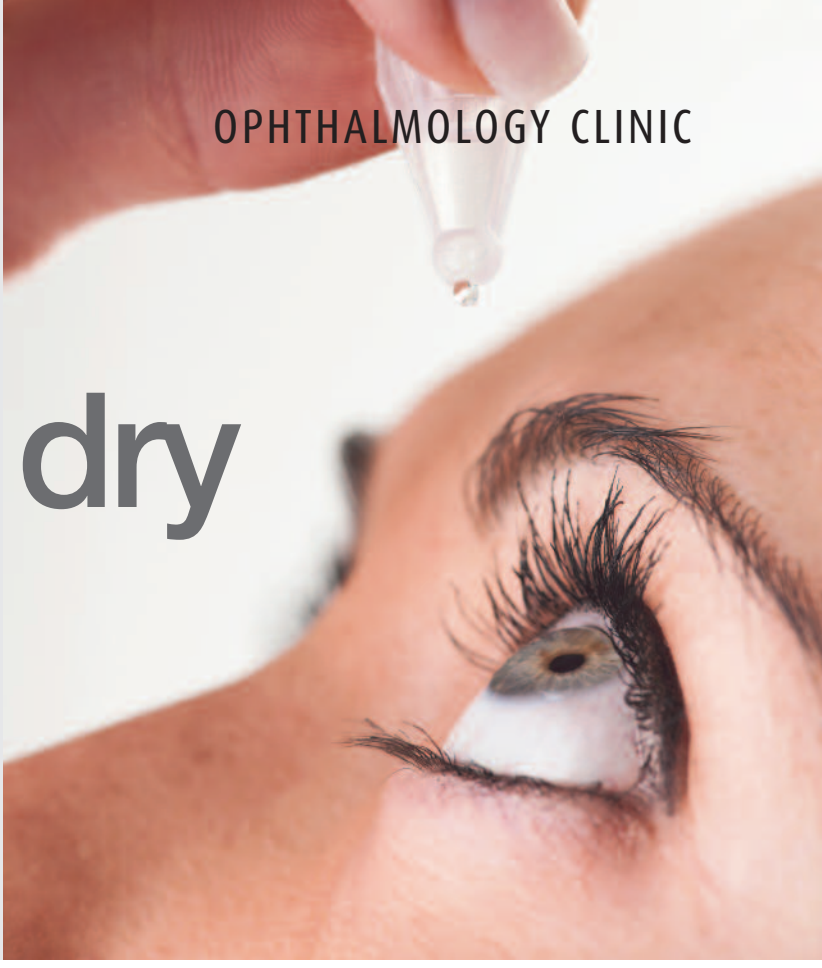

High and dry
An update on dry eye syndrome

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Artificial tears are the usual first-line therapy in dry eye syndrome. Topical cyclosporin is a treatment for more severe disease and confidence in its use has grown, although it is not a TGA approved medication. Other interventions for this multifactorial condition are also discussed.

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Dry eye syndrome (DES) is a prevalent multifactorial condition, the significance of which is frequently underestimated. Dry eye has been defined as: 'a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.'[1]

The symptoms of discomfort and visual disturbance, the increased osmolarity of the tear film and the inflammation of the ocular surface are key to understanding and managing this condition. Tear function includes mechanical, optical, antimicrobial and nutritional roles, and tear deficiency or dysfunction has a major impact on quality of vision and life. Historically DES has been treated as a trivial condition and the limited teaching of ophthalmology provided in undergraduate medical curricula does not help this situation.

There is an ever-increasing amount of information provided by Dr Google, of which many patients are aware. It is therefore important to assess the various interventions for DES and whether claims of efficacy are evidence-based. Furthermore, there are several paradoxes that may make explanation of this condition to patients challenging (see the box on page 54). These include the facts that symptoms and signs often do not correlate in this condition and that wateriness (or epiphora) is common (the explanation for the latter being that mucus deficiency retards adhesion of the tear film to the ocular surface).

A review of DES by this author was published in *Medicine Today* in 2008.[2] Since then, confidence in using cyclosporin has

PARADOXES CONCERNING DRY EYE SYNDROME

- Patients with dry eye often complain that their eyes are 'wet'.
- Some patients are relatively asymptomatic until another insult to their ocular surface (such as cataract surgery or an episode of infectious conjunctivitis) induces an exacerbation.
- A frequent complaint is difficulty reading, particularly sustained reading, even though the patient can see fine print on a reading chart.
- Eyes do not always look inflamed yet inflammation is a hallmark of this disease.
- Signs do not always correlate with symptoms.
- Artificial tears do not always work, no matter how frequently they are applied – frequent use of preservative-containing lubricants can exacerbate symptoms and signs.
- Lacrimal punctum plugs can sometimes exacerbate symptoms.
- In quality of life assessments, moderate to severe dry eye is equivalent to having angina.
- 'Presenteeism' – presence at work but suboptimal functioning – is the main cause of financial loss due to dry eyes.
- Newer treatments may be expensive. Thus the cost to the community and individuals can be substantial for what is considered by many to be a trivial disease.
- Although patients often present with dry eye, drying of other mucosal surfaces can also severely impact on quality of life. Team management is essential.
- Topical cyclosporin is more efficacious than systemic cyclosporin. Early in the treatment, stinging after eye drop application can discourage continued use. Awareness of this is essential as some months of topical cyclosporin therapy may be required before beneficial effects are evident.
- Prevalence of dry eye may be underestimated as many patients use over-the-counter eye lubricants or astringents.

grown with its longer safety record. Cyclosporin is now being used earlier to reduce organ damage, and patients are helped with its side effect of stinging by the use of preservative-free low-dose dexamethasone when starting the therapy. Also, the use of tear film osmolarity measurement is more widespread now and a new physical therapy for blepharitis is being evaluated. However, there is still a lack of evidence of efficacy in DES for most oral supplements for eye health and for acupuncture.

SIGNIFICANCE OF DES

DES remains a leading reason for visits to eye care professionals.[3] Patients complain of poor quality of vision, eye redness and sandy, gritty, burning, stinging, itching and dryness sensations, contact lens intolerance, mucus discharge, photophobia, eye fatigue and pain.

On the one hand, DES afflicts the elderly population and those with systemic illness (either directly as in Sjögren's syndrome or indirectly as a side effect of medication). On the other hand, it has become increasingly prevalent in younger patients as a consequence of computer or smart device use (often while in adverse air-conditioned environments). It is also ultimately a concern following refractive surgical procedures that disturb corneal innervation.

DES is a significant public health issue and is estimated to affect 14 to 33% of the population worldwide.[4] Australian data from the Blue Mountains Eye Study show that dry eye symptoms are reported in 15 to 56% of a population over the age of 50 years. Prevalence increases with increasing age, and DES is common in peri- and postmenopausal women.[2,5,6] The high prevalence in Australia, with its ageing population and dry climate, is not unexpected. Low humidity (as encountered in air-conditioned environments such as commercial premises and aircraft cabins) can increase tear evaporation rates substantially, with adverse effects on ocular comfort, tear stability and tear production.[7]

Effect on quality of life and work productivity

DES can have a major impact on the quality of life of patients, and psychological stress related to this disease is significant.[8-13] One model of the impact of DES likened the effect of moderate dry eye on quality of life to that of moderate to severe angina, and that of severe dry eye to severe angina or hospital dialysis.[8,9] Quality of life scores were correlated with patient anxiety and depression levels, even in patients with mildly reduced tear production.[11-13]

Work productivity and daily activity assessment studies have reported a significantly greater reduction in productivity in patients with moderate DES (18% reduction) or severe DES (35% reduction) than in patients with mild DES (11% reduction), with similar reductions in daily activity.[14] Loss of work productivity through absenteeism in patients with DES has been estimated to be two to five days per year.[15] A greater issue, however, may be presenteeism (productivity loss when employees come to work but are not fully productive). It has also been reported that patients with DES experienced symptoms at work on between 191 and 208 days annually.[15]

A recent study has confirmed work performance loss in office workers with symptoms of dry eye, which can lead to a

substantial loss in work productivity.[16] Fortunately, medical costs for the treatment of DES were shown to outweigh productivity losses. The importance of treating DES was highlighted in this study as not only were there improvements in quality of life for individuals, but also increased productivity would be expected. Educational activities important to improve awareness of DES were suggested.

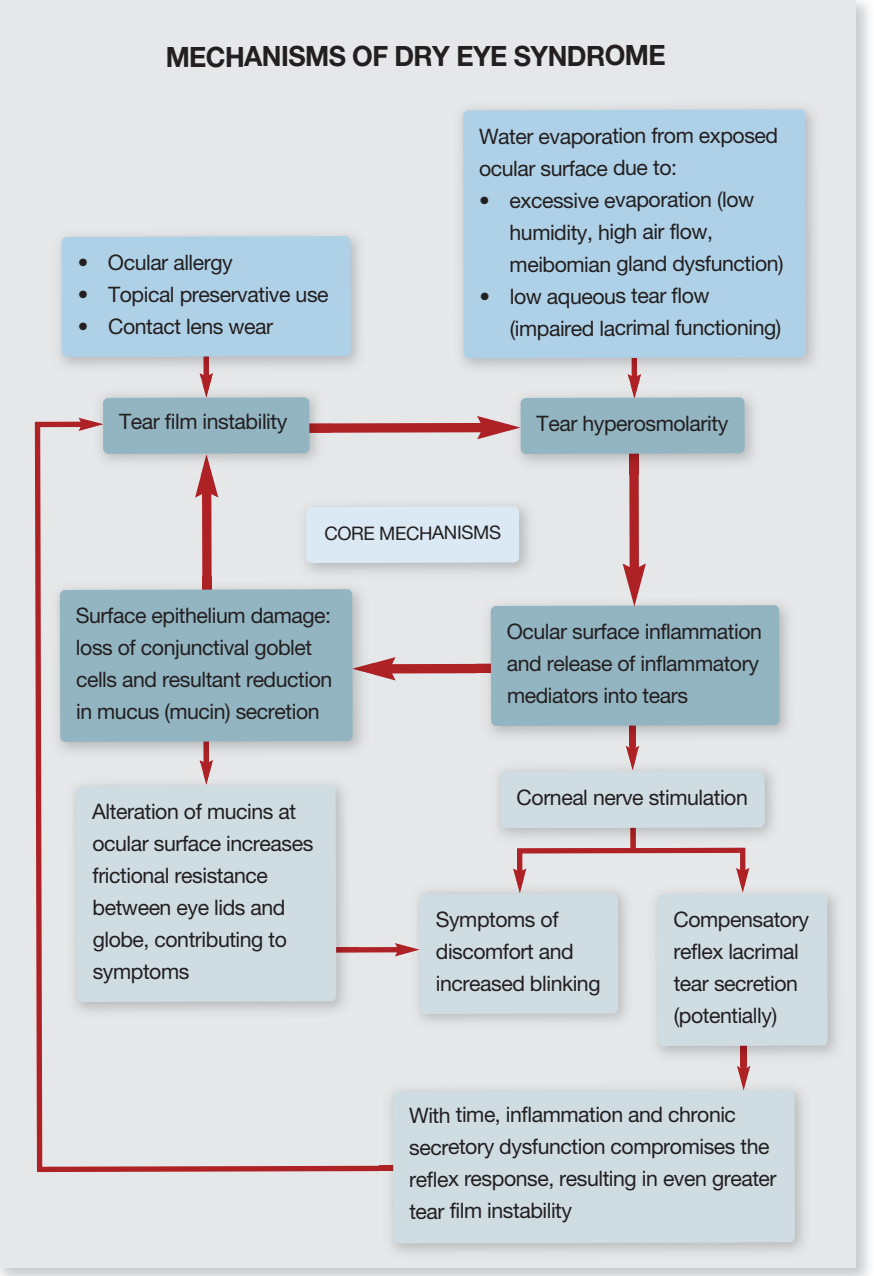
A recent estimate of the direct and indirect annual costs of managing DES in the USA has shown that DES is a substantial burden not just to individuals but also to society.[17] Not surprisingly, there has been an increase in dry eye medication use and expenditures in recent years – driven in part by increased disease prevalence but also by the introduction of topical cyclosporin as a treatment – see below.[18]

PATHOPHYSIOLOGY

The paradigm shift in the modern understanding of DES is the recognition that chronic inflammation plays a major part in this condition, and may represent the central role in its pathogenesis.[19] This has driven the therapeutic approach in patients with moderate or severe DES, which is now based on the long-term use of safe anti-inflammatory agents.

The translation of research on the treatment of keratitis in dogs with cyclosporin eye drops to the use of topical cyclosporin in the treatment of human DES (with the attendant advantage of minimal risk of systemic side effects) is perhaps the biggest advance in the management of DES in modern times.[20,21]

The core mechanisms of dry eye are driven by tear hyperosmolarity and tear film instability (see the flowchart on this page).[1] Triggering factors initiate a vicious cycle of inflammation that afflicts the ocular surface and lacrimal gland in patients with DES. Associated antigen presentation and cytokine secretion by epithelial cells stimulates secretion by T-cells of proinflammatory cytokines, further increasing the inflammatory response. Tears containing inflammatory mediators fuel inflammation, with associated inflammatory cell infiltration, epithelial activation and increased production of cytokines and other inflammatory mediators, as well as increased matrix metalloproteinase activation.



ASSOCIATIONS

The main causes of DES and the key associated eye conditions/procedures and exacerbating factors are summarised in the box on page 56.

Associations of DES with depression, post-traumatic stress disorder, obstructive sleep apnoea, benign prostatic hyper - trophy, migraine, alcohol intake and

DRY EYE SYNDROME: MAIN CAUSES, ASSOCIATED EYE CONDITIONS/PROCEDURES AND EXACERBATING FACTORS

Main causes

Age and disease

- Ageing
- Sjögren's syndrome
- Other systemic diseases
  - autoimmune disease: rheumatoid arthritis, systemic lupus erythematosus, autoimmune liver disease
  - other inflammatory disease: lymphoma, AIDS, sarcoidosis, graft-versus-host disease
  - diabetes mellitus
  - hypertension
  - thyroid disease
  - Parkinson's disease
  - depression
  - post-traumatic stress disorder
  - obstructive sleep apnoea
  - benign prostatic hypertrophy
  - migraine

Systemic drug side effects*

- Antihypertensives – beta-blockers, diuretics, ACE inhibitors (captopril), angiotensin II receptor antagonists (losartan)
- Antidepressants – tricyclic monoamine oxidase inhibitors
- Antihistamines – diphenhydramine, promethazine, cetirizine loratadine
- Anticholinergics – oxybutynin, ipratropium
- Antiarrhythmics – amiodarone, disopyramide
- Antiosteoporotic drugs – bisphosphonates (alendronate, etidronate
- Anticancer drugs – aromatase inhibitors, methotrexate
- Antiwrinkle drugs – botulinum toxin
- Antiacne drugs – isotretinoin
- Antiulcer drugs – cimetidine, ranitidine
- Anti-Parkinson's drugs – benzhexol, levodopa
- Antithyroid drugs – carbimazole, propylthiouracil
- Other drugs – marijuana
- Hormonal treatments (hormone replacement therapy, antiandrogens)

Other

- Alcohol
- Cosmetics (possibly)
- Smoking
- Topical ocular drugs and preservatives
- Poor whole body hydration

* A more exhaustive list is provided in: Wong J, Lan W, Ong LM, et al. Non-hormonal systemic medications and dry eye. *Ocul Surf* 2011; 9: 212-26.[28]

Associated eye conditions/procedures

- Blepharitis
- Glaucoma (due to its medications)
- Pterygium
- Refractive surgery
- Post cataract surgery
- Post blepharoplasty
- Contact lens wear
- Conjunctivochalasis (Figure 1)
- Concretions (Figure 2)
- Allergy
- Eyelid malposition – ectropion, entropion, trichiasis
- Meibomian gland disease

Exacerbating environmental factors

- Pollution
- Allergens
- Computer use
- High altitude
- Hot or dry atmosphere
- Aeroplane transport
- Sick buildings/air conditioning

suboptimal whole body hydration have been recognised relatively recently.[22-27] Many of these associations are 'proinflammatory', consistent with exacerbating ocular surface inflammation.

It is important to take a drug history in a patient presenting with dry eye as the condition is often associated with medications that are now commonly used in an ageing population.[28] Although changing these medications may be challenging and ultimately may not be possible, communication and occasionally negotiation with sometimes several specialists has the potential to greatly improve the quality of life of patients.

The role of aromatase inhibitors has recently been described.[29] It should be appreciated that there can be a time lag between the introduction of new therapies and when their effect on tear secretion is recognised. Botulinum toxin, whose use to improve ocular cosmesis is widespread, can contribute to DES symptomatology, as can the use of eye cosmetics.[30,31]

A recent study has identified a significantly higher prevalence of medical comorbidities in patients with DES.[27] These comorbidities include ischaemic heart disease, hyperlipidaemia, cardiac arrhythmias, peripheral vascular disorders, stroke, migraine, myasthenia gravis, systemic lupus erythematosus, asthma, pulmonary circulation disorders, diabetes with complications, hypothyroidism, liver disease, hepatitis B, peptic ulcers, deficiency anaemias, depression, psychosis and solid tumours without metastasis.

DES not infrequently develops following cataract or refractive surgery and may be responsible for dissatisfaction with the results of these surgeries, even though visual acuity may be improved.[32-34] It appears that although the prevalence of DES in people undergoing cataract surgery is a high, more than half of these patients are asymptomatic. It is important for surgeons to be vigilant in diagnosing and treating patients with dry eye preoperatively because patients with inadequately

treated DES may notice fluctuations in their vision postoperatively, as well as the usual symptoms of DES. Several factors may play a role, including pre operative eye disease, treatment (typically topical antibiotics and NSAIDs, often preservative-containing), intraoperative ocular surface damage and postoperative topical treatment.

DES is not uncommon for several months after refractive surgery such as laser-assisted in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK), and is thought to be largely due to interference with corneal innervation. With newer surgical techniques and aggressive preoperative treatment of pre-existing DES, postoperative DES appears to be less prevalent.

DES is associated with several ocular conditions (see the box on page 56 and Figures 1 and 2). In particular, meibomian gland disease (associated with blepharitis) is often seen in DES – in one study, about half the subjects with DES had this condition.[35] Treating the blepharitis, often quite simply with regular eyelid hygiene, can dramatically reduce DES symptoms. DES is also commonly seen in patients being treated for glaucoma, and modification of glaucoma therapy may be required (away from medical treatment, as the medications almost always contain preservatives).[36] Patients with pterygium may also have DES; surgery can sometimes be avoided by treating their dry eye state.[37]

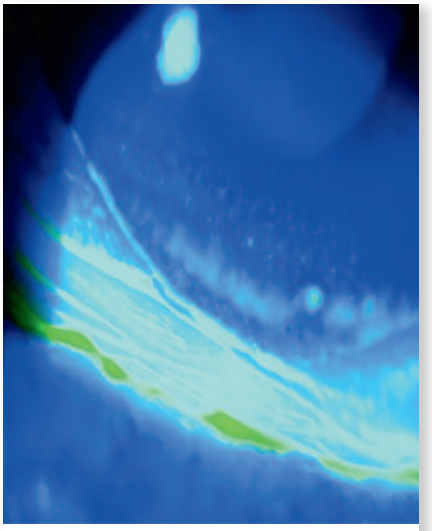


Figure 1. Conjunctivochalasis. Redundant folds of conjunctiva, typically seen along the edge of the lower eyelid and often contributing to symptoms of ocular discomfort. If there is no response to ocular lubricants, surgical repair can be effective. In this case, conjunctivochalasis is associated with punctate staining of the adjacent cornea.

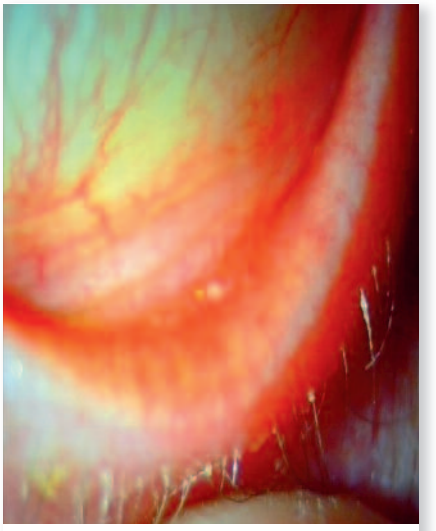


Figure 2. Concretions. These are often seen in patients with DES and blepharitis and contribute to ocular discomfort. They can extrude spontaneously and become symptomatic when they 'break through' the conjunctival epithelium. The concretions that cause a problem in relation to the ocular surface are stained with fluorescein. They can easily be removed under topical anaesthesia. Note the dilated meibomian glands near the eyelid margin. These are a feature of concurrent posterior blepharitis.

DIAGNOSIS

The assessment of the patient's history, signs and symptoms is often combined with several tests. Unfortunately DES cannot be diagnosed by a single test and, as a consequence, various investigations (including tear film break-up time, ocular surface staining with dyes such as fluorescein or lissamine green, and Schirmer's test) have traditionally been used.

Tear film hyperosmolarity is recognised as an important component of DES pathogenesis and newer methods of measuring tear film osmolarity have been developed (the Tearlab Osmolarity System Device is available commercially). There are still issues of access, cost and specificity with tear osmolarity assessment, and it is not yet in regular clinical use in Australia.

Matrix metalloproteinase-9 (MMP-9) detection is another test in development, and is showing promise in identifying patients with inflammatory dry eye and ocular surface disease (MMP-9 is a cyto - kine produced by epithelial cells experiencing inflammation).[38] This test uses a rapid, in-office immunoassay based on a 'dipstick' system, appears to be sensitive and specific, and may identify those patients who should receive anti-inflammatory therapy (and perhaps also predict response to this therapy).

In practical terms, tear break-up time (TBUT) is often useful in the assessment of DES. In this test, fluorescein dye, usually in strip form, is added to the ocular surface and the patient asked to blink a few times. The patient is then told to avoid blinking and the tear film is observed with the slit lamp (using a cobalt blue light) until small dry spots are seen (Figure 3). The longer it takes for dry spots to appear, the more stable the tear film: a TBUT of more than 10 seconds is usually considered normal; 5 to 10 seconds, marginal; and less than 5 seconds, low (and often associated with symptoms of dry eye).

Given the likelihood that the number of patients with DES presenting in general practice will increase, the development of quick, reliable, cost-effective and minimally invasive diagnostic tests should have priority.

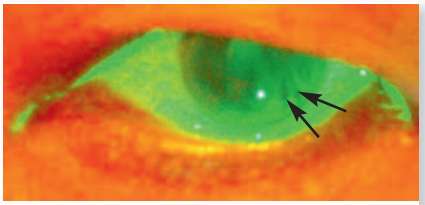


Figure 3. Tear break-up time (TBUT). Discontinuities in the tear film appear as dark spots on the cornea. A rapid TBUT is almost always seen in patients with DES. The arrows indicate areas in the tear film where the cornea is not staining, reflecting drying of the ocular surface.

Another approach to diagnosis is the Ocular Surface Disease Index (OSDI) developed by Allergan Inc (and available online at http://dryeyezone.com/encyclopedia/documents/OSDI.pdf). This is a validated questionnaire that provides a reliable, rapid assessment of key symptoms associated with DES, their severity and impact on visual function and effect of environmental factors.[39,40] GPs can administer this test and have a reasonable chance of diagnosing dry eye and its severity using this questionnaire alone. Also, it has become part of the patient review process when topical cyclosporin is prescribed via the TGA's Special Access Scheme.

The OSDI includes 12 questions in three groups: the first group of questions relates to DES ocular symptoms, the second to ocular symptoms while watching television or reading a book, and the third to ocular symptoms induced by environmental factors. A scale of 0 to 100 is used, with higher scores representing greater disability. The overall OSDI score defines the ocular surface as normal (0 to 12 points) or as having mild (13 to 22 points), moderate (23 to 32 points) or severe (33 to 100 points) disease.[41] The cut-off OSDI score for the diagnosis of DES is 35.[39]

It has been shown that there is a significant inverse correlation between the OSDI and TBUT scores and that the two assessments can be performed easily and used to support the diagnosis of DES.[39] If a simplified TBUT assessment were available for GPs, they could become more involved in the diagnosis and management of DES.

In patients with moderate to severe DES, a system review can suggest that physician review may be necessary to assess the possible association of the DES with significant systemic illness. Although several serological tests, mostly to assess autoimmunity, are often performed, a useful test in the diagnosis of Sjögren's syndrome is minor salivary gland biopsy, with assessment using established histopathological criteria of focal lymphocytic salivary gland infiltration.[42] This can now be performed under local anaesthesia as an office procedure, using a minimally invasive technique (Figure 4). This technique may become increasingly important because managing more severe, unresponsive forms of DES can involve systemic treatment with agents such as hydroxychloroquine or biologic agents such as rituximab.[43,44] Although there is an increased risk of side effects from such treatment, there is the potential benefit of improvement of function of other exocrine glands as well as improvement of other systemic manifestations.

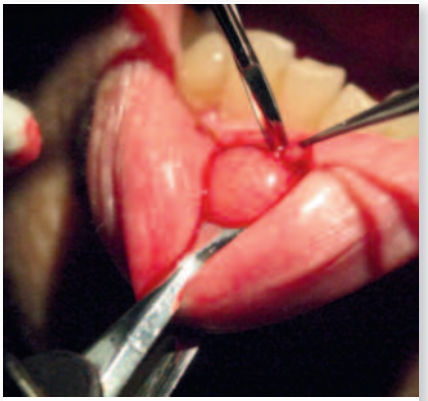


Figure 4. Minor salivary gland biopsy carried out under local anaesthesia as an office procedure. The lip is stabilised with a chalazion clamp and glands are excised via small incisions using ophthalmic microinstrumentation. Sutures are not required.

MANAGEMENT

DES is a chronic disease and symptoms may fluctuate but often worsen over time. Key to managing patients with DES are counselling, explaining the apparent paradoxes, managing disease exacerbations and involving the whole medical team when appropriate.[45,46] Advice should be given on water intake, smoking and alcohol cessation or reduction, and environmental management (such as using a humidifier, decreasing room temperatures, using hypoallergenic products – particularly cosmetics – and avoiding hair dryers and windy conditions).[45] Other recommendations include managing blepharitis with eyelid hygiene, reducing reliance on topical and preserved glaucoma medications and, in more advanced cases, the use of custom wrap-around spectacles that increase local humidity (Figure 5).

Pharmacological therapies include the use of artificial tears (especially those that are preservative-free), anti-inflammatory agents, dietary intervention and systemic therapies.

Surgical interventions include lacrimal punctum plug insertion or punctal cautery (which is more permanent), treatment of associated conditions (such as conjunctivochalasis) and tarsorrhaphy (to reduce the size of the palpebral aperture and its associated tear film evaporation). Temporary (dissolvable) lacrimal punctum plugs can be used initially to judge response, and more permanent plugs (made of long-lasting materials such as silicone) placed after this initial trial (Figure 6). Salivary gland transplantation to the ocular surface has been used in the past but recently a simplified technique using labial mucous membrane and minor salivary gland transplantation has been shown to be effective in severe forms of DES.[47]

A new physical therapy for blepharitis, the LipiFlow system, is being evaluated.[48]

This system provides controlled heat to the inner aspects of the eyelids, and mild intermittent pressure across and along most of the horizontal extent of the eyelids, with the aim of releasing meibomian secretions. Issues of cost and access remain.

Guidelines

Several guidelines providing treatment recommendations for DES have been published. Widely cited is that of Behrens and colleagues – the Delphi Panel Report (Table).[49] In this study, disease severity was considered the most important factor for treatment decision-making, and was categorised into four levels based on the frequency of tear substitute use, ocular discomfort symptoms, visual disturbance and clinical signs in the lids, tear film, conjunctiva and cornea.

The American Academy of Ophthalmology (AAO) has developed a Preferred Practice Pattern (PPP) guideline for DES.[50] These guidelines recommend anti-inflammatory agents (topical cyclosporin and topical corticosteroids) and systemic omega-3 fatty acid supplements for moderate and severe DES. Topical cyclosporin and corticosteroids are often used concurrently, usually at the start of treatment. The topical corticosteroids are generally discontinued after a short period (two to three months) because of the risk of side effects (glaucoma, cataract, infection). However, the use of low-dose, preservative-free dexamethasone (0.01%; obtained from compounding pharmacies) is safe for medium-term use.[51] Lacrimal punctum plugs are recommended in the next stage (see Table), after the initiation of topical anti-inflammatory therapy, with the aim of reducing inflammatory mediators prior to slowing tear outflow.

The effects of cyclosporin and punctual occlusion appear to be additive.[52] Early treatment with cyclosporin is now advocated as there has been a realisation that this may reduce the risk of disease progression (as is the case for other chronic inflammatory conditions).[53-55]

Figure 5. Close-fitting wrap-around spectacles, used to decrease 'cross-wind' and to increase local humidity. Although effective in managing DES, their cosmesis is unacceptable for some people.

Artificial tears and gels

Artificial tears are the usual first-line therapy for DES, and are often adequate, especially in mild forms of the disease. They aim to moisturise and lubricate the eye and the different preparations contain similar ingredients (lubricants, water, electrolytes, buffers and a preservative). The proliferation of such products confirms that the ideal preparation has yet to be developed. In practice, the product that the patient feels works best after trialling a 'sample bag' of different DES products is generally that which continues to be used. As DES progresses, patients complain of the short duration of relief afforded by artificial tear preparations and their increased frequency of use, and also continual worsening of the DES.[56] A significant advance is the widespread availability of preservative-free lubricants, the use of which eliminates the toxic effects of preservatives.

An ongoing problem is that older patients with arthritic hands or arms can find it difficult to instil eye drops. We have recently described a technique by which eye drops can be applied using clean fingertips (Figure 7).[57] The use of gels can also address this problem (and can be helpful with nocturnal symptoms), but the vehicle used often results in further blurring of vision and for this

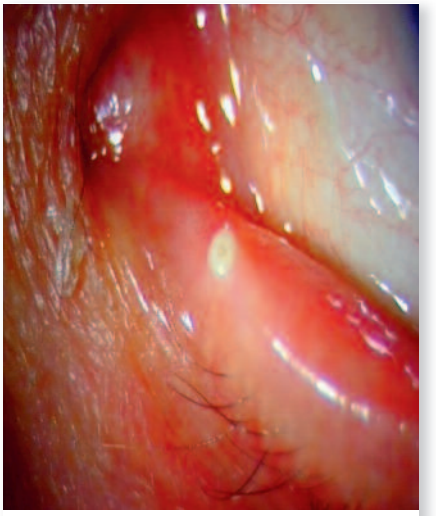


Figure 6. Lacrimal punctum plug placed in the left inferior punctum.

reason gels are often discontinued. Various spray formulations, some containing a lipid solution, have been tried but are not in regular use. Preservative-free nasal sprays are available and may be useful in this setting.

Perhaps one of the best topical treatments for DES consists of eye drops prepared from autologous serum (autologous serum eyedrops; ASEs), which more closely approximate the composition of natural tears.[58] The efficacy of ASEs in the treatment of DES has been demonstrated in a prospective, randomised, case-control study.[59] Interestingly, serum products were used for dry eye in Australia as early as 1949.[60] There are patients in whom this is the only form of treatment that is efficacious, yet access to it remains restricted.

Corticosteroids

Corticosteroids have a restricted role in the management of DES. Fluorometholone eye drops are useful in managing exacerbations but contain preservatives and can be associated with side effects.

Low-dose (0.01%) preservative-free dexamethasone eye drops have a good safety profile and are useful for flare-ups.[51]

TABLE. CLASSIFICATION AND TREATMENT OF DES[45] *

DES severity level	Signs and symptoms	Treatment
1	Mild to moderate symptoms and no signs Mild to moderate conjunctival signs	Patient counselling, preserved tears, environmental management, allergy eye drops, water intake, hypoallergenic products If no improvement, add level 2
2	Moderate to severe symptoms Tear film signs Mild corneal punctate staining Conjunctival staining Visual signs	Unpreserved tears, gels, ointments, topical cyclosporin A, secretagogues, topical corticosteroids, nutritional support (flaxseed oil) If no improvement, add level 3
3	Severe symptoms Marked corneal punctate staining Central corneal staining Filamentary keratitis	Tetracycline, punctal plugs If no improvement, add level 4
4	Severe symptoms Severe corneal staining, erosions Conjunctival scarring	Systemic anti-inflammatory therapy, oral cyclosporin, moisture goggles, acetylcysteine, punctal cautery
At least one sign and one symptom of each category should be present to qualify for corresponding level assignment.		

* Adapted from Behrens, et al. *Cornea* 2006; 25: 900-907.[49]

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These eye drops are also used in the introduction of topical cyclosporin: in the early phases of cyclosporin treatment, stinging is common and dexamethasone helps to alleviate this symptom, thereby encouraging the patient to persist with this treatment. Drugs used overseas, such as loteprednol etabonate, are not available in Australia.

Topical cyclosporin

Topical cyclosporin 0.05% is approved for the treatment of DES in the USA but not in Australia.[45] It can, however, be obtained in Australia either as the imported product (Restasis) via the Special Access Scheme or as products prepared by compounding pharmacies.

Topical cyclosporin 0.05% is the first agent that safely treats a key component of the underlying pathophysiology of DES, rather than providing palliation. It is applied twice daily and generally well tolerated. Stinging and burning are the most commonly reported side effects and occur usually in the first month of treatment. It is best to warn patients of this possibility and to add low-dose corticosteroid eye drops in this phase. Patients who research this drug require reassurance that systemic side effects have not been reported (serum concentrations are very low, well below detectable levels).

Topical cyclosporin applied to the eye suppresses T-cell activation on the ocular surface and in the lacrimal gland. This suppresses production of the inflammatory cytokines that result in increased recruitment of T-cells, increased cytokine production and tissue damage. Topical cyclosporin 0.05% has been extensively investigated and in one prospective study of patients with DES unresponsive to artificial tears, 74% of patients with mild DES, 72% of patients with moderate DES and 66.7% of patients with severe DES (72% overall) showed improvement with topical cyclosporin treatment for three to 16 months.[53] The treatment confers considerable patient value and is a cost-effective therapy for moderate to severe DES that is unresponsive to conventional therapy.[61]

A recent study examined reintroducing topical cyclosporin in patients with DES after a prior treatment failure and found that 80% of patients achieved clinical benefit with a second trial of the medication.[46] The previous failure was due to burning/stinging in 60% of the patients, and about 30% of the patients received topical corticosteroids at initiation of the second trial. It was thought that direct patient education via the physician and staff was key and that patient education may overcome adherence issues, particularly with respect to the need for long-term treatment.

Oral medications

Oral tetracycline (often doxycycline) is used in the treatment of blepharitis (especially in patients with rosacea) and is thought to have anti-inflammatory actions via inhibition of matrix metalloproteinases

and/or inflammatory cytokines in addition to antibacterial effects. Doxycycline is effective in low doses, as little as 25 to 50 mg/day, and is better tolerated when taken with food; patients should be warned about photosensitivity, although uncommon, associated with its use. It should not be taken on retiring at night (because of the possibility of drug-induced oesophagitis). Topical azithromycin is also effective in the treatment of blepharitis in patients with DES but is not available in Australia.

Cholinergic agents increase ocular secretions in patients with DES. However, oral pilocarpine or cevimeline (not available in Australia) often produce cholinergic side effects (e.g. nausea, diarrhoea, increased sweating and headache) and their use is usually limited to more severe DES.

As indicated previously, systemic agents such as hydroxychloroquine and rituximab have roles in the treatment of more severe forms of DES.

The discomfort associated with dry eye may be part of a chronic pain syndrome, and referral of patients to established pain clinics can be useful.[62] Interestingly, a recent study has shown medium-term efficacy of acupuncture in patients with moderate to severe dry eye.[63]

Systemic dehydroepiandrosterone (DHEA) has been trialled in patients with Sjögren's syndrome and androgen cream preparations applied to the eyelids of patients with blepharitis/dry eye, but the results have been disappointing.[64] This may be due to defective intracrine tissue-specific conversion to active sex steroids, described in Sjögren's syndrome.[65]

Nutritional supplements

There is evidence that dietary supplementation with omega-3 fatty acids, antioxidants and vitamins is beneficial for patients with DES. An early indication of benefit was suggested in an Australian report in 1949 of patients with dry eye who were treated with Campolon, a preparation derived from the fresh liver of Antarctic whales and apparently rich in omega-3 fatty acids and probably vitamins A and B.[60] It has also been shown that a multivitamin preparation (comprising vitamins A, B_1, B_2, B_6 and E) and trace elements (calcium, iron and manganese) was superior to vitamin C in improving tear quality, although both treatments worked.[66]

A recent review identified eight relevant studies, including six randomised controlled trials that provided preliminary confirmation of a relation between essential fatty acid supplementation and improvement in DES.[67] However, strong conclusions could not be made because of limitations in the research reported, and well-conducted prospective studies were recommended. On balance it would seem that omega-3 fatty acid supplementation and Mediterranean-style diets are likely to be beneficial in DES via postulated anti-inflammatory effects.[68] Further work is required to standardise indications for the use of nutritional supplements in the treatment of DES, and their composition and dosing.[69]

There is evidence that certain foods may exacerbate rosacea (and perhaps, by association, blepharitis). Typically, red wine, chocolate and cheese may be trigger factors.[70] A list of food, beverage and other factors triggering rosacea flare-ups is provided on the National Rosacea Society (USA) website (http://www.rosacea.org/patients/materials/triggers.php).

CONCLUSION

The prevalence of DES in people of all ages is likely to increase in the coming years. DES is a multifactorial disease and often requires a multipronged management approach. A patient with DES in a more severe form becomes a meeting ground for several medical specialties, and this will require co-ordination.

Improved diagnostic tests that are both sensitive and rapid are needed as inadequate recognition and then treatment has significant consequences, including depression, reduced quality of life, ocular discomfort, reduced vision and reduced productivity. Informed counselling and patient education are important, and a supportive approach is required for this chronic illness. Improvements in disease grading and treatment guidelines have helped management. The recognition of the role of ocular surface inflammation in the pathophysiology of DES has facilitated the introduction of safe, long-term anti-inflammatory strategies that have revolutionised the treatment of moderate to severe forms of this disease. MT

Figure 7. Digital eye drop instillation. A drop of artificial tear, placed on a clean fingertip, can be applied to the medial fornix, as much of the drop enters the ocular surface. This technique is useful for patients with arthritic limbs and restricted movement.

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High and dry: an update on dry eye syndrome

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