these patients it is necessary to rely on clinical judgement irrespective of whether there is a positive culture result.

It is not known why so many women with significant long-term symptoms present with a negative result for *Candida* on culture and even polymerase chain reaction (PCR) testing. Nevertheless, in my experience, most patients relate if questioned that culture has been positive for *Candida* at some stage while they were symptomatic in the past.

Biopsy shows only nonspecific inflammatory changes and usually does not demonstrate the presence of yeast in the epidermis. Microscopy is time-consuming and difficult for practitioners and, as stated above, is not always positive. The pH of vaginal discharge, which is normal in VVC, serves only to differentiate VVC from bacterial vaginosis.[1,10]

Figure 1. Typical chronic candidiasis showing nonerosive erythema of the vagina, labia minora and the sulcus between the labia minora and majora. Note that the typical discharge seen in acute vaginal candidiasis is absent.

Figure 2. Erythema may involve the perianal skin. Note the presence of a scaly edge and perineal fissuring.

Figure 3. Perineal fissuring is a source of significant dyspareunia.

As there is no definitive diagnostic test for chronic VVC, the diagnosis rests on:
- a typical history
- a nonerosive erythematous vulvovaginitis seen on examination (although this can be nonspecific and vary with the menstrual cycle)
- a convincing objective return to a normal vulvovaginal appearance and self-reported symptomatic response to antifungal therapy.

Previous studies have demonstrated the unreliability of clinical diagnosis, but diagnostic accuracy can be improved by ensuring that patients satisfy at least five of the diagnostic criteria listed in Box 1.[5,12] A vaginal swab positive for *C. albicans* or *C. glabrata* supports the diagnosis but does not confirm it, and a negative swab does not rule it out.

Why do healthy patients develop chronic VVC?

Candida is a dimorphic yeast, a commensal of the genital and gastrointestinal tracts. Many studies have shown it is responsible for VVC and that in about 85 to 95% of cases, *C. albicans* is isolated on culture. In the other 5 to 15% of cases, other *Candida* species are isolated, with the most frequent being *C. glabrata*.[1,10] In certain geographic areas, non-albicans species are isolated at higher rates than 5 to 15% but this is not true of the Australian population.[13] An important practice point is that non-albicans species are azole-resistant, although susceptible to topical boric acid and to oral voriconazole.[14,15] The prevalence of non-albicans strains appears to be increasing.[10]

Most diseases caused by commensal organisms occur as opportunistic infections in patients who are immunosuppressed or have diabetes, so it is of great interest that chronic VVC is an exception. The role of the organism itself has been studied; virulence factors are not relevant, which possibly explains the rarity of drug resistance.[16]

Many studies have attempted to discover an immune deficiency underlying VVC but none have been successful. Why or how a commensal organism that is tolerated by most individuals evolves to cause severe vulvovaginal symptoms in a few otherwise healthy women is unknown. Our understanding of pathogenesis involving organisms of the normal microbiota (the community of organisms making up a tissue microbiome) is in its infancy. As tissue microbiomes become better understood some of the paradoxes of this condition may be better explained.

Symptom severity and signs of inflammation in VVC appear to be unrelated to the severity of infection. Some patients who are heavily colonised by *Candida* remain asymptomatic, while others with low or negative colony counts may display severe symptoms.

Predisposing and trigger factors

Although there is much we do not know about the cause of VVC, there are factors that have been shown to play a part, others that may play a part and some that have been shown not to play a part (summarised in Box 4).[11]

Recent evidence points to two aetiological factors that appear to be the most important in susceptibility to chronic VVC: host immune response and oestrogen. Other factors that are well recognised to predispose to or trigger attacks include antibiotics and sexual activity, although the condition is not sexually transmitted and treating the male partner does not enhance treatment response.[10] After menopause, hormone replacement therapy can trigger VVC but studies have not shown that the OCP has any effect on it. There are reports implicating progesterone-releasing intrauterine devices, and my experience corroborates this.[17]

Host immune response
Cell-mediated and humoral immunity
In the past, *Candida*-specific cell-mediated immunity has been considered to be the most likely host defence mechanism against mucosal *Candida* infection. However, studies using mouse models as well as cross-sectional clinical studies have

3. CAUSES OF CHRONIC VULVOVAGINITIS[11]

Common
- Recurrent or chronic vulvovaginal candidiasis (VVC)
- Recurrent bacterial vaginosis

Uncommon
- Desquamative inflammatory vaginitis
- Intravaginal foreign body (e.g. retained tampon)
- Chronic fixed drug eruption
- Allergy (e.g. contact dermatitis to intravaginal substance)

Rare
- Mucosal lichen planus
- Oestrogen hypersensitivity vulvovaginitis

Very rare
- Crohn's disease
- Immunobullous disease
- Graft versus host disease

4. TRIGGERING FACTORS IN VULVOVAGINAL CANDIDIASIS

Relevant factors
- Endogenous and exogenous oestrogen
- Alteration of normal flora by antibiotics
- Systemic immunosuppression
- Sexual activity
- Uncontrolled diabetes
- Intrauterine device

Nonrelevant factors
- Species of *Candida*
- Virulence factors
- Tissue invasion
- Host receptors
- Humoral immunoglobulin
- Systemic cell-mediated immunity
- Iron deficiency anaemia
- Colonisation of the male partner

Factors of undetermined relevance
- Genetic susceptibility
- High carbohydrate diet
- High-oestrogen oral contraceptive pill
- Tight occlusive clothing and pads
- Pregnancy
- HIV infection

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been shown to be more prevalent in this group than in the general population.[21]

Much of our data come from murine experiments, but in 2004 a breakthrough study used an intravaginal challenge with *C. albicans* in healthy human volunteers.[22] This study demonstrated that, counterintuitively at first, susceptibility to acute symptomatic candidiasis was associated with a brisk inflammatory leucocyte response, while protection from symptoms was associated with lack of inflammation. Patients with a previous history of candidiasis were more susceptible than those without. Vaginal lavage fluid from women with symptomatic infection had the ability to stimulate neutrophil migration in vitro.

This same study demonstrated that inoculation of *Candida* into the vagina was much more likely to result in colonisation in women with a previous history of recurrent attacks of candidiasis than in those without such a history, thus suggesting an individual, possibly genetic susceptibility.[22] Vaginal cells in these patients both lacked anti-*Candida* activity and were highly intolerant to the presence of *Candida*, generating an exaggerated immune response triggered by very low numbers of the organism.

A study that evaluated vaginal epithelial cell anti-*Candida* activity prior to intravaginal challenge showed that cells in women who develop symptoms have significantly lower activity compared with those in women who do not develop symptoms. This suggests an inherent but as yet not elucidated protective mechanism at the level of the vaginal epithelial cell.[23]

T cells can be demonstrated in large numbers in the vagina in patients with candidiasis and appear to migrate in response to local antigenic stimuli or inflammatory chemokines. Their exact role in VVC is unclear.[24]

A study examining immune mediators found elevated levels of prostaglandin as well as *Candida*-specific intravaginal IgE. This study also postulated a hypersensitivity response.[25]

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convincingly ruled out a role for either local or adaptive immunity in VVC. Humoral immunity similarly has not been shown to have a role. No study has been able to demonstrate a difference in total or *Candida*-specific antibodies in sera or vaginal secretions between women with recurrent VVC and control women.[18]

It is now accepted, therefore, that systemic immunity is not relevant and the problem is specific to the vagina. This is supported by the observation that women with recurrent VVC are almost never susceptible to oral candidiasis, and conversely that immunosuppressed women with HIV disease are susceptible to oral but not vaginal candidiasis.[19]

Local immunoregulatory mechanisms
Data suggest that host-specific innate immunoregulatory mechanisms play a role in susceptibility to VVC. The concept that symptoms are the result of an allergic reaction mediated by *Candida*-specific IgE has been explored by several researchers and does appear relevant in a small number of patients.[20] Interestingly, atopy has

It thus appears that VVC is associated with signals following interactions between *Candida* and vaginal epithelial cells that promote a nonprotective inflammatory response, which results in symptoms. Resistance to disease is associated with a lack of these signals. Vaginal cells in patients with VVC have a low tolerance for even small numbers of organisms (theoretically so small in some cases that they are not able to be cultured) and signal an inflammatory response. The threshold above which this signalling takes place varies from patient to patient. It is possible also that, given the numbers of women with significant symptoms despite negative culture, the inflammatory response continues after initiation in the absence of detectable antigen.[18]

These studies raise a paradigm for understanding chronic VVC, suggesting a host-mediated individual genetic susceptibility to a commensal organism that is tolerated by most women.[26] This may explain the paradoxes that have so far confounded investigators, including lack of local or systemic immune deficiency, the fact that chronic VVC is no more common in HIV-infected patients than in healthy patients, the lack of oral involvement and irrelevance of infection of the male partner.

This may also explain why continuous suppression is required in patients with chronic VVC to keep the levels of *Candida* in the vagina below the threshold for inflammation and why some patients need more suppression than others. It is of interest here to compare chronic VVC with autoimmune conditions where the antigenic stimulus is not known. In these conditions, treatment requires nonspecific suppression of the immune system. In chronic VVC we need to suppress only the known antigen.

Oestrogen

The role of oestrogen appears obvious but is largely unexplored. Chronic VVC is usually characterised clinically by oestrogen-related cyclicity. Most patients report that symptoms worsen after ovulation when oestrogen levels are highest, peak in the premenstrual week and rapidly decrease during menstruation. Similarly, clinical appearance varies over the menstrual cycle and is often near to normal during menstruation and for a few days after.

A 2001 study suggested that postmenopausal women could become susceptible to candidiasis as a result of hormone replacement therapy.[13] Among 339 consecutive patients aged 55 years or over presenting to a dermogynaecology clinic, 26% of women using oestrogen had a positive vaginal swab for *C. albicans* as opposed to 4% in the group not using oestrogen.

A more recent study supports these findings. It demonstrated that after menopause, VVC occurs almost exclusively in women using oestrogen (but not progesterone) replacement therapy and that most of these patients were susceptible to it before menopause, thus demonstrating the importance of oestrogen in the aetiology of chronic VVC.[7]

Healthy patients with chronic VVC typically do not have oral or oesophageal involvement, in contrast to immunosuppressed and diabetic individuals who often do. This fact may support the contention that the pathology of VVC is particular to the vaginal microenvironment and that the pathogenesis in healthy people differs from that in those who are immunocompromised. The difference may be in part related to the density or type of oestrogen receptors but also to the nature of the immunological response involved.

Current recommended management of chronic VVC

There is a paucity of grade A evidence for treatment of chronic VVC. A recent systematic review identified only two studies suitable for meta-analysis in the past 10 years.[27] Both these trials examined long-term maintenance therapy with fluconazole 150 mg per week. However, my experience is that weekly regimens often fail in patients with chronic VVC, a point that was not addressed in the review. Long-term treatment regimens have all tended to recommend oral azoles, because long-term use of pessaries is difficult to comply with and often causes irritant skin reactions that complicate the assessment of treatment response. Two recent Australian studies have demonstrated the successful use of a daily oral azole regimen to suppress the disease and for ongoing maintenance therapy to prevent relapse, with a mean follow-up duration of 26.2 months.[8,9]

Principles of treatment

The principles of treating patients with chronic VVC are as follows.[8]

- Commence therapy with an induction course, usually with an oral antifungal medication such as fluconazole or itraconazole taken daily. Continue until the patient is asymptomatic and vulval appearance on examination is essentially normal, other than erythema of the sulcus between the labia minora and majora. The usual dose is fluconazole 50 to 100 mg daily or itraconazole 100 mg daily.
- Where *C. glabrata* is found and the patient fits the diagnostic criteria, boric acid suppositories 600 mg daily are used. If patients are unable to tolerate boric acid then oral voriconazole is an alternative although this drug has potential toxicities not shared by fluconazole or itraconazole.
- After symptom remission is achieved, maintenance therapy should be undertaken. The dose required differs between patients. For most, a twice weekly dose of fluconazole 50 to 100 mg or itraconazole 100 mg is adequate, but some cannot reduce from daily dosing without a relapse of symptoms. Patients are instructed to titrate their dose according to symptoms and to increase to daily dosing when taking antibiotics.

Signs and symptoms usually resolve with these regimens, so much so that the response becomes a diagnostic test in itself. Once symptoms have resolved there is usually an objective improvement, but some degree of persistent erythema in the sulcus between the labia minora and majora is common (Figure 4). Although patients taking these medications almost always have negative cultures when using treatment, relapse is common after the medications are ceased. In another study, 208 patients who had recovered with the induction course were contacted after treatment.[9] All but three patients (one pregnant, one who reached menopause and one who remitted) were still taking oral antifungal treatment at dosages ranging from daily to once or twice a week with a mean follow up of 26.2 months (range five months to 8.5 years). Relapse appears not to be caused by drug resistance as re-treatment is usually effective.

Figure 4. Even when patients are treated and become asymptomatic, they may retain some erythema in the sulcus between the labia minora and majora.

Oral antifungal agents and their impact on quality of life

The antimycotic agents itraconazole and fluconazole are well tolerated with low rates of side effects. Unlike ketoconazole, which was associated with drug-induced hepatitis in 10% of patients and has now been withdrawn in Australia, itraconazole and fluconazole rarely affect the liver and are safe to take orally long term. Neither drug is supported by the PBS for the indication of chronic VVC, but the cost of fluconazole has reduced significantly recently and the cost–benefit ratio is high. The effect of chronic VVC on quality of life is high as measured by the Dermatology Life Quality Index (DLQI), indeed higher than most other inflammatory vulval conditions. In a recent study, the mean DLQI in patients before treatment with oral fluconazole was found to be high with a mean of 15.[8] This fell to a mean of 3.4 after 12 weeks of oral azole treatment. In the long term, patients' symptoms remained well controlled with ongoing oral azoles. These were well tolerated and there were no instances of drug-induced hepatitis. Neither drug is safe in pregnancy and should be ceased; however, fortuitously, patients symptoms often remit when pregnant. In general, antifungal resistance is rare although it has been reported.[28]

Natural therapies

Patients often request 'natural therapies' for treatment of candidiasis, which have been reviewed previously.[29] The role of diet and probiotics is as yet undetermined. In my experience, although many women express reservations about long-term antifungal therapy with fluconazole and itraconazole, fuelled largely by unsubstantiated reports of liver toxicity, they are sufficiently frustrated with other treatment options to embark on it and happy to remain on it once they realise its efficacy.

Antifungal pessaries

In theory, antifungal pessaries containing azoles such as miconazole and clotrimazole, nystatin or boric acid may be used with once-daily dosing. Indeed, where swabs have demonstrated atypical candidiasis, caused most commonly by *C. glabrata*, boric acid suppositories 600 mg daily are indicated as this organism is generally resistant to azoles. The problem with long-term use of pessaries is poor adherence.

Ancillary treatments

Ancillary treatment, including topical corticosteroids and avoidance of soap and irritants (including pads, liners, perfumed sprays and G-string underwear) is helpful, particularly in patients who have a concurrent atopic or psoriatic tendency and may have a concurrent dermatosis.

What to do if treatment fails

If the diagnosis is correct then there is usually a rapid and pleasing response with significant improvement in quality of life score and reduction in observable vulval redness by three months of treatment. If treatment fails then the possibilities are as follows.
- The diagnosis was incorrect, and other possibilities should be considered (Box 3).
- The diagnosis was correct but comorbidities such as pain syndromes, pelvic floor spasm or dermatoses have prevented a complete symptom response.

Patients are usually much improved but still have residual complaints.
- The patient is not absorbing the medication. This may indicate coeliac disease, although not invariably.
- The organism is either resistant to the medication or has an unusually high minimum inhibitory concentration, and a higher dose is required.
- The patient is postmenopausal and taking oestrogen replacement therapy and has not ceased it during the induction course.
- The patient has a progesterone-releasing intrauterine device in situ.
In these situations, specialist referral is suggested.

Practice points for clinicians

At present, the diagnosis of chronic VVC is not defined. I suggest, based on the criteria presented in Box 1, the following guide to diagnosis.
- Patients who have a nonerosive chronic vulvovaginitis that worsens premenstrually and also with antibiotic treatment, who have had a positive culture result for *Candida* at any time while they were symptomatic and who have a history of a positive response to antifungal medication are likely to have chronic VVC.
- These patients are likely to benefit from a trial of oral antifungal medication. My practice is to initiate treatment with a minimum of three months of continuous oral antifungal medication, continued until the patient is completely asymptomatic and objectively appears close to normal (many patients always retain slight erythema in the sulcus between the labia minora and majora).[8,9]
- Fluconazole is significantly cheaper than itraconazole and has less potential for drug interactions. If swabs show *C. glabrata* then boric acid pessaries should be used instead. Most patients

given a choice indicate they would rather take oral medication than use pessaries. *C. glabrata* is sensitive to voriconazole but this drug is potentially more toxic than fluconazole and itraconazole.

- Maintenance therapy is then continued, reducing the dose to the minimum that maintains symptom control. It is normal for patients to require continued maintenance therapy for many years.

There are no data at present on how many patients are able to completely withdraw from therapy without relapse in the long term. A study suggested 50% can do so, but follow up was of short duration.[25] The safety of maintenance therapy appears high despite the requirement for long-term oral antifungal medication using either fluconazole and itraconazole, akin to long-term antiviral therapy for genital herpes. To date no more effective treatment has been identified.

Conclusion

There is still much that we do not know about chronic VVC. Research suggests it is an oestrogen-related hypersensitivity response, which may be genetic, and which appears to best explain the clinical features. As none of the clinical features of chronic VVC are highly specific or sensitive, diagnosis has required the development of a set of diagnostic criteria. Our research group has proposed a definition and diagnostic criteria for chronic VVC.[5] Over the past 10 years there have been only two well-controlled trials to determine the best evidence-based treatment regimen.[27] Our recent research has demonstrated the safety and efficacy of oral azoles in suppressing symptoms both in the short and long term and also demonstrates that this is a chronic condition requiring ongoing maintenance therapy in some cases until menopause.[8,9] Using our criteria, the probable response to a trial of oral antifungal treatment can be predicted, even when a vaginal swab on presentation is not positive for *Candida*. MT

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An elderly woman with recurrent zosteriform eruptions

Commentary by:

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A 73-year-old woman has recurrent zoster-like blistering on her face and persistent pain after having shingles three years ago. Would an antiviral agent and zoster vaccination be appropriate?

Case scenario

Barbara is 73 years of age and has endured ongoing pain and relapses of blistering after a herpes zoster (shingles) outbreak in the ophthalmic branch of the trigeminal nerve (C5) three years ago. At the time she had a protracted stay in the intensive care unit, requiring a ketamine infusion due to the severity of her herpetic neuralgia, before being discharged home on analgesia. Since then she has used pregabalin, narcotics and amitriptyline but finds nothing really helps and so is on minimal medication. The blistering is recurring in the same region each time.

- Would a prophylactic antiviral agent be indicated for this patient?
- Would she benefit from a zoster vaccination?

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Commentary

It is interesting to note that in this 73-year-old woman the relapses are frequent, which is unusual in herpes zoster. The literature reports cases of recurrence occurring usually over a period of 12 to 15 months in immunocompetent individuals, and a few cases of more frequent recurrence in immunocompromised individuals. Very rarely a recurrence for the third time has been reported in immunocompetent individuals.

There is a report of recurrent herpes zoster in a 67-year-old woman with a four-year history of actinic reticuloid treated with oral prednisone over that time period. The patient developed three episodes of a vesicular eruption over a five-month period, which resolved with valaciclovir therapy.[1]

Prednisone is a well-recognised risk factor for herpes zoster, as varicella–zoster virus reactivation is related in part to host cell-mediated immunity.[1] However, despite the increased number of patients taking immunosuppressive medications, there are few reports of increased risk of recurrent herpes zoster in these patients, as is the case with the HIV-infected population too. Although patients with haematological malignancies exhibit higher rates of herpes zoster, increased rates of recurrent herpes zoster are not frequently reported in them either.

A case was reported in 2004 of a 5-year-old boy with two episodes of herpes zoster occurring 15 months apart in separate dermatomes, with both outbreaks confirmed on laboratory testing.[2] Among immunocompetent individuals, there are few other reports of recurrent herpes zoster that has been laboratory confirmed.

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Zosteriform herpes simplex or herpes zoster?

The relapses with blistering in the same region occurring periodically in this 73-year-old woman could be due to varicella–zoster virus if she were severely immunocompromised. An alternative diagnosis is a distinct type of cutaneous herpes called 'zosteriform herpes simplex', a rare presentation of herpes simplex virus infection where lesions appear in a dermatomal distribution similar to herpes zoster, but they are however recurrent. Unless confirmatory laboratory tests are carried out, these lesions may be misdiagnosed as herpes zoster. The herpes simplex virus infections are characterised by a shorter and milder prodrome, followed by skin vesicles that are more uniform, smaller and closely clustered. These infections are also more likely to be recurrent with multidermatomal involvement in immunocompromised individuals.

There are articles dating back to 1900 purporting cases of recurrent zoster, although most of them predated the laboratory testing for varicella–zoster virus, with the virus being first cultured from herpes zoster lesions in 1952.[1] In 1965, a review was published of 192 cases of herpes zoster seen in a 16-year period in Cirencester, England, classifying eight as second attacks and one as a third attack.[3] However, among the immunocompetent patients there are more misdiagnosed cases of recurrent zoster than there are of actual recurrent zoster based on laboratory diagnosis. One report describes three patients initially diagnosed with recurrent herpes zoster, all of which were later confirmed as herpes simplex virus infection following culture of the vesicle fluid.[4]

Viral culture or examination of vesicle contents using nucleic acid tests such as polymerase chain reaction (PCR) or much less frequently by direct immunofluorescent techniques provide definitive diagnosis of the aetiology of a zosteriform eruption. By real-time nested multiplex PCR, a single specimen from a patient can be tested for herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) and varicella–zoster virus, with a faster turnaround time, increased sensitivity and specificity.[5,6] Serological tests are useful in cases where nucleic acid testing, viral culture or direct immunofluorescent techniques are either unavailable or cannot be performed due to lack of appropriate lesions at the time of consultation. Type-specific serological tests are based on the detection of antibodies to herpes simplex virus-specific glycoproteins G1 (in HSV-1) and G2 (in HSV-2) with good specificity and sensitivity. These tests aid in counselling of patient's sexual partners, are useful in the detection of unrecognised infection and assist in epidemiological studies.[6] A retrospective diagnosis of herpes zoster can be made by varicella–zoster virus serology demonstrating a fourfold rise in titre in convalescent specimens.

It is important to employ specific laboratory diagnostic methods especially in immunocompromised patients presenting with atypical manifestations in whom the clinical diagnosis may be missed leading to delayed institution of appropriate antiviral therapy. The aetiological diagnosis for the differentiation of varicella–zoster virus, HSV-1 and HSV-2 infections is hence critical for patient care and infection control.

Antiviral treatment

It is important to make the distinction between herpes simplex virus infection and varicella–zoster virus infection. Although herpes simplex virus and varicella–zoster virus respond to the antiviral medications aciclovir, famciclovir and valaciclovir, the virus susceptibility to these antiviral drugs differ; for example, the concentration of aciclovir that inhibits varicella–zoster virus is more than is needed to inhibit herpes simplex virus.[6] Valaciclovir or famciclovir are used for oral treatment, and aciclovir if intravenous therapy is needed in hospitalised patients. Proper diagnosis reduces the risk of instituting improper treatment, which can lead to complications.[6] There is also emerging evidence that early treatment of herpes zoster with antiviral agents at dosages effective against varicella–zoster virus will reduce the development of postherpetic neuralgia.[6]

Use of aciclovir, famciclovir or valaciclovir usually alleviates acute pain and reduces the risk of long-term pain in patients with herpes zoster; however, it is unclear to what extent these antiviral agents reduce the incidence of prolonged postherpetic neuralgia.[7] By inhibiting the replication of varicella–zoster virus, these drugs attenuate the severity of zoster – specifically, they decrease the duration of viral shedding, hasten rash healing and reduce the severity and duration of acute pain. Elderly patients with herpes zoster should be treated with antiviral agents if they have presented less than 72 hours from rash onset as they will still derive benefit.

Vaccination of people with a history of herpes zoster

It is recommended that adults who are aged 60 years and older and not immunocompromised should receive a single dose of the zoster vaccine.[8]

People over 60 years of age with a clinical history of herpes zoster should also receive the vaccine.[8] This recommendation is based on the difficulty in predicting when a repeat episode may occur, and that the patient may have inaccurately recalled previous shingles or the illness may have been misdiagnosed. The zoster vaccine is, however, not indicated for use during an acute herpes zoster episode or for the treatment of patients with postherpetic neuralgia.

Zoster vaccine has not been shown to prevent recurrent episodes of herpes zoster and there are few studies to inform this. A US retrospective cohort study did not show any effect of the vaccine on recurrent zoster in adults with recent acute zoster.[9] Leaving a gap of at least 12 months between recent zoster and vaccination is recommended, although there is little evidence to inform this decision. The vaccine has a similar safety profile

in immunocompetent adults with recent herpes zoster as in those with no history of herpes zoster.[8]

Conclusion

Many recurrent zosteriform eruptions are caused by herpes simplex virus rather than being due to varicella–zoster virus (i.e. recurrent herpes zoster), as illustrated by the presented case of an elderly woman with recurrent zoster-like blistering on her face. The cause of recurrent zosteriform eruptions should be confirmed microbiologically, and if true recurrent varicella–zoster virus infection is documented then possible underlying immunosuppression should be investigated. Depending on the frequency and severity of the recurrences, long-term prophylactic antiviral therapy should be considered.   MT

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