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Assessment and Management of Dry Eye Disease and Meibomian Gland Dysfunction: Providing a Singapore Framework

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Abstract: The purpose of this article is to provide a framework for general ophthalmologists in Singapore to manage dry eye. This framework considers the evidence in the literature as well as recommendations from expert panels such as the Tear Film & Ocular Surface Society Dry Eye Workshop II and the Asia Cornea Society Workgroup.

This article covers the assessment of patient medical history and ask triage questions to identify local and systemic causes of dry eye disease (DED), excluding other possible causes, as well as the risk factors for DED and ocular surface inflammation. Evaluation of clinical signs to establish the diagnosis of DED and differentiation from other causes of irritable, red eyes are described. Tests for understanding the underlying disease processes and severity of DED are also presented.

Management of dry eye should involve patient education and engagement. Information about the natural history and chronic nature of DED should be provided to improve long-term management of the disease and enhance compliance. Aggravating factors should be removed or lessened. We provide a guide to determine the most appropriate treatment (or combination of treatments) based on the severity and cause(s) of the disease, as well as the patient's needs and preferences. The aim of the management is to relieve ocular discomfort and prevent worsening of symptoms and signs, as well as to optimize visual function and minimize structural ocular damage. We also discuss the systematic follow-up and assessment of treatment response, as well as monitoring side effects of treatment, bearing in mind continuous support and reassurance to patients.

Key Words: clinical guidelines, dry eye, meibomian gland, review, therapy

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Dry eye disease (DED) affects millions of people globally and is one of the most frequent causes of patient visits to eye care specialists.

The Tear Film Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS II) defined DED in 2015 as: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[1]

The 2017 consensus report of the Asia Dry Eye Society (ADES) described DED as: "Dry eye is a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage."[2,3]

DED commonly results from reduced tear stability, which may be compromised by abnormalities in the lipid, aqueous and mucin layers of the tear, or anomalies in tear spreading. For example, mucus-secreting goblet cells in the conjunctiva may be damaged after previous infectious conjunctivitis,[4] and aqueous tear deficiency may be age-related or resulted from anticholinergic drugs. Other prominent risk factors including female sex, hormonal changes, eyelid disease, refractive surgery, autoimmune diseases, smoking, prolonged exposure to screens (such as televisions, mobile phones, computers), and many environmental influences (such as humidity, wind, or altitude).[5] The differences in the DEWS II and ADES recommendations are summarized in Supplementary Digital Content, Table 1, http://links.lww.com/APJO/A106.

The prevalence of DED ranges from 5% to 50% according to population studies in Asia and Europe. According to the TFOS DEWS II report, the Asian race is proposed as a significant risk factor for DED, alongside recognized linear increases in risk with age.[5] For many large and developing Asian countries, new lifestyles are driven by information technology,[6] and an association with a rapidly changing aging process, may lead DED to become a significant public health concern in both young and old generations.[7–10]

Ocular surface stress and a proinflammatory tear film can lead to a vicious cycle of ocular surface damage and tear film instability, which exacerbates symptoms within chronic DED.[11] Furthermore, reduced mucosal defenses may result in an increased risk of ocular infection, or even abrasion or corneal ulceration in severe cases.[7]

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Although most cases of DED do not lead to severe visual impairment and blindness, they commonly reduce the vision-related quality of life and limit daily activities.[12,13] In addition, whereas symptoms can improve with treatment, long-term treatment may be required to provide sustained benefits, which may be a source of frustration for both ophthalmologists and patients.[14]Because severe DED is particularly linked to a decreased quality of life, impairment of work productivity and daily activities,[15–18] and requires medical expertise (often even beyond ophthalmology) to treat,[19–21] it is *worth defining* for practice in Singapore. In addition to symptoms, DED is diagnosed based on objective findings with slitlamp examination. However, across clinics, there is heterogeneity in DED diagnosis and management, partly related to the availability of additional diagnostic and treatment equipment. Additionally, in DED, clinical examinations may be unremarkable in the presence of symptoms.[22] The lack of practical and consistent guidance in assessment, diagnosis and management may represent a barrier for ophthalmologists to appropriately handle DED, especially in the context of limited time for consultation.[23–26] This framework aims to address these unmet needs.

The key objective of this document is to provide ophthalmologists a standard approach to the management of DED. This framework may be used as the base and adapted to specific practice conditions, thus improving the quality of care for patients.

RECOMMENDED FRAMEWORK

Assessment: History

DED may present with a range of symptoms including irritative symptoms such as grittiness, photophobia, burning, fatigue or a feeling of "heavy" eyelids. Additionally, there may be paradoxical watery eyes to reflex tearing and transient visual blurring or disturbance associated with prolonged visual tasks.[4] Patients with DED may frequently present with itchiness and other forms of ocular irritation.[27,28] Prolonged exposure to exacerbating conditions, that is, wind, air travel, air conditioning, low humidity, worsens symptoms. Extended viewing tasks such as reading and computer work are associated with decreased blink rate.[4,26]

Assessment of patient medical history should include triage questions to identify local and systemic causes of DED, excluding other possible causes, and analysis of risk factors for DED (Table 1). Take note of ocular factors such as surgery,[29] allergy, contact lens wear,[30] and the use of topical medications [such as glaucoma medications,[31] or eye drops containing preservatives like benzalkonium chloride (BAK)].[32]

Severe DED resulting from systemic diseases (Table 2) is uncommon in primary care, but these should be documented if present. Other common systemic causes include postmenopausal state or post-oophorectomy, diabetes mellitus, rosacea, thyroid disease or Parkinson disease. Less common systemic causes of severe dry eye include lymphoma and leukemia, Bell's palsy and graft-versus-host disease. A history of orbital radiation and any ocular (especially refractive), facial and/or intracranial surgery should also be documented.[14,33,34]

A validated symptom questionnaire is recommended at the beginning of the patient interaction—potentially in the waiting room to save time.[32] In DED, these tools can measure ocular surface discomfort and symptoms, as well as the impact on everyday function over a specified period, eg, 2 to 4 weeks before the consultation. Standardized Patient Evaluation of Eye Dryness (SPEED)[35] and 5-Item Dry Eye Questionnaire (DEQ-5)[36] are widely implemented and require only 2 minutes each to complete. The Ocular Surface Disease Index (OSDI) is a potential alternative.[32] Please refer to a previous discussion on the use of various questionnaires.[37]

Assessment: Examination

Objective evaluation of signs should be done to diagnose DED and differentiate from other causes of irritable eyes that may complicate management.[14,38]

The external examination should cover the following:

- *Skin*—acne, eczema, malar rash, target lesions, scleroderma, psoriasis, facial changes consistent with rosacea, seborrhea
- *Eyelids*—eyelid lag, incomplete closure/malposition, incomplete or infrequent blink, erythema of eyelid margins, abnormal deposits or secretions, entropion, ectropion, and excessive blinks (blepharospasm)
- *Adnexa*—enlargement of the lacrimal glands
- *Neck*—goiter
- Proptosis
- *Cranial nerve function*—eg, trigeminal (V) and facial (VII)
- *Hands*—features of rheumatoid arthritis, Raynaud phenomenon
- *Parkinsonian features*—in Parkinson disease there is reduced blinking, resulting in excessive tear evaporation between blinks.

The slitlamp biomicroscopy examination should focus on the following:

- *Tear film*—height of the meniscus (meniscometry; <0.25 mm is abnormal), debris, increased viscosity, mucus strands
- *Eyelashes*—trichiasis, distichiasis, madarosis, deposits
- *Lid margins and meibomian gland*—expressibility, abnormalities or blockage of meibomian gland orifices, character of meibomian gland secretions, keratinization, scarring, Demodex infestation and rosacea features. Meibomian gland expressibility can be quantified with a standard force evaluator, if available.
- *Lacrimal Puncta*—presence and position of plugs
- *Conjunctiva*—mucus threads, scarring, erythema, papillary reaction, keratinization, follicle enlargement, punctate staining, hyperemia, localized drying, chemosis, chalasis
- *Cornea*—interpalpebral area of epithelial erosions or defects, mucus plaques, opacification, thinning, new vessels, signs indicating previous refractive surgery.

We highly recommend examining the completeness of blinking and lid abnormalities, as well as examining for lid-wiper disease, superior limbic keratoconjunctivitis, ocular allergy, and conjunctivochalasis.[32]

To confirm the diagnosis of dry eye, at least 1 clinical test or DED process should be abnormal on examination. This may include 1) a test demonstrating tear instability, 2) a test of ocular surface damage, evidenced by dye staining, or 3) a test of impaired tear osmolarity.[32]

Fluorescein Tear Breakup Time (FTBUT) ≤ 5 seconds is considered abnormal (note that the pattern and distribution of tear breakup is more informative than the timing alone, Fig. 1).

TABLE 1. Risk Factors and Potential Causes of DED*

Recognized	Suggestive or Probable	Inconclusive
Older age	Asian ethnicity	**Cigarette smoking**
Female		Demodex infestation
Excessive computer or screen use	**Clear corneal phacoemulsification, large-incision ECCE and penetrating keratoplasty**	Hispanic ethnicity
Contact lens wear	**Use of medications; anticholinergics, anxiolytics, antipsychotics**	**Botulinum toxin injection**
Lack of sleep	Parkinson disease	**Alcohol use**
Use of medications; antihistamines	**Use of medications; tricyclic antidepressants, SSRIs, diuretics, beta-blockers**	**Multivitamins**
Allergies or atopy (or allergic conjunctivitis)	Stevens-Johnson syndrome, toxic epidermal necrolysis	**Pregnancy**
Meibomian gland dysfunction	Menopause	Gout
Laser insitu keratomileusis (LASIK) and refractive surgery	Diabetes mellitus	
Autoimmune disorders; Sjögren syndrome, rheumatoid arthritis, lupus, scleroderma	HIV/HTLV1 infection (or other viral infection)	
Connective tissue disorders	**Low humidity environments**	
Radiation therapy	Psoriasis	
Hematopoietic stem cell transplantation	**Poor eyelid or eyelash hygiene**	
Low dietary intake of omega-3 fatty acids	**Use of cosmetics**	
Thyroid diseases	Pterygium	
Hormone replacement therapy	Sarcoidosis	
Androgen deficiency	Ovarian dysfunction	
Vitamin A deficiency	Acne	
Trauma (eg, mechanical, chemical, thermal)	**Isotretinoin**	

DED indicates dry eye disease; ECCE, extracapsular cataract extraction; HIV, human immunodeficiency virus; HTLV1, human T-cell lymphotropic virus type 1.

*Recognized evidence: with adequately powered studies, and plausible biological rationale. Suggestive or probable evidence: recognized association, but inconclusive or limited information in published studies. Unclear evidence implies either directly conflicting information in peer-reviewed publications or inconclusive information but with some basis for a biological rationale.

Risk factors highlighted in bold are modifiable.

The FTBUT is measured as the time that elapses between the last blink and the appearance of the first dry spot in the tear film.

- Fluorescein should be administered without drastically impacting tear volume. We recommend the use of a minimum amount of nonirritating fluorescein dye.
- Breakup patterns are classified into 5 types (see Fig. 1). Attention should be paid to breakup occurrence timing (just after eye opening, during upward migration of fluorescein, after the end of upward migration of fluorescein/after tear film completion), breakup occurrence distribution, shape/pattern, and breakup extension. Examination of breakup patterns allows DED to be classified into 3 subtypes: decreased-lacrimation type (line breaks, area breaks), decreased wettability/mucin-deficient dry eye (spot breaks, dimple breaks), and evaporative (random breaks).[39]

Ocular surface staining, if significant, on the cornea, conjunctiva or subtarsus, will constitute one abnormal sign towards diagnosis.

- Staining should be documented using a digital image of the ocular surface after staining under cobalt blue illumination.

TABLE 2. Tests for Systemic Conditions Associated With DED

Suspected Condition	Diagnostic Tests
Sjögren syndrome*	SS-A, SS-B, ANA, rheumatoid factor, SP1, CA6, PSP
Thyroid disease (eg, Hashimoto thyroiditis)	Anti-thyroid peroxidase antibody, anti-thyroglobulin antibody, orbital imaging (CT or MRI)
Rheumatoid arthritis	Rheumatoid factor, CRP, anti-CCP
Lupus	ANA
Sarcoidosis	Serum lysozome, ACE, chest CT, conjunctival biopsy
Ocular mucus membrane pemphigoid	Conjunctival biopsy (including immunofluorescent or immunohistochemical studies)

ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; CA6, anti-carbonic anhydrase 6; CRP, C-reactive protein; CCP, cyclic citrullinated peptide; CT, computed tomography; DED, dry eye disease; MRI, magnetic resonance imaging; PSP, anti-parotid secretory protein; SP1, anti-salivary gland protein 1; SS, Sjögren syndrome.

*Traditionally, diagnosis of Sjögren syndrome is determined by using SS-A (anti-Ro) and SS-B (anti-La) autoantibodies in serum. Recently, additional autoantibodies have been identified as diagnostics for Sjögren syndrome. The novel auto-antibodies may be present earlier in the disease course. Currently in clinical practice, the levels of some of these can be determined using a commercially available blood test called *Sjö*, which also includes SS-A, SS-B, ANA, and rheumatoid factor levels in its panel. The test can be administered in clinic using a simple finger stick with a lancet. The sample requires one large blood drop and test results are typically available within 1 week.

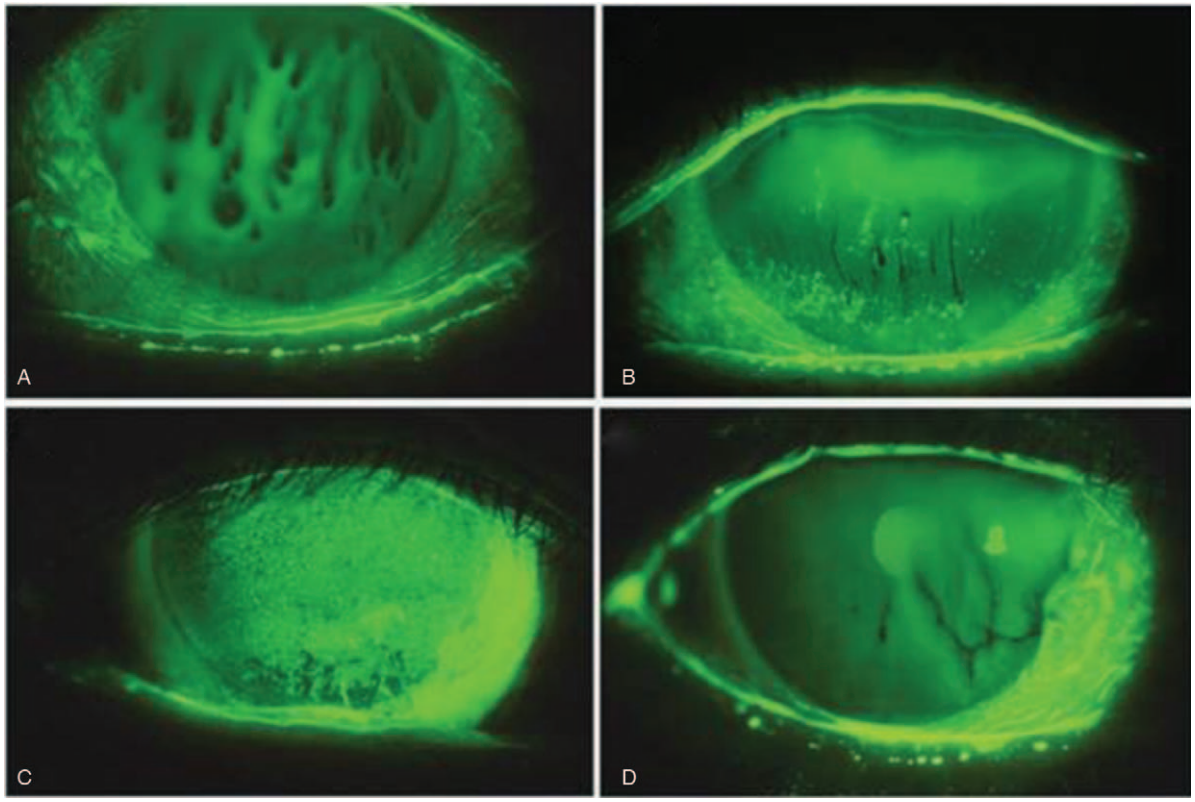

FIGURE 1. Four patterns of tear film breakup clinically observed. Image from Yokoi N, Georgiev AG: Tear-film-oriented diagnosis and therapy for dry eye. In Dry Eye Syndrome: Basic and Clinical Perspectives (Yokoi N. ed.), pp96–108, Future Medicine Ltd, London, 2013 reproduced with permission from Future Medicine Ltd.

- Analysis of the staining distribution is important (Fig. 2). For example, if the staining is dominant in the inferior part of the cornea, ophthalmologists should pay attention to the inferior lid margin for blepharoconjunctivitis or trichiasis. In dry eye, the pattern of staining may not always be limited to the interpalpebral region of the ocular surface.
- Inferior staining of the cornea is common. Dry eye is suspected in the presence of >5 corneal spots, >9 conjunctival spots, or lid margin staining (≥2 mm length and ≥25% width).[32,40] or some other validated schemes previously reviewed.[41]

Tear osmolarity can be considered elevated if (≥308 mOsm/L) in either eye or an interocular difference of >8 mOsm/L is considered abnormal. If tear osmolarity is performed, we recommend undertaking this first to prevent the introduction of measurement artefacts.[32]

If required, the Schirmer test may be used as a proxy for aqueous tear production, and guide treatment for dry eye. Beware of excessive reflex tearing when this test is performed. For example, a value of above 25 mm, especially within 1 minute of the test, may render the results noninformative. Other tools may be available: such as tear film interferometry,[42] optical coherence tomography[43] and use of the Oculus Keratograph 5 M.[44] Decreased tear meniscus height/area suggests an aqueous deficiency in DED, but these tools should not be used alone to confirm the diagnosis of DED, as no population-based data are currently available. It is not necessary to perform *all* these tests to make a diagnosis or to begin the treatment for DED.[32,45]

Any decisions should be based on the time and instruments available and consider patient preference. Where time allows and where available, additional DED tests may yield information related to DED processes that may be amenable to treatment.[46] In cases where presurgical assessment and surgical outcomes are highly dependent on tear function, more extensive testing may be justified. Costs of these diagnostic tests should always be considered, but these should be calculated from a holistic standpoint. For example, if the tests can assist the channeling of patients to appropriate health care services there may be cost savings for the health system, through reduced referrals.[21]

Meibomian gland dysfunction (MGD) is a common and chronic disorder and is one of the leading causes of poor tear stability (other than mucin abnormalities of the tear film) but may also be present in other kinds of dry eye. Active MGD may be detected via increased viscosity and opacification of meibum, and difficulty of expressing meibum. Hyperemia and edema of lid margin may indicate active disease, whereas scalloping and notching, and rounding of the lid margins suggest chronic, fibrotic MGD. Meibum expression may alter baseline findings of the tear film. Therefore, we only recommend expressing meibum to assess MGD to be performed after the other tests.[11]

Meibomian gland dropout may be a prognostic measure, as measured by the loss of acinar tissue—which is detected by noncontact infrared meibography[47,48] or by meibography whereby the meibomian glands are viewed in silhouette by transillumination through the everted eyelids using a clearly defined technique to score the dropout. Meibography is not used alone to diagnose MGD, but instead should be interpreted in the context of other clinical parameters.[45]

Ophthalmologists should then consider whether the patient has severe dry eye. In general, patients who have more severe dry eye may benefit from more modalities or more extensive treatment.[46]

Significant epitheliopathy is evidenced by Corneal Fluorescein Staining (CFS) via slitlamp examination. In the Modified Oxford Scale, Grade III indicates moderate DED, and Grade IV

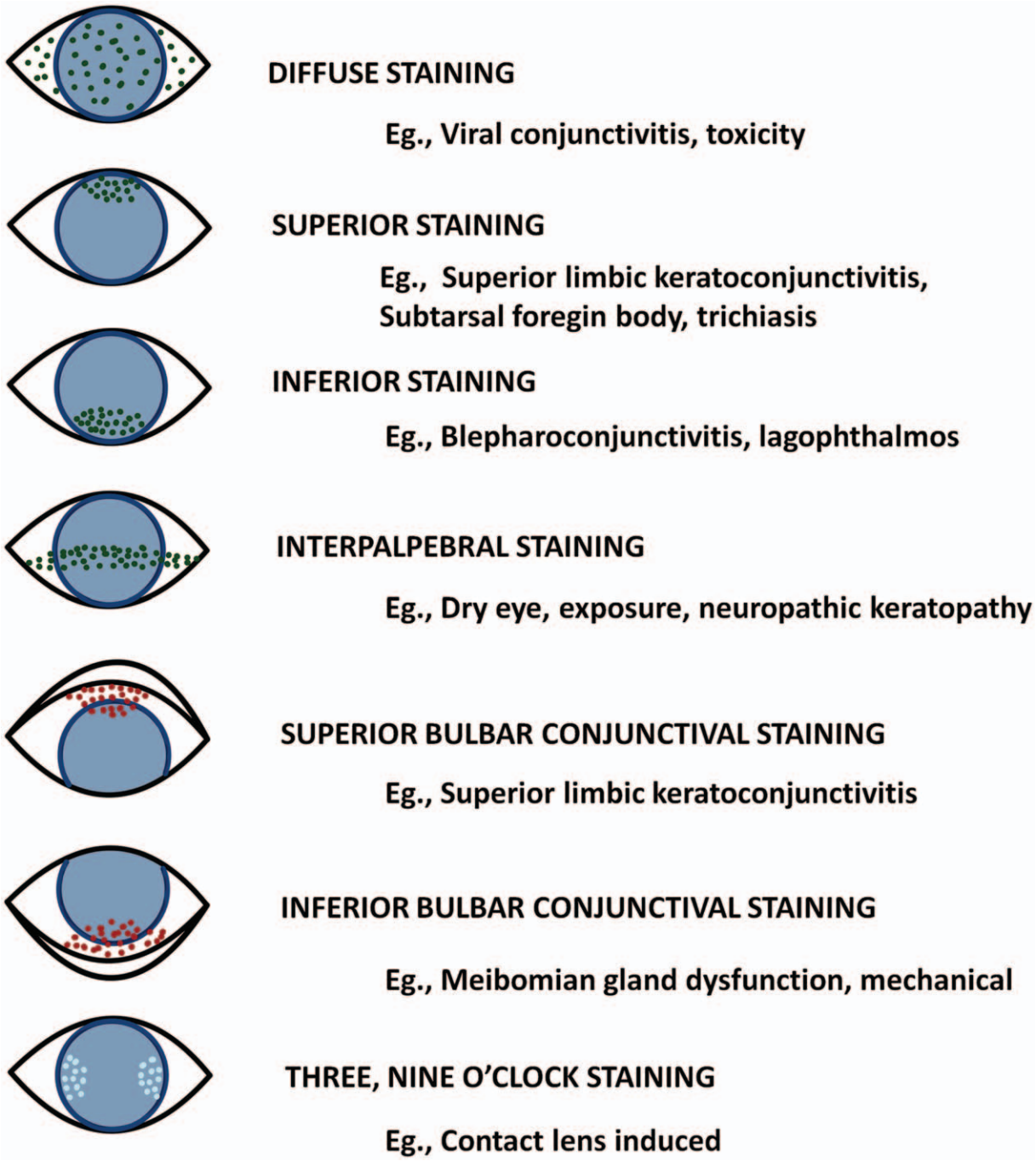

FIGURE 2. Patterns of ocular surface staining.

or V indicates marked or severe DED.[46] Patients with severe aqueous tear deficiency often show an "area" breakup pattern on testing tear stability.[39] It may be difficult to ascertain the FTBUT because it can be close to zero, and such patients often find it difficult to open their eyes for the FTBUT evaluation.[14]

Other indicators of severe disease include the presence of corneal filaments, the presence of conjunctivalization and deep corneal vascularization, or persistent epithelial defects.[4,14]

Differential Diagnosis

Mild conjunctival redness or signs of an otherwise normal eye could still indicate dry eye. In patients with a more acute presentation, DED may be confused with allergic and infective conjunctivitis, or viral keratoconjunctivitis.[4,14] Here, we propose a series of simple steps to make a probable diagnosis:

- *Inspect and evert lids*. Large subtarsal papillae suggest allergic conjunctivitis, especially in patients with history of atopy, asthma, eczema, or contact lens use. Subtarsal petechiae or membranes suggest infective conjunctivitis. Examine eyelashes for both anterior blepharitis and signs of Demodex infestation. Examine the palpebral conjunctiva for the presence of follicles or swelling.
- *Inspect conjunctiva*. Look for copious discharge or chemosis suggesting infective conjunctivitis, sectorial redness

suggesting episcleritis, and prolapse over the lower lid margin with epiphora suggesting conjunctivochalasis. Examine bulbar conjunctiva for pattern of redness and signs of swelling.
- *Examine the cornea* for ulceration and infections. Exclude abrasions and foreign bodies.
- *Proptosis and lid lag*. Suggest thyroid eye disease.
- *Red reflex*. Irregular pupils suggest uveitis. Examine the anterior chamber for the presence of cells or flare.
- *Visual acuity*. Should not be severely impaired in most cases of dry eye, as blinking helps to maintain normal acuity during the examination.

Missing comorbidities could have serious consequences, bearing in mind the higher risk of malignancy in Sjögren syndrome.[49] Investigate with relevant blood tests[50] in patients with suspicious symptoms such as dry mouth (Table 2). Autoimmune diseases could present with other ophthalmic signs such as restriction of ocular motility, blepharitis, conjunctival scarring, symblepharon, episcleritis, uveitis, retinitis, and even optic neuropathy although none of these features may be present in any single patient.[51] Particular attention should be paid to patients who are compliant but do not respond to initial therapy.

DED symptoms may be associated with corneal neuropathic pain. The richly innervated corneal tissue is on the most powerful pain initiators in the body, and corneal neuropathic pain may result from dysfunctional nerves causing perceptions such as burning, stinging, eye ache and pain. Various inflammatory diseases, neurological diseases, and surgical interventions can contribute to this condition. These patients may present with vague perceptions of DED symptoms without significant findings on slitlamp examination. Neuropathic corneal pain in itself results from a complex interplay of various central and peripheral mechanisms. Patients with migraine, neck aches, fibromyalgia and postmenopausal women may be predisposed to neuropathic pain. Only the peripheral type of neuropathic pain, and not the central type, is relieved by the instillation of local anesthetic eyedrops.[11,52–60]

Currently, no single therapeutic approach or drug is sufficient to tackle DED with neurosensory dysfunction, but it is important to treat tear instability, MGD, manage comorbidities, and tackle inflammation. For more severe cases, regenerative therapy, specialist contact lenses or systemic pharmacotherapy for pain could be used, alongside complementary and alternative measures (like acupuncture, omega 3–rich diet, and mindfulness training).[11,52–60]

Management

The ultimate aim of DED management is to restore homeostasis of the ocular surface by breaking the vicious cycle of the disease, as well as offering long-term options to prevent a return to the pathophysiological cycle and resurgence of symptoms.[61]

Many factors contribute to symptoms of DED. It is necessary to manage any such factors that are amenable to treatment. Giving tear replacement without attending to the other causative factors is likely to result in an unhappy patient.[61]

Patient Education

After excluding more serious conditions, the patient should be reassured that DED is generally a non–sight threatening condition. This should be followed by educating on the course and chronic nature of this disease, and discussing appropriate options according to individual needs and underlying disease.[61]

It is important to provide specific instructions for therapy, and reassure the patient of any initial complaints, for example, patients may experience stinging sensations with some treatments shortly after instillation when there is a mismatch between the acidity of the eye drops and the tear film. Very often, trial and error are required to ascertain the most comfortable eye drop. The ophthalmologist should make it clear that DED management is typically long-term due to the underlying pathophysiology, and symptoms may not be ameliorated, or the disease cured.[61]

Compliance with treatment is vital to maintain therapeutic benefits. Therapeutic goals should be set with realistic expectations. The use of point-of-care evidence in follow-up consultations with patients may aid compliance by emphasizing any improvements in disease and clinical measurement scores, where symptoms may not be improving.[61]

Target Aggravating Factors

After confirming the diagnosis of DED, ophthalmologists should try to eliminate or modify factors that may contribute to the aggravation of DED. Any implemented approach should consider the patient's needs and preferences, whereas considering what options are locally available and whether they are affordable.[61]

- Modification of local environment, such as limiting exposure to air conditioning, air travel, and low humidity environments
  - Use of a humidifier may be of particular help for patients with increased evaporative loss
- Modification of diet, including oral dietary (omega 3) fatty acid supplementation
- Increased general hydration
- Adjustment or elimination of offending systemic and topical medications (particularly if prolonged unnecessarily), such as antihistamines, diuretics, and tricyclic antidepressants [these can be substituted by selective serotonin reuptake inhibitors (SSRIs)] or any other drugs with anticholinergic effects
- Lifestyle changes, such as reducing cigarette smoking, alcohol intake and digital screen time (computer, tablet or mobile phone), as well as enhancing sleep quality and quantity
- Assessment of contact lens use—removed on the days where dry eye symptoms are present, and silicon-hydrogel or rigid gas permeable lenses should be considered

Patients with severe DED are at greater risk for contact lens intolerance and associated complications. Patients with pre-existing DED should be cautioned that LASIK or refractive surgery may worsen their condition and that symptoms could persist for up to 3 months after surgery. Any pre-existing DED should be preoperatively treated before such surgery.[61]

Treatment Options

DED has a multifactorial etiology. Any treatment decisions should be made on an individual patient basis after evaluation of the benefits and risks of available therapies.[61]

Although there are treatments that may be indicated for one particular DED process, a number of treatments might be recommended to address multiple aspects of DED, for example, to address eyelid disease, inflammation, or decreased wettability.[61]

Almost 80% of patients with DED have tear instability, including those with aqueous tear deficiency, so we recommend

a treatment strategy to target tear instability and the mixed form of DED (with aqueous-deficient, evaporative, and mucin-deficient components). Because of the high prevalence of MGD, it is sensible to optimize the MGD status for most patients with DED. The objective for eyelid warming in MGD is to maintain a temperature of at least 40°C for a minimum period of 8 to 10 minutes a day.[62]

Chronically obstructed meibomian glands undergo atrophy. Loss of meibomian glands on meibography is not a contraindication for treatment. The long-term progression of MGD may be documented in this way, but currently there is no level of gland dropout which prevents benefit from treatment of MGD. Nevertheless, it is possible that the benefit for treatment may be reduced if there are minimal residual glands, and practitioners should weigh the pros and cons of treatment if the treatment is expensive or associated with significant side effects.[62]

Since the loss of meibomian glands may be considered to be irreversible at this time, procedures for optimizing MGD based on the principle of eyelid warming or facilitation of the meibum production may be considered to be *medical procedures*. In addition, procedures that aimed to rescue or restore dysfunctional meibomian or lacrimal glands should be considered to be *medical procedures*.[62]

Artificial Tears

Preservative-based lubricants should be used with caution as they may cause sensitivity (especially in patients who use the drops many times a day over a long period). Most eye drops tend to contain BAK, which could be counterproductive in treating symptoms of DED as it may lead to ocular discomfort on instillation, stinging sensation, foreign body sensation, dry eye, tearing, and itchy eyelids. Additionally, BAK-preserved eye drops have been associated with superficial punctate keratitis, conjunctival hyperemia, blepharitis, increased osmolarity, as well as reduced tear production and TBUT. The use of BAK-free eye drops may be beneficial to avoid these associations, particularly in the long term.[63] However, a recent meta-analysis has found the use of nonpreserved medications to be similar to preserved medications in terms of effects on TBUT and symptoms, but corneal staining as an outcome was not evaluated.[64]

We recommend the use of *preservative-free formulations* in conditions where frequent instillation of ocular lubricant is necessary (>5 instillations per day) or the ocular surface epithelium is compromised so that these can be used as often as desired and titrated to visual activities. However, unit-dose vials are at risk of microbial contamination and therefore should be discarded within a few hours after use. The multidose preservative-free formulations are a good alternative because they are safe, cost-effective, and environmentally friendly. There is a trend towards such formulations, even for prescription eyedrops like cyclosporine and corticosteroids.[63]

If initial formulations do not relieve symptoms, consider adding transient gels, or hypo-osmolar eye drops that contain hyaluronate and lipids. *Ointments and viscous gels* are best used before bedtime as these induce blurring. Some trial and error may be necessary to determine what is most comfortable for each patient.[63] *Hypotonic sodium hyaluronate eye drops* are effective in decreasing inflammatory cytokines and corneal epithelial staining. Therefore, they can be used for inflammatory DED with ocular surface damage.[65]

In addition, *lipid-containing eye drops or ointments* have grown in availability and can be considered, primarily to help address MGD and lipid deficiency. A variety of oils, such as mineral oils and phospholipids, have been incorporated in formulations to help restore the lipid layer of the tear film by mimicking natural meibum.[66–69]

Other agents have been shown to reduce symptoms of DED such as mucolytics (N-acetylcysteine).[70–72]

Treatments for Tear Conservation

The concept of temporary or permanent occlusion of one or both puncta is to retain tears on the ocular surface by slowing drainage. Punctal occlusion is most commonly undertaken using punctal plugs, whether this is absorbable/temporary or non-absorbable/permanent. However, these can sometimes cause foreign body sensation in the corner of the eye and if misplaced or rubbed potentially cause corneal abrasion and increase conjunctival microbial flora.[73,74]

The use of punctal occlusion in the presence of ocular surface inflammation is debated because theoretically occlusion of tear outflow could prolong the presence of proinflammatory cytokines on the ocular surface. Therefore, we recommend concurrent occlusion and treatment of inflammation with steroids, if punctal occlusion is required.[75] Recent meta-analyses have shown inconclusive results for the use of punctal plugs on the treatment of dry eye symptoms and signs.[76,77]

Moisture chamber spectacles/goggles are eyeglasses specially designed to slow evaporation of the tears, by providing a humid environment and minimizing airflow over the ocular surface. These are particularly useful in treating evaporative dry eye (EDE). A number of such devices are available.[78]

Production of Tear Components

Diquafosol eyedrops can be considered in patients who require an increase in tear mucus or aqueous tear. This eyedrop should be ideally used 5 to 6 times a day, reaching maximal effects in 1 to 3 months.[79–84]

Neurostimulation may be an additional strategy.[85]

Anti-inflammatory Therapy

Clinical evidence supports the efficacy of anti-inflammatory eye drops in improving symptoms and decreasing corneal staining in moderate-to-severe DED, when compared with ocular lubricant therapy alone. This may be because it acts on the underlying pathophysiology of the condition rather than on tear supplementation.[11,50,82]

Corticosteroid eyedrops are effective due to their efficacy and fast action. Commonly used options include loteprednol, prednisolone acetate (methylprednisolone), dexamethasone, and fluorometholone. Preservative-free options are recommended to not damage the ocular surface. Long-term use should only be considered in later stages of DED and staged management. Longer durations of use are associated with an increased risk of increased intraocular pressure, glaucoma, cataracts, and opportunistic infections.[86–88]

The estimated duration of topical steroid use varies according to potency and formulation, the severity of ocular surface inflammation, intraocular pressure level and patient compliance. We recommend the use of corticosteroids for ~2 to 6 weeks (short-term; with tapering for high doses). Simultaneous use of

cyclosporine A for patients with recurrent inflammation is a reasonable strategy, and should be continued for as long as necessary. For patients with moderate-to-severe disease that are not controlled with other concomitant therapies, repeated short-term pulse therapy of corticosteroids can be an alternative approach.[86–88]

Patients with concurrent allergic eye disease could benefit from combinatory treatment with topical mast cell stabilizers.

Cyclosporine A is an immunomodulatory drug with anti-inflammatory properties and can be used for the treatment of ocular inflammation and DED.[63,89] Topical cyclosporine A was approved based on an improvement in tear production, but has also been shown to reduce inflammatory markers, reduce hyperosmolarity, increase conjunctival goblet cell density, and have antiapoptotic properties. It has been shown to lead to significant improvements in symptoms, prevent disease progression, and rarely, even "cure" the disease. Cyclosporine A is available in various formulations and emulsions for topical use in moderate-to-severe DED, including 0.1% (in cationic emulsion, Ikervis) and 0.05% (Restasis).[90–94]

The effects of cyclosporine A tend to only appear after several weeks due to the mechanism of action and T cell physiology. However, cationic emulsion formulation means Ikervis only has to be administered once per day.[95]

Patients may report a burning or stinging sensation upon application. Initiation tolerance is a frequently observed reason for the discontinuation of cyclosporin. However, ophthalmologists should educate the patient about potential initial discomfort and make the patient aware that any instillation site pain may fade within 2 to 4 weeks, to support treatment compliance. As mentioned, steroids or artificial tears may be prescribed in combination to help reduce this and increase tolerability. For example, use of artificial tears before instillation of cyclosporine may decrease ocular burning.[90–93,96–98]

Additional Treatment for MGD

This may involve warm compresses, doxycycline or azithromycin. Exfoliation and debridement of the eyelid (available tools include BlephEx) may be considered. Latent heat with or without pressure to the eyelids may be used (commercially available as Blephasteam, EyeGiene mask, iLux). Other options include therapeutic expression, vector thermal pulse (eg, with LipiFlow), intense pulsed light, and intraductal probing.[62]

Table 3 summarizes treatment recommendations for DED (adapted from TFOS DEWS II).[61]

TABLE 3. Treatment Recommendations for DED Processes* (All Causative Factors of DED Amenable to Treatment Should Be Treated)

Initial treatment (available in the community and primary care)
- Ocular lubricants of various types such as sodium hyaluronate [or hyaluronic acid (HA)], hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose (CMC), and polyethylene glycol (PEG)
- Nonpreserved ocular lubricants to minimize preservative-induced toxicity
- Lid hygiene and warm compresses

For inflammation
- Prescription topical corticosteroids (short-term only)
- Prescription topical nonglucocorticoid immunomodulatory drugs (such as cyclosporine A), and maintained for the long-term (as long as necessary)
- Lymphocyte function-associated antigen-1 (LFA-1) antagonists (if available)

For tear deficiency
- Topical mucin secretagogues (such as diquafosol, if available)

For tear preservation
- Punctal occlusion or diathermy
- Moisture chamber spectacles/goggles
- Overnight ointment or other occlusion methods

For anterior blepharitis
- Oral macrolide or tetracycline antibiotics
- Topical antibiotic or antibiotic/steroid combinations to eyelids
- Eyelid debridement, including devices such as BlephEx
- Tea tree oil treatment for Demodex (if present)

For MGD
- Consider ocular lubricants with lipid-containing supplements
- Macrolide or tetracycline antibiotics
- Eyelid warming, including devices such as USB-eyemasks
- Eyelid debridement, including devices such as BlephEx
- Intense pulsed light or light modulation therapy
- Heating and expression of the meibomian glands (including devices such as LipiFlow)

For specialists, if the approaches in earlier steps are inadequate
- Biological tear substitutes (autologous/allogeneic/umbilical cord serum or plasma eye drops)
- Therapeutic contact lens options
- Soft bandage lenses
- Rigid scleral lenses
- Oral secretagogues
- Amniotic membrane grafts
- Surgical punctal occlusion
- Tarsorrhaphy

Treatment of underlying systemic conditions associated with DED

*Availability and access to treatments may vary across clinics, hospitals, regions, and countries. Consider options concurrently if necessary. These are not ranked according to the importance and new evidence should be evaluated when available.

Follow-up

Many people with DED who persist with their prescribed treatment achieve symptomatic control, allowing them to function with minimal difficulty. However, since DED is chronic some patients may have "episodes" and require further attention. Patients may discontinue use of the recommended eye drops because of complicated regimens, high frequency of dosage, side effects, and/or the high cost. Other contributing patient factors include the perception that the disease is mild, an inability to remember the treatment regime, and a lack of understanding of the objectives of the treatment.[61]

The aim of follow-up evaluations is to monitor response to treatment, and if necessary change or adjust the ongoing therapy, to evaluate for structural ocular damage, and to reassure the patient. If artificial tears are used infrequently, there may be tear film instability, so the dosing should be individualized to obtain the desired clinical response. The optimal instillation frequency may be around 4 to 6 times per day for mild DED. Another important purpose of follow-up is to monitor for eye drop toxicities.[61]

The frequency and extent of follow-up evaluation will depend on the severity of the disease, the therapeutic approach used, and the response to therapy. Once formal diagnosis has been made, patients with mild DED, especially those without corneal

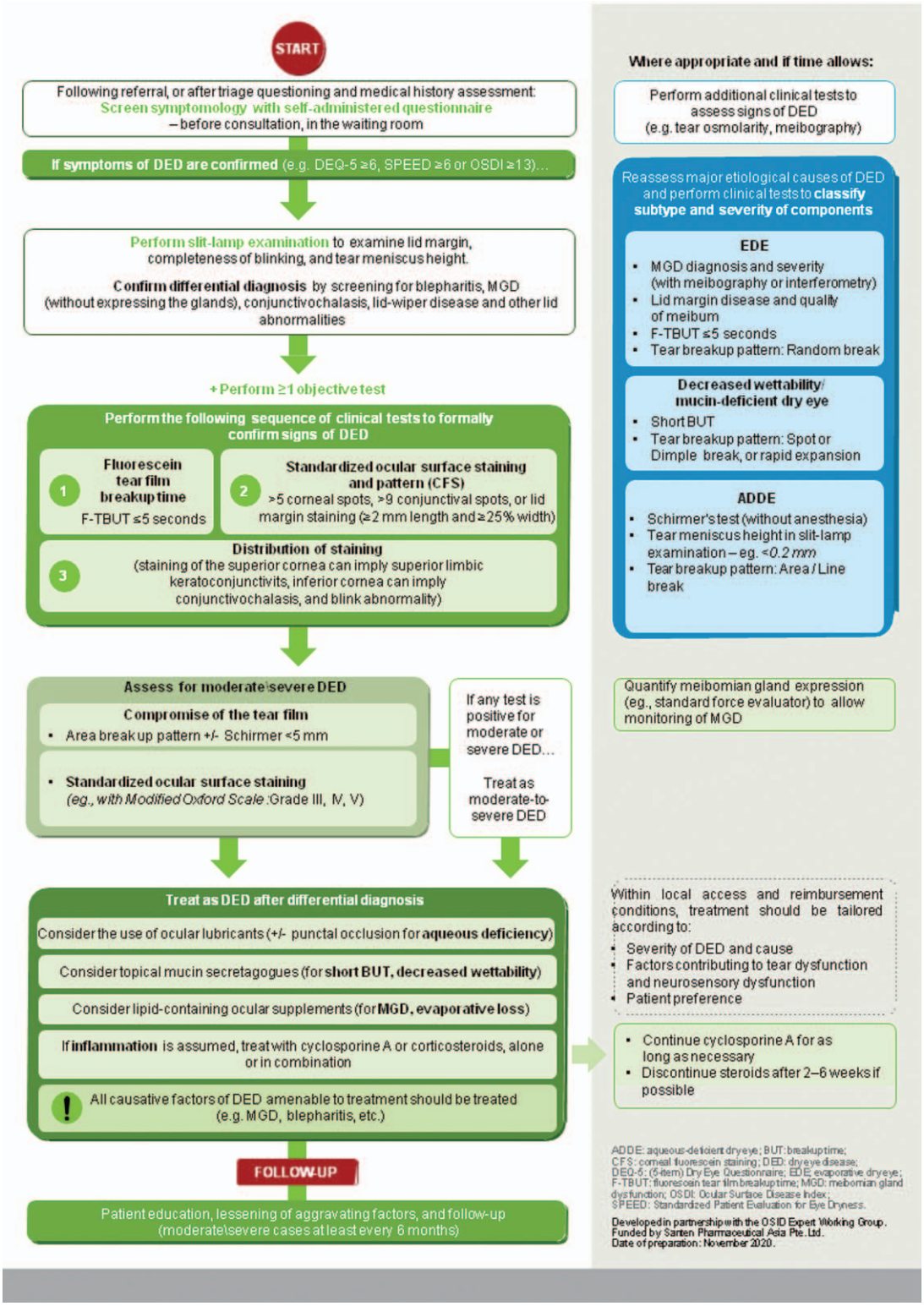

FIGURE 3. Summary chart for DED framework. ADDE indicates aqueous deficient dry eye; BUT, breakup time; DED, dry eye disease; EDE, evaporative dry eye; MGD, meibomian gland dysfunction.

epitheliopathy and not related to systemic conditions, may be referred back to primary care.[61]

The recommendations in this framework are summarized in Figure 3.

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