

Aqueous-deficient dry eye disease: Preferred practice pattern guidelines on clinical approach, diagnosis, and management

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Dry eye disease (DED) is a broad term that includes a diverse group of clinical disorders. Aqueous-deficient dry eye (ADDE), a subtype of DED, is characterized by decreased tear production by the lacrimal gland. It can be seen in up to one-third of individuals with DED and can be comorbid with a systemic autoimmune process or occur secondary to an environmental insult. Since ADDE can be a source of long-term suffering and severe visual impairment, early identification and adequate treatment are imperative. Multiple etiologies can underlie ADDE, and it is critical to identify the underlying cause to not only improve the ocular health but also to improve the overall quality of life and well-being of affected individuals. This review discusses the various etiologies of ADDE, highlights a pathophysiology-based approach for evaluating underlying contributors, outlines various diagnostic tests, and reviews treatment options. We present the current standards and discuss ongoing research in this field. Through this review, we propose a treatment algorithm that would be useful for an ophthalmologist in diagnosing and managing individuals with ADDE.

Key words: ADDE, aqueous deficiency dry eye disease, DED, dry eye disease, lacrimal gland, Sjögren's syndrome

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Dry eye disease (DED) is an umbrella term that includes multiple clinical subtypes, and the symptoms of DED affect millions of people worldwide.^[1,2] The overall premise of DED is that tear film instability and hyperosmolarity lead to ocular surface inflammation, damage, and neurosensory abnormalities causing varied grades of symptoms. The prevalence of DED can vary widely (5%–50%) based on the disease definition and the population studied.^[2] Of particular relevance to India, it is estimated that 60% of the Indian urban population will be affected by DED symptoms by the year 2030.^[1] DED produces an economic burden due to long-term medical expenses and lost productivity and a social burden due to disturbance in the visual, physical, and psychological aspects, eventually creating a negative impact on quality of life.^[2,3] In 2007, the first Tear Film and Ocular Surface Society Dry Eye workshop (TFOS-DEWS) classified DED into evaporative (EDE) and aqueous-deficient (ADDE) subtypes. However, clinically, there may be an overlap between the two.

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Therefore, the second Tear Film and Ocular Surface Society Dry Eye workshop (TFOS-DEWS II) classified DED into three categories: predominant ADDE, EDE, and a mixed form.^[4] The aqueous component of tears is contributed by main and accessory lacrimal glands. ADDE encompasses conditions where lacrimal gland output is primarily affected rather than Meibomian gland function. Although the natural history of the disease varies between individuals and can be impacted by underlying comorbidities, in individuals with primary lacrimal gland dysfunction, characteristics of EDE often occur with progression of disease. Clinically, there is a need to identify when ADDE is a component of DED as various etiologies can underlie lacrimal gland dysfunction that impacts diagnosis and management. The subtle clinical signs in the initial stages of ADDE may be overlooked, which if not identified in time, can cause chronic irreversible lacrimal gland damage in some cases. This review summarizes the different etiologies of ADDE, clinical and laboratory tests for diagnosing ADDE, and treatment algorithms based on literature and authors' preferred practice pattern.

Causes of ADDE

ADDE due to lacrimal gland insufficiency can present in up to a third of all cases diagnosed with DED in India.^[1]

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In this section, the authors classify the different etiologies based on pathomechanisms of lacrimal gland damage, which include direct immune-mediated damage to the lacrimal gland, lacrimal gland insufficiency secondary to conjunctival cicatrization, neurogenic causes, and absence or loss of the lacrimal gland. Though conventionally, ADDE has been divided into Sjögren’s and non-Sjögren’s subtypes [Fig. 1], we believe the classification outlined below aids the clinician in arriving at a correct diagnosis and individualizing treatment based on the underlying etiology [Fig. 2].

Immune-mediated lacrimal gland inflammation

Immune-mediated primary lacrimal gland damage occurs in Sjögren’s syndrome (SS) and graft-versus-host

disease (GVHD). SS is a chronic systemic autoimmune disorder causing oral and ocular dryness due to the lymphocytic infiltration of salivary and lacrimal glands. It is classically defined as primary without any associated autoimmune disease and secondary with an underlying autoimmune disease such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). It predominantly affects middle-aged women and is commonly seen as a triad of dry mouth, dry eyes, and dry skin. Patients may also complain of dryness of the skin. For the classification and diagnosis, various criteria have been developed,^[5-7] the most recent being the American College of Rheumatology and the European League Against Rheumatism (EULAR) 2016 [Fig. 3].^[7] It has the advantage of evaluating DED by having two different scoring systems depending on the different dyes used for ocular surface

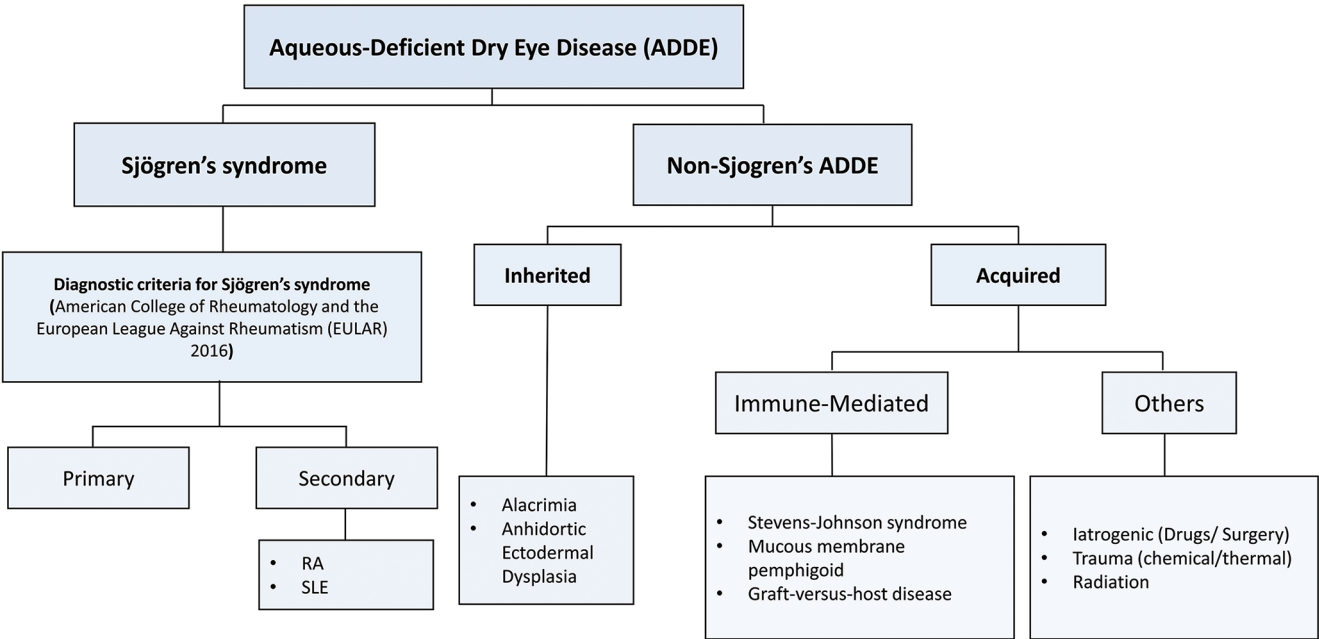


Figure 1: Conventional etiological classification of ADDE differentiating Sjögren’s syndrome, which is the major etiology, from other causes. ADDE = aqueous-deficient dry eye disease, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus

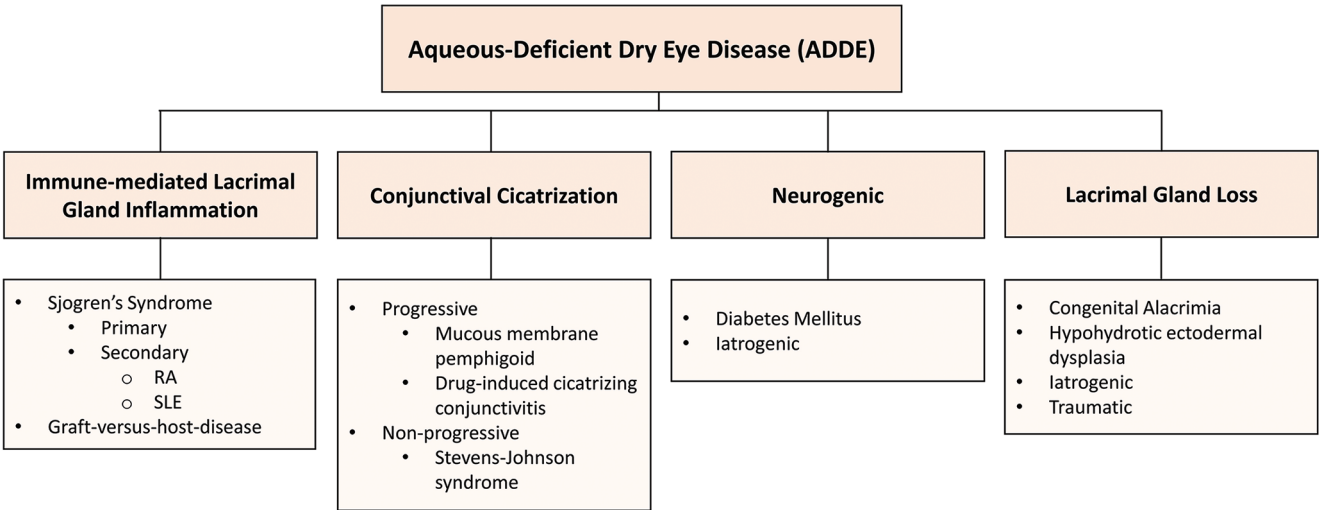


Figure 2: Proposed pathophysiology-based classification of ADDE. ADDE = aqueous-deficient dry eye disease

ACR-EULAR classification criteria, 2016⁸

The classification of SS applies to any individual who meets the inclusion criteria, does not have any condition listed as exclusion criteria, and who has a score ≥ 4 when summing the weights from the following items

Inclusion criteria: At least one symptom of ocular or oral dryness (At least one positive response)

- 1) Have you had daily, persistent, troublesome dry eyes for more than 3 months?
- 2) Do you have a recurrent sensation of sand or gravel in the eyes?
- 3) Do you use tear substitutes more than 3 times a day?
- 4) Have you had a daily feeling of dry mouth for more than 3 months?
- 5) Do you frequently drink liquids to aid in swallowing dry food?
- 6) or suspicion of SS from ESSDAI questionnaire (at least one domain with positive item)

Exclusion criteria:

- History of head and neck radiation treatment
- Active Hepatitis C infection (with positive PCR)
- Acquired immunodeficiency syndrome
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

Item	Score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 foci/4 mm ² (Daniels et al 2011)	3
Anti-SSA/anti-Ro positive	3
Ocular staining score ≥ 5 (Whitcher et al 2010) or van Bijsterveld score ≥ 4 in at least one eye	1
Schirmer's test ≤ 5 mm/5 min in at least one eye	1
Unstimulated whole saliva flow rate ≤ 0.1 ml min ⁻¹ (Navazesh & Kumar, 2008)	1

Figure 3: American College of Rheumatology–European League Against Rheumatism criteria for diagnosing Sjögren's syndrome^[7]

staining (rose bengal, fluorescein, lissamine green). The pathogenesis of SS is multifactorial. Genetic susceptibility or viral infections are thought to cause dysregulation in both the innate and acquired immune systems (overactivation of B cells, increase in interferons, a role for Th1 and Th17 cells, and increase in the proinflammatory cytokines such as matrix metalloproteinases).^[8,9]

GVHD is the most common adverse event following allogeneic hematopoietic stem cell transplantation (HSCT), mediated by immune dysregulation and tissue inflammation.^[10,11] It occurs in about 30%–70% of the patients undergoing HSCT and usually within the first year following transplantation. Ocular involvement (oGVHD) is seen in 40%–60% of patients with GVHD, with a T-cell-mediated immune response that affects the lacrimal glands and conjunctiva.^[10,11] Although the main cause of ADDE in GVHD is lymphocytic infiltration of the accessory and major lacrimal glands, there can also be a decrease in the density of conjunctival goblet cells as well as Meibomian gland atrophy. The International Chronic oGVHD (ICCGVHD) consensus group diagnostic criteria [Fig. 4] can be used for diagnosis, which is based on the Ocular Surface Disease Index (OSDI) score, Schirmer's test, corneal staining, conjunctival injection, and presence of systemic GVHD.^[12]

Conjunctival cicatrization

Cicatrizing conjunctivitis is a chronic disorder with a common clinical presentation of conjunctival scarring. Some causes of cicatrizing conjunctivitis are nonprogressive, such as Stevens–Johnson syndrome (SJS), ocular chemical burns, and post-viral conjunctivitis, while others are progressive, such as mucus membrane pemphigoid (MMP) and drug-induced cicatrizing conjunctivitis (DICC).^[13] The clinical features vary from subtle subconjunctival fibrosis to gross ankyloblepharon.

The inflicting agent can be a local or systemic factor, causing nonprogressive or progressive cicatrization. It is important to identify the underlying cause since treatment varies accordingly.^[13] Herein, we briefly discuss the common ones seen in our Indian population.

SJS is an acute, potentially fatal, mucocutaneous blistering disease, which can be triggered by drugs or viral infections.^[14,15] The acute phase is life-threatening, wherein widespread denudation of skin and mucosa occurs as a result of a dysregulated immune response, mainly a T-cell-mediated, type IV hypersensitivity reaction.^[16] In addition, neutrophils deposit in the conjunctiva, leading to persistent inflammation and ocular surface damage.^[17] Bilateral conjunctivitis commonly goes unnoticed during the acute phase and later develops into cicatricial conjunctivitis.^[13,18] ADDE in individuals with SJS occurs due to the periductular fibrosis and obstruction of the ductules secondary to subconjunctival fibrosis observed in superotemporal fornix. The palpebral and orbital lobes of the lacrimal glands can have different grades of involvement ranging from distended to apoptotic acini, reduced secretory activity, and ultrastructural changes in myoepithelial cells.^[19]

MMP is a group of systemic autoimmune blistering diseases that cause chronic bilateral conjunctivitis leading to cicatrization. One subtype that presents predominantly with conjunctival involvement is ocular cicatricial pemphigoid (OCP or ocular MMP). It predominantly affects middle-aged women, manifesting as subtle conjunctival hyperemia and DED in the early phase, which if left untreated, can lead to conjunctival scarring, symblepharon, limbal stem cell deficiency, severe ADDE, and blinding keratopathy. The diagnosis of MMP is usually missed in the early phase due to nonspecific symptoms and signs. DICC is a condition

International Chronic ocular graft-versus-host disease (ICCGVHD) consensus group diagnostic criteria ¹²				
Severity Score (Points)	Schirmer's Test (mm)	Corneal fluorescein staining (points)	OSDI (points)	Conjunctival Injection (points)
0	>15	0	<13	None
1	11-15	<2	13-22	Mild/Moderate
2	6-10	2-3	23-32	Severe
3	≤5	≥4	≥33	

	None (points)	Probable GVHD (points)	Definite GVHD (points)
Systemic GVHD (-)	0-5	6-7	≥8
Systemic GVHD (+)	0-3	4-5	≥6

Figure 4: Diagnostic criteria laid by the international chronic ocular graft-versus-host disease consensus group.^[12]

clinically similar to MMP (pseudo-pemphigoid), where ocular surface cicatrization occurs as a reaction to the use of topical medications, commonly antiglaucoma medications, or rarely, some systemic drugs.^[20] The cicatrizing changes in DICC usually stop progressing once the inciting agent is withdrawn; however, the changes are irreversible. Also, an associated MMP must be excluded, since it can concurrently be present, in which case, long-term immunosuppression is needed.^[20] It is assumed that ADDE in MMP and DICC also occurs due to periductular fibrosis around the lacrimal gland, similar to SJS.

Neurogenic

As the human lacrimal gland is densely innervated with sympathetic and parasympathetic fibers, involvement of any component of the neural arc can result in ADDE. The possible etiologies in this category can be neurotrophic keratitis (NK), upper motor facial nerve palsy, diabetes mellitus (with or without associated NK), hypothyroidism, and rarely, hereditary sensory and autonomic neuropathy.^[21-23] Decreased innervation of the cornea results in NK, which can occur due to a list of reasons, the most common being herpetic infection.^[21] Normal corneal innervation is important since it initiates the blink reflex, has a role in maintaining the tear secretion pathway, and provides the neurotrophic factors necessary for epithelial cell homeostasis. Loss of corneal innervation causes altered epithelial healing, leading to persistent epithelial erosions (Grade 1 NK), defects (Grade 2 NK), or ulcers (Grade 3 NK).^[21] Patients usually have no complaints until the advanced stage, when the vision is impaired. In addition to an NK component, ADDE can also be seen as comorbid with neuropathic pain,^[24] in which nerves spontaneously fire, or fire inappropriately to environmental stimuli, producing symptoms such as burning and evoked pain to wind and light.

Alacrimia

Alacrimia can be congenital or acquired. Congenital alacrimia is a rare cause of pediatric ADDE with the absence of tear production from birth. It occurs due to abnormal/absent gland or ductal tissue.^[25] It can present with absent/hyposecretion of tears, severe multisystemic involvement, or developmental delay. Ectodermal dysplasia (ED) is a group

of congenital disorders which involves an abnormality in the development of one of the ectodermal derivatives such as hair, teeth, nail, and sweat glands. The anomalies in ED usually affect multiple organs and systems, hence requiring a multidisciplinary approach. Clinical manifestation includes scanty eyebrows and eyelashes and ichthyosis, with ocular surface features like keratitis, ectropion, lacrimal duct obstruction, blepharitis, absence of meibomian glands, limbal stem cell deficiency, and severe DED. Early recognition and treatment in pediatric age helps prevent the long-term blinding keratopathy in these patients.^[25,26] Further, the parasympathetic autonomic system needs to be evaluated to confirm the diagnosis.^[27] Acquired alacrimia can occur post-radiation therapy and after the surgical removal of lacrimal gland tumors.

Diagnosing ADDE in Clinics

The diagnosis of ADDE can be ascertained through a combination of clues obtained from the history and clinical examination of the patient [Fig. 5]. Below we describe the tests that are specific for picking up deficient lacrimal gland output in DED and then discuss the tests needed to comprehensively examine the eyelids and ocular surface. Identifying a reduction in tear volume in DED patients can also provide a clue that an individual has ADDE. It is critical to note that the diagnosis of SS is often made by the ophthalmologist, as symptoms of dry eyes are a presenting feature.^[14] As such, the ophthalmologist has opportunity to reduce the delay in initiating treatment and improve long-term quality of life by examining for ADDE and its accompanying features.

History

Dry eye symptoms are nonspecific in ADDE and can be similar to those of individuals with EDE. Symptoms include a sensation of dryness, burning or foreign body sensation, boring aching pain, and/or photophobia. Different dry eye questionnaires have been used to quantify symptoms, but no symptoms have been found to be specific for ADDE. A high suspicion of ADDE should be entertained if the patient gives a history of dry mouth, dry skin, and/or joint pains, history of allogeneic HSCT, or history of skin or mucous membrane involvement in the form of rashes, eruptions, or ulceration.

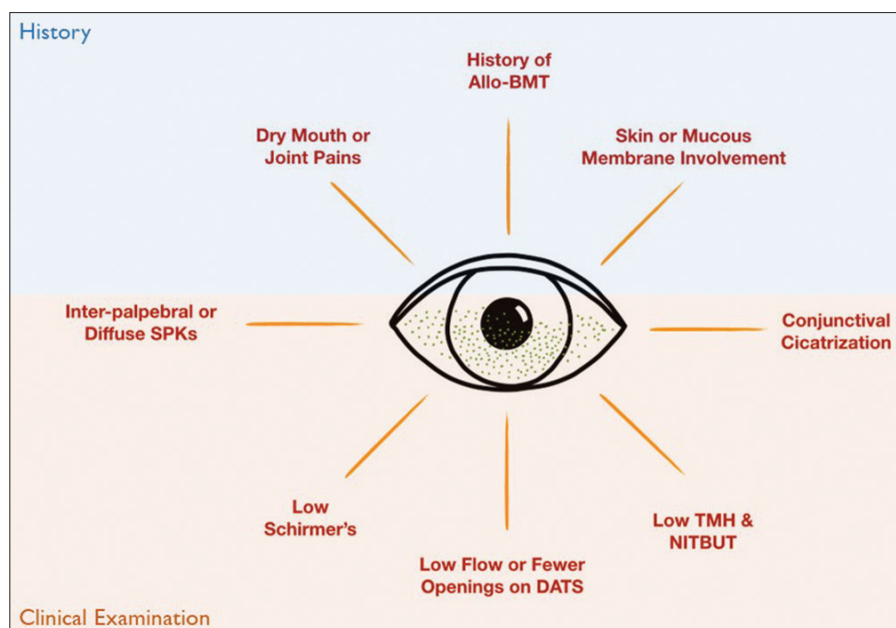


Figure 5: Clues in the patient's history and clinical findings that are suggestive of ADDE. ADDE = aqueous-deficient dry eye disease

In patients with DICC, characteristic temporal association of history of long-term use of medications, particularly antiglaucoma medications, and ocular surface changes helps in clinching the diagnosis.^[19]

Clinical examination of tear production and ocular surface

Schirmer test

A Whatman 41 filter paper is used for performing the Schirmer test, which measures the tear flow rate determined by measuring the length of wetting of the strip after 5 min. Historically, the Schirmer I test is performed without anesthesia and, thus, measures basal and reflex tearing. The Schirmer II test is also performed without anesthesia but is done following nasal stimulation and as such measures reflex tearing. The Schirmer test can also be performed with anesthesia, and this approach is thought to capture basal tearing. There is no consensus on the best way to perform the Schirmer test, and options include with or without anesthesia and with open or closed eyes. When performed with closed eyes and without anesthesia, the values show less variation.^[27] The authors recommend performing the test without anesthesia and not immediately after the instillation of eyedrops. The authors consider a value less than 10 mm to indicate aqueous deficiency. Other groups consider a value less than 5 mm as the cutoff for diagnosing ADDE.^[27]

Tear volume

Tear volume can be measured by assessing the tear meniscus height (TMH) on slit lamp or by using the anterior segment optical coherence tomography (OCT). TMH measured using OCT is more repeatable and reliable than slit-lamp-based assessment. However, even with OCT, the value is highly subjective, operator dependent, and variable, depending on the time of last blink, prior fluorescein instillation, time of the day, illumination, temperature, and surrounding humidity. The reported normal TMH value using SD-OCT is 0.19–0.34 mm (standard deviation [SD] 0.02–0.15 mm, spectral domain optical coherence tomography (SD-OCT)).^[28,29] The reported TMH value in ADDE of SS

etiology is 0.138 ± 0.05 mm and of non-SS etiology is 0.24 ± 0.081 mm, though specific etiology for non-SS ADDE is not mentioned.^[30] The TMH cutoff of 0.2 mm gave 98.3% sensitivity and 96.7% specificity in subjects diagnosed with ADDE based on the TFOS-DEWS II criteria.^[28] However, different OCT-based TMH studies have used different cutoffs for diagnosing ADDE.

Measuring TMH using spectral domain OCT has also been reported in ADDE. In one study, an OCT-measured TMH of $<141 \mu\text{m}$ had a 91% sensitivity compared to a combination of DED tests, which were taken as the gold standard.^[30] OCT-measured TMH has been reported the lowest in SS, followed by other causes of ADDE.^[29,31] However, it depends upon ADDE severity as well, and correlation of TMH and other measures of ADDE (Schirmer) needs to be studied. Swept-source OCT has also been used to measure TMH. One study reported the cutoff values of TMH, tear meniscus area, and volume of $191 \mu\text{m}$, $12,360 \mu\text{m}^2$, and 0.0473 mm^3 , respectively, as helpful in diagnosing DED but not specifically ADDE.^[30] Tear strip meniscometry is a device similar to Schirmer test, which helps in assessing the wetness of the eye. It has the added benefit that it is quick, provides results within 5 s, and is a noninvasive method to quantify the tear volume.^[32,33] However, its potential role in diagnosing ADDE or reliability in differentiating between types of DED is unclear. In clinical practice (without access to diagnostic devices), tear volume is assessed using Schirmer without anesthesia, and in eyes with variable readings or borderline values, lacrimal gland examination performed on slit lamp helps in differentiating the gland involvement in DED.

Lacrimal gland examination

Direct examination of the lacrimal gland's palpebral lobe can differentiate between ADDE and other causes of DED. The palpebral lobe of the lacrimal gland can be assessed on slit-lamp examination by asking the patient to look inferonasally while the examiner holds the upper eyelid

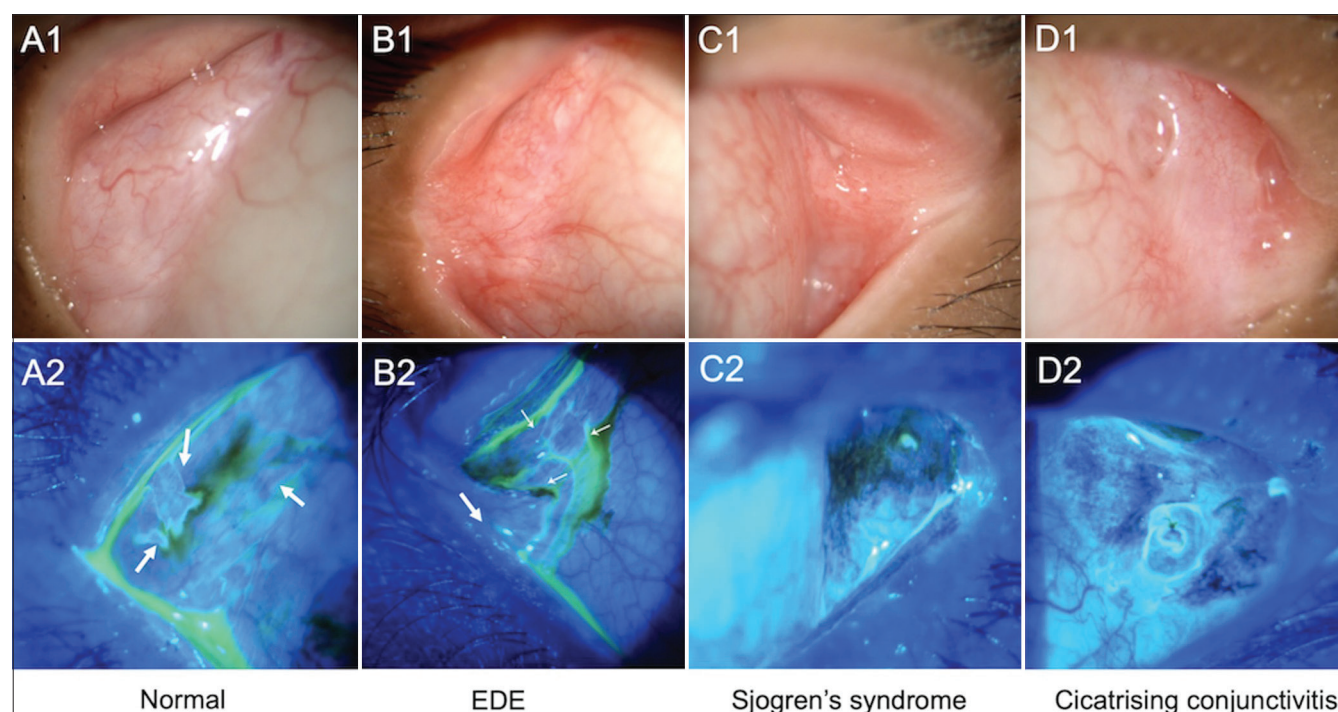


Figure 6: Direct lacrimal gland examination in healthy and patients with ADDE and EDE. (A1, A2, B1, B2) Convex, pinkish palpebral lobe appearance with three or four secreting points observed in normal and EDE patients, respectively. (C1, 2) A small left palpebral lobe of a secondary Sjögren's syndrome patient with only one secreting point, whereas in cicatrizing conjunctivitis, the palpebral lobe has whitish scarred appearance with a central area (spared of scarring) having secretory opening (D1, D2). ADDE = aqueous-deficient dry eye disease, EDE = evaporative dry eye

superotemporally. In normal individuals and those with EDE, the palpebral lobe has a convex shape and smooth surface with a pinkish appearance, while in ADDE, the lobe becomes smaller, flatter in contour, and can have areas of fibrosis in patients with a cicatricial etiology of ADDE [Fig. 6]. The gland area might not be visible due to symblepharon in cicatrizing conjunctivitis.^[34] Tear flow can be measured using a fluorescein strip applied over the exposed lobe area. The tear flow is significantly reduced in patients with ADDE compared to EDE.^[19,35] In patients with alacrimia, one can find absent palpebral lobe of the lacrimal gland clinically or absent orbital lobe alone on radiological imaging of the lacrimal gland.^[25] However, patients are symptomatic and have significant tear volume reduction in both total and isolated orbital lobe alacrimia.

Clinical examinations for other aspects of ocular surface health

Ocular surface staining

Due to the ongoing inflammation and subsequent injury to the epithelial cells and microvilli, the ocular surface often shows positive staining with vital dyes in individuals with ADDE. Sodium fluorescein, rose bengal, and lissamine green dyes are the most commonly used vital dyes. Positive fluorescein staining is seen when there is an epithelial defect or disruption in the tight junctions. Rose bengal stains devitalized cells and cells with absent mucin on the ocular surface, but associated stinging with instillation and reflex tearing limits its use in DED. Lissamine green stains the epithelial cells whose cell membrane is damaged. Our performed technique is to wet a fluorescein or lissamine green strip with one drop of saline and then lightly touch the

inferior temporal fornix in upgaze, while the lower eyelid is pulled temporally. The ocular surface is assessed between 1 and 3 min after instillation.^[27] Use of predetermined volume of 10 µl of dye has also been advised, but this degree of precision is difficult to achieve in the clinic. There is no consensus on a gold standard value that should be included under the umbrella of DED. Despite this, important aspects to notice include the type (micro-/macro-punctate, coalescent macro-punctate, or patch), extent, location, and depth of staining.^[27,36,37] In ADDE, typically, the staining is in the interpalpebral area involving the mid to inferior cornea and bulbar conjunctiva [Fig. 7]. Different grading systems have been used in DED, including the van Bijsterveld system, the National Eye Institute/Industry Workshop guidelines, and the Oxford ocular surface staining score, to name a few. Analysis of 3514 patients of Sjögren's International Collaborative Clinical Alliance Registry found that corneal staining with fluorescein and conjunctival staining with lissamine green (>5 on Oxford ocular surface staining score) was highly sensitive (91.1%) and specific (83.9%) for identifying patients of SS with keratoconjunctivitis sicca from SS patients without DED.^[38]

Tear stability

Tear film instability can occur in ADDE and tests like tear film breakup time (TBUT) and clearance pattern assessment measure the degree of instability. The TBUT measures the time taken for the appearance of the first dry spot after a complete blink. A value <10 s indicates tear instability; however, it is a subjective test.^[39,40] A study evaluated the different patterns of tear break up (area, line, spot, random) in 106 DED patients diagnosed using the Japanese dry eye

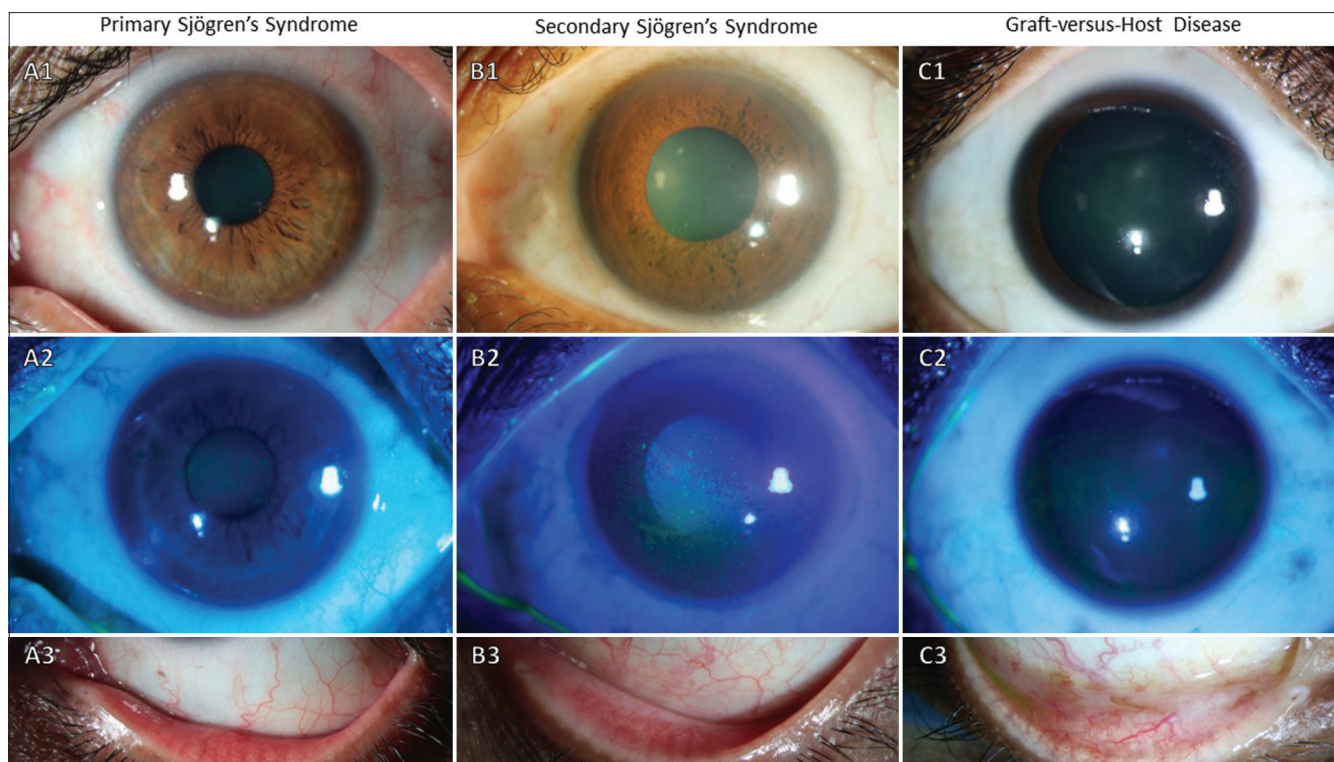


Figure 7: Clinical presentation of aqueous-deficient dry eye disease in patients with immune-mediated lacrimal gland damage. (A1–3) The ocular surface of the left eye of a middle-aged female with serology positive for primary SS. (B1–3) The left eye of a middle-aged female with secondary SS in the setting of rheumatoid arthritis. (C1–3) The right eye of a young male with GVHD. In all three cases, there is interpalpebral ocular surface staining, with minimal bulbar conjunctival congestion, and unlike the GVHD case (C3), no tarsal inflammation or forniceal shortening is noted in SS. GVHD = graft-versus-host disease, SS = Sjögren's syndrome

criteria (DED symptoms and TBUT ≤ 5 s or Schirmer ≤ 5 mm with positive staining). The fluorescein break in the shape of area and line correlated more with ADDE, rather than spot or random break shapes.^[41] Fluorescein dye itself can cause tear film instability, and instilling it is considered invasive by some. Hence, placido disk-based noncontact assessment of the tear film, known as noninvasive TBUT (NITBUT), was developed. Studies have found significant differences in TBUT and NITBUT values, and hence, these values cannot be used interchangeably. Overall, if the technology is available, an average value of multiple NIBUT measurements is preferred.^[42–44] A low NIBUT, on its own, however, does not differentiate between DED subtypes. One study found similar NIBUT times in 22 individuals with SS (6.36 ± 4.32 s) compared to 22 individuals with non-SS DED (7.98 ± 4.60 s).^[45] However, it is a useful metric to evaluate tear stability.

Meibomian gland health

Meibomian gland involvement in ADDE can be detected with clinical examination of lid margin (for vascular engorgement, irregularity, displacement of Marx line, or plugging of orifices), meibum quality (which can be graded as 0 [clear fluid], 1 [cloudy fluid], 2 [cloudy particulate], or 3 [toothpaste like]), expressibility of the central eight glands of the upper and lower eyelids, and meibography.^[27] Areas of gland loss and shortening of glands on meibography along with changes in meibum indicate abnormalities in the meibomian glands.

Examination for ocular surface scarring

The conjunctival changes in early stages of cicatricial ocular surface diseases can be easily missed unless we look carefully. The underlying pathology that we are most concerned about is MMP because it is progressive and can result in bilateral blinding keratopathy. It is, therefore, imperative to evert the eyelids and examine the lid margins, tarsal conjunctiva, medial and lateral canthal areas, and the fornices. Typically, patients with ocular MMP have diffuse bulbar conjunctival congestion, meibomian gland dropout, medial or lateral canthal fibrosis, or inferior forniceal foreshortening [Fig. 8]. An important differential of MMP is DICC, which can have specific features like periocular pigmentation, medial canthal fibrosis, and conjunctival fibrosis and keratinization which are more localized near the puncta and medial part of the inferior fornix.^[19] Patients with SJS typically have a definite history of skin necrolysis and hospital admission, pigmentary changes in the skin, nail changes, lid margin keratinization, and distichiasis.^[18] Most cases of cicatrizing conjunctivitis presenting with ADDE are limited to these three underlying diseases.

Nerve status

In vivo confocal microscopy of the lacrimal gland has been used to assess the acinar unit density, acinar unit diameter, and inflammatory cell density. However, it is difficult to use and specific data related to ADDE in large number of patients is not available.^[46] Confocal microscopy of the corneal sub-basal nerve plexus has been explored for differentiating the DED

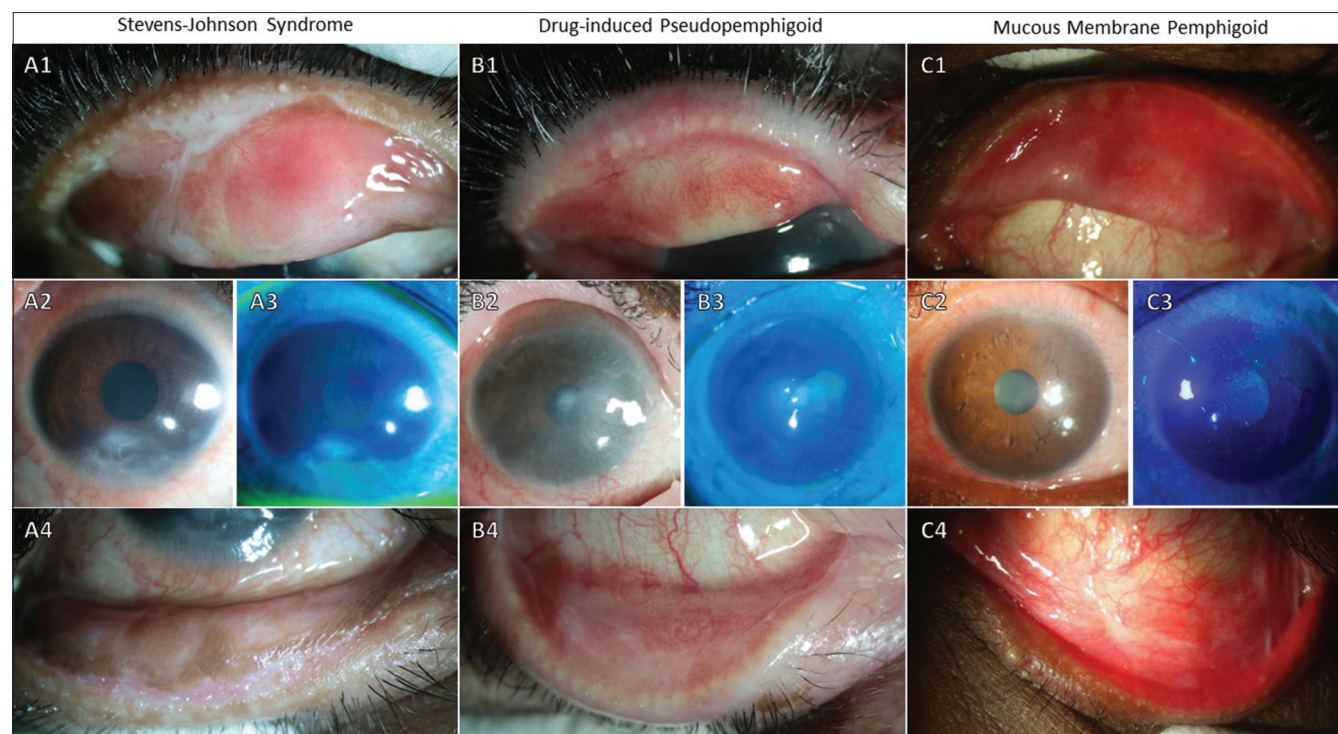


Figure 8: Clinical presentation of aqueous-deficient dry eye disease in patients with SS versus cicatrizing conjunctivitis. (A1-4) The ocular surface of the left eye of a middle-aged female with serology positive for primary SS. (B1-4) The left eye of a middle-aged female with secondary SS in the setting of rheumatoid arthritis. In both cases (a and b), there is interpalpebral staining on the corneal surface but no bulbar conjunctival inflammation or forniceal shortening. In case (C1-4), which is biopsy positive for mucus membrane pemphigoid, there is diffuse conjunctival congestion, along with corneal fluorescein staining and inferior forniceal foreshortening. SS = Sjögren's syndrome

subtypes. Studies have shown that patients with ADDE have an increase in nerve beading and an increase in dendritic cell number compared to controls; however, there is variability between studies and it is difficult to apply these findings to an individual patient.^[47,48]

Individuals with ADDE can have a component of NK, neuropathic pain, or both. The diagnosis of NK is made by finding decreased corneal sensation and some degree of corneal epithelial staining. A component of neuropathic pain should be considered when individuals report evoked pain to wind and light, when increased corneal sensitivity (based on prompt blink, head retraction with light touch of the cotton tip) is elicited, or when there is an overall disconnect between patient-reported symptoms and signs of disease. Clinical diagnosis of nerve involvement is based on cranial nerve examinations, assessing the corneal sensations, thorough ocular adnexal examination, and blink rate. Corneal sensations are checked with cotton tip or dental floss and are reported subjectively as normal, reduced, or hyperesthesia (increased based on prompt blink). Since the trigeminal nerve carries sensation from the ocular surface and periocular region, a palpation around the eye can provide information about allodynia and should be performed on both sides. A central component to pain is further suspected when individuals report persistent pain after topical anesthetic placement or report pain with light touch around the eye (i.e., cutaneous allodynia).^[23]

Tear osmolarity

Inflammation and increased osmolarity typically accompany ADDE. The TearLab Osmolarity System (TearLab Corporation,

San Diego, CA, USA) is currently the only US Food and Drug Administration (US FDA)-approved, commercially available, in-office device for measuring tear film osmolarity, with results available in a few seconds. Normal tear osmolarity has a value around 302 mOsm/L, with an inter-eye difference of less than 8 mOsm/L. Usually, a value above >308 mOsm/L or a difference between the eyes >8 mOsm/L is considered abnormal, but there are studies where different cutoffs have been used (308–315 mOsm/L).^[27,49,50] Tear osmolarity increases with disease severity and displays higher variation at higher levels. There are conflicting reports about its utility as a differentiator between normal and DED patients.^[4,49] The average osmolarity in 629 subjects with DED was no different than in 29 healthy subjects (310.6 ± 16.2 vs. 310.3 ± 19.4 mOsm/L). Tear osmolarity has not been studied as a marker to differentiate between ADDE and EDE.

Cytokines and biomarkers

Matrix metalloproteinase-9 (MMP-9) is an important endopeptidase released in the tear film due to chronic inflammation and extracellular matrix remodeling. MMP-9 destroys the tight junctions and causes loss of the ocular surface barrier function. Currently, InflammDry® (Quidel, San Diego, CA, USA) is the only FDA-approved device for the semi-quantitative detection of MMP-9 in patients. In one study, raised MMP-9 levels predicted reduction in tear production over the next 6 months.^[51] However, MMP-9 can be elevated in a number of chronic inflammatory conditions, such as with microbial keratitis, and hence, the test is nonspecific for DED.^[52-54] Lactoferrin and lysozyme have also been explored

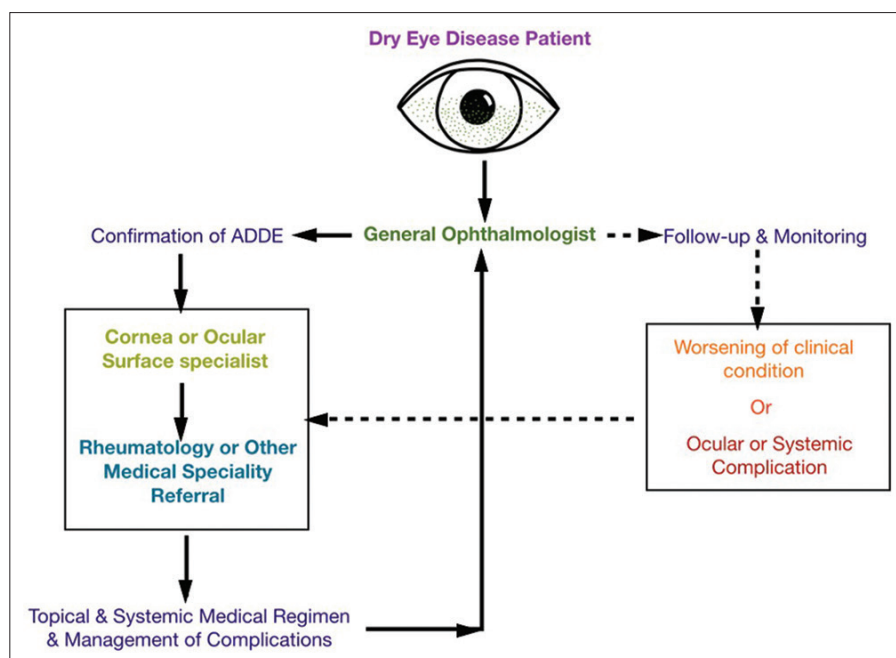


Figure 9: The multidisciplinary teamwork and coordination needed to diagnose and comprehensively manage patients with ADDE. Once the diagnosis of ADDE is confirmed by the general ophthalmologist, the patient can be referred to a cornea/ocular surface specialist, who in conjunction with a rheumatologist, dermatologist, and/or oncologist can prepare the treatment plan and systemic medical regimen, as needed. The patient can then be followed by the general ophthalmologist, who can refer the patient back in case of worsening of symptoms or in the event of corneal or systemic complications. ADDE = aqueous-deficient dry eye disease

as surrogate markers for lacrimal gland damage. Their levels are said to decrease in conditions such as SS; however, their application in the clinical setting to diagnose ADDE is yet to be determined.^[55-58]

Tests for cicatricial etiology

In eyes with a cicatricial ADDE etiology, after ruling out SJS,^[18] conjunctival biopsy is performed to evaluate for MMP. The diagnosis is made by observing IgG, IgM, or complement deposition at the basement membrane zone by direct immunofluorescence. However, a negative biopsy result is still possible in individuals with MMP.^[59] To maximize accuracy, the biopsy should be taken from noninflamed conjunctiva and transferred appropriately to the laboratory. Some studies have shown that about 25% of patients need a repeat biopsy for a positive result.^[59] In patients with negative biopsy and strong suspicion of MMP, clinical cues can help in reaching the diagnosis and treatment of MMP is pursued.^[13] As MMP is a progressive, blinding disease, an increase in lacrimal gland damage over time is likely if individuals are not treated with systemic immunosuppressives.

Blood work-up for underlying systemic disease

Since ADDE can be associated with an underlying systemic disease like SS, a systemic work-up to identify potential causes of disease is very important. For SS, anti-Ro/La antibodies are evaluated which are part of the diagnostic criteria. However, not all patients with SS (diagnosed by clinical signs and positive biopsy) show antibody positivity. For such patients, rheumatoid factor, C-reactive protein, and anti-citrullinated peptide antibody can be tested.^[6,60] Consultation with a rheumatologist is helpful in diagnosing suspected underlying autoimmune diseases, as they can advise on which tests to order (ANA profile, serum antinuclear antibody, angiotensin

converting enzyme (ACE)) based on patients' symptoms and signs [Fig. 9].

Management of ADDE

The prescribed step-by-step approach is based on the confirmation of aqueous deficiency as the cause of DED and elucidating the underlying cause of ADDE. In cases with suspected immune etiology, collaboration with a rheumatologist can be of benefit in a patient with both ocular and systemic involvement. Signs of conjunctival cicatrization necessitate a referral to an ocular surface disease specialist to assist in diagnosis. Once the cause has been established and disease-specific systemic therapy, if necessary, has been initiated, several therapeutic and surgical approaches can help in improving signs and symptoms of disease. The mechanisms of action of different topical drugs used for ADDE are highlighted in Fig. 10.

Nonspecific therapy in ADDE

Lubricants

Since the root cause of symptoms and signs of DED is a deficiency of tears, tear substitutes are used as the first-line agents in ADDE management. They lubricate the ocular surface, increase the tear film reservoir, and stabilize osmolarity. There are various types of artificial tears available that mimic the different layers of tear film; hence, they must be individualized as per the patient's need. The various formulations available include cellulose ethers, carbomers, polyvinyl alcohol, and lipid-based formulations, which mainly differ in their viscosity and retention power. Many of these products are mixed with preservatives, which cause a stinging sensation upon instillation and worsen symptoms temporarily. Since the preservative itself can cause ocular surface toxicity, a preservative-free compound is preferred for patients with severe DED.^[61,62]

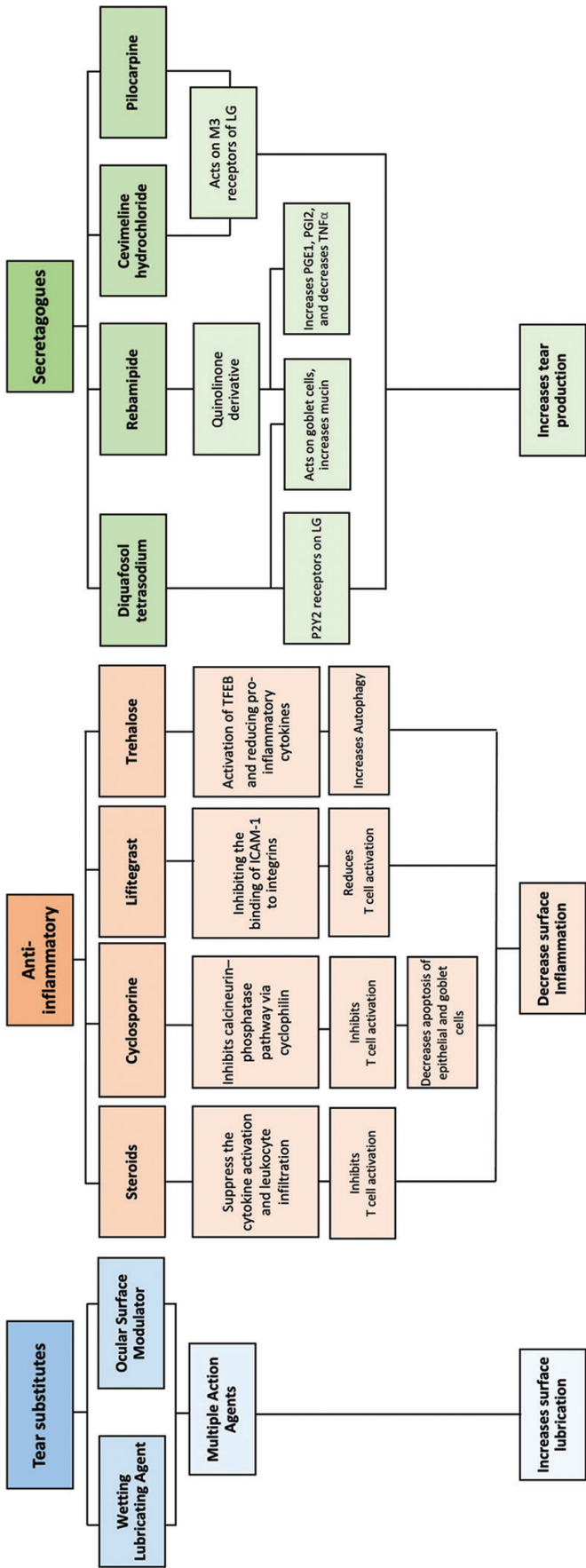


Figure 10: Classification, mechanism of action, and the effect on ocular surface of various topical drugs used in the treatment of ADDE. ADDE = aqueous-deficient dry eye disease, ICAM-1 = intercellular adhesion molecule 1, LG = lacrimal gland, M3 = muscarinic 3, PG = prostaglandins, TFEB = transcription factor EB, TNF- α = tumor necrosis factor- α

Topical immunosuppressants or immunomodulators

Most cases of ADDE have a component of inflammation and immune system dysregulation. ADDE of cicatricial etiology usually has persistent ocular surface inflammation. As such, topical immunosuppressive agents and immune modulators are often used in ADDE. Topical corticosteroids are generally used for a short term to address ocular surface inflammation. However, as their long-term use is associated with various side effects, immunomodulatory drugs are preferred. Cyclosporine A (CsA) inhibits T-cell activation by inhibiting the calcineurin–phosphatase pathway. It also reduces the apoptosis of goblet cells. Several strengths of CsA are approved by the FDA, including 0.05%, 0.09%, and 0.1% (the latter of which is approved for atopic keratoconjunctivitis and not dry eye). The 0.05% cyclosporine emulsion (Restasis; Allergan Inc., Irvine, CA, USA) showed increase in tear production and reduced ocular surface staining in a randomized clinical trial of 877 subjects with ADDE (Schirmer <5 mm at 5 min).^[63–64] A preservative-free nanoformulation of cyclosporine, 0.09% cyclosporine aqueous solution (Cequa; Sun Pharmaceutical Industries, Inc., Cranbury, NJ, USA), has shown better drug penetration in the conjunctival and scleral tissues of New Zealand white rabbits, compared to 0.05% cyclosporine emulsion. Studies have shown a reduction in conjunctival and corneal staining with an increase in Schirmer values at 3 months of its use in 371 DED patients (diagnosed based on symptom and conjunctival staining score ≥ 3). Of note, the mean baseline Schirmer value was 11.9 ± 7.8 mm in this population, and hence, not all individuals had ADDE.^[65] Lifitegrast 5% (Xiidra; Novartis, East Hanover, NJ, USA), is a nanoparticle formulation that inhibits the binding of intercellular adhesion molecule 1 (ICAM-1) to lymphocyte function-associated antigen 1 (LFA-1) required for T-cell activation and was approved in 2016 for DED. A reduction in corneal staining score and an improvement in symptomatology were observed in 718 subjects with DED (<10 mm Schirmer and >2 corneal staining score) who used lifitegrast for 84 days. Its efficacy for mild–moderate DED has been established, but further studies are needed for severe ADDE.^[66–69] Many other anti-inflammatory and immune-modulatory molecules are under investigation, including an siRNA inhibitor, a nonspecific kinase inhibitor, the tear protein lacritin, and tumor necrosis factor (TNF) inhibitors. Multiple other treatment modalities to promote the body's natural anti-inflammatory mechanism are described, which include oral supplementation with omega-3 polyunsaturated fatty acids (PUFAs), curcumin, and antioxidants, which suppress interleukins and the inflammatory cascade.^[70,71] However their specific role in ADDE is uncertain.

Secretagogues

These are drugs which mainly act on the receptors in the ocular surface and help in increasing the tear production. Diquafosol tetrasodium, 3% ophthalmic solution, currently approved in Japan for patients with DED, acts on P2Y2 receptors in the conjunctiva, meibomian and lacrimal glands, and corneal and conjunctival epithelium.^[72] It increases tear production by increasing intracellular calcium and stimulating fluid and mucin secretion from conjunctival epithelial and goblet cells.^[72] Thus, it is believed that diquafosol achieves rehydration of the ocular surface independent of the lacrimal gland secretion. In a study of 15 individuals with ADDE, diquafosol improved

ocular surface staining, TMH, and symptoms when used for 6 months.^[72,73] However, no significant change was noted in Schirmer values, contrary to it being a secretagogue. Rebamipide 2% increases both the membrane-associated and secreted mucins by acting on the conjunctival goblet cells and corneal epithelial cells, causing improved surface healing and an increase in tear film stability. In addition, it prevents macrophage infiltration into the conjunctiva by increasing prostaglandins (PGE2 and PGI2) and reducing TNF- α , with an overall effect of lowering ocular surface inflammation. In a study of 308 individuals with DED (not ADDE specifically), 4 weeks of rebamipide use improved ocular surface staining, TBUT, and symptoms of DED, but no change in Schirmer values was noted.^[74–77] Cevimeline hydrochloride, a cholinergic agonist, binds to muscarinic acetylcholine receptors, thereby increasing lacrimal gland secretion.^[78,79] Four weeks of cevimeline 20 mg three times a day improved corneal staining in 47% of SS patients (total = 19), with a mean change of 0.9 ± 2.22 in Schirmer with anesthesia test. Oral pilocarpine has a similar mechanism and has been used to increase both salivary and aqueous tear production. It has been shown to improve symptoms of dry mouth and dry eye and the salivary flow rate in 373 individuals with SS, but objective signs related to DED were not studied.^[80] Hence, its efficacy in improving tear secretion is uncertain. Recently, a nasal spray, varenicline (Tyrvaya; Oyster Point Pharma, New Jersey, USA), has shown promising results in improving tear production in ADDE. It acts by stimulating the nicotinic receptors in nasal mucosa which relay signals to the secretomotor pathway of the lacrimal gland.^[81]

Autologous serum

Serum has lysozyme, fibronectin, vitamin A, and others, which resemble the constituents of natural tears needed for maintenance of the ocular surface and are thus a good option for supplementation in patients with ADDE. In a study of 20 individuals with severe ADDE (mean Schirmer of 3.8 mm), 20% autologous serum (higher concentration of 50% has also been used) was useful in reducing symptoms and improving corneal staining.^[82]

Alternative therapies

Scleral contact lenses are used in ADDE with severe epitheliopathy when conventional treatments have failed to offer symptomatic relief. These large-diameter lenses are commonly used in cicatricial ADDE. Neuronal stimulation to increase the tear production has shown to be an effective treatment approach for lacrimal gland-associated ADDE. Intranasal anterior ethmoidal nerve stimulation done with TrueTear (Allergan, Dublin, Ireland) increased tear production compared to sham treatment in 48 individuals with ADDE (<10 mm Schirmer values).^[83] However, the product is no longer available. The iTEAR[®]100 device, which is currently available, stimulates the anterior ethmoidal nerves from an external approach. Studies have shown reduction in OSDI scores and an increase in post-stimulation Schirmer value in 101 individuals with anesthetized Schirmer value of <10 mm pre-stimulation. However, for enrollment, subjects were required to demonstrate an increase of 10 mm in Schirmer value upon nasal stimulation using a cotton wisp.^[84] Hence, this study only examined subjects who could obtain a 10 mm improvement with simple nasal stimulation.

Trehalose, present naturally in various species of plants and nonmammalian animals, is a disaccharide with high water retention ability. It protects the corneal epithelium against desiccation, inflammation, and apoptosis occurring due to hyperosmotic and oxidative stress and also has an adjuvant role in autophagy, thereby possibly improving tear film homeostasis in DED.^[85] Other treatment alternatives being studied in ADDE include royal jelly, platelet-rich plasma, omega-3 fatty acids, and botulinum toxin A. However, further studies are needed to test their safety and efficacy in ADDE.^[86,87]

Punctal occlusion

Punctal occlusion can be done by insertion of punctal plugs or by performing punctal cautery. These are useful in patients with moderate to severe ADDE to block the drainage pathway of the tears, thereby increasing tear retention. However, there is some concern that occluding the lacrimal punctum may build up the inflammatory load in the conjunctival sac, and thus, it is recommended that ocular surface inflammation be controlled before placement. Of 80 patients with DED, punctal plugs improved symptoms (in 54%) and decreased the frequency of lubricant instillation but the outcomes specific to ADDE are not known.^[88] However, there is no conclusive evidence that punctal plugs are superior to other treatments such as topical lubricants or secretagogues. Punctal cautery has also been used in individuals with chronic severe ADDE, especially for those with punctal plug fitting issues. The evidence is of low certainty regarding the effects of punctal cautery on dry eye symptoms, tear volume, and ocular staining in a Cochrane review.^[89] Furthermore, the intervention may need to be repeated due to recanalization, especially when concurrent steroids are used.^[88,89]

Disease-specific therapy in ADDE

Systemic immunomodulation in SS

Patients with primary SS who have ocular involvement in isolation are usually managed with topical immunomodulation. Systemic immunosuppression is indicated when the disease is progressive and extraglandular involvement, such as arthritis or Raynaud's phenomenon, is seen.^[5,8] Mild cases are managed with hydroxychloroquine, while those with moderate to severe disease are treated with oral corticosteroids and nonsteroidal immunosuppressive agents.^[5,8] The latter group includes mycophenolate mofetil. The primary underlying autoimmune disease in patients with secondary SS usually dictates the immunomodulatory agent chosen. Additionally, the duration of disease and the severity at presentation also determine the type and degree of immunosuppression instituted. Oral methotrexate is preferred as a first-line agent in patients who have RA.^[60] This medication has a once-weekly dosing regimen and an overall safe side effect profile.^[90] Both oral azathioprine and mycophenolate mofetil are used as second-line agents, and several biological agents (e.g., adalimumab, rituximab, and tocilizumab) have shown promising results in controlling the disease progression.^[88] A similar protocol which combines oral corticosteroids with calcineurin inhibitors and antimetabolites is also considered in patients with SLE.^[91]

Systemic immunosuppression in MMP

MMP (including the subtype OCP) is a progressive group

of diseases, which if left unchecked, can lead to sight- and globe-threatening sequelae. As discussed earlier, these are autoimmune disorders, and thus require systemic immunosuppression for their management.^[90,92] Several agents have been described for the control of inflammation in MMP, and a step ladder approach has been proposed to systematically manage this entity. The first line of therapy for cases with mild disease is dapsone, and screening of cases with glucose-6-phosphate dehydrogenase deficiency is required to prevent hemolytic anemia.^[90,92,93] Patients with moderately severe disease are started on a course of oral corticosteroid (prednisolone 1 mg/kg/day), which is given as a tapering dose.^[90] This is combined with methotrexate, mycophenolate mofetil, or azathioprine to provide long-term immunosuppression.^[92,93] Patients who present with a severe stage of the disease or with acute exacerbations will require a pulse dose of intravenous methylprednisolone in isolation or in combination with intravenous cyclophosphamide.^[90,92] Biologic agents (infliximab, etanercept, and rituximab) and intravenous immunoglobulins have been proven to be efficacious in patients with refractory disease.^[92]

Minor salivary gland transplantation for cicatricial severe ADDE

The surgery was first described in 1997 for patients with severe ADDE (<2 mm Schirmer value) of cicatricial origin and persistent symptoms despite lubricant use.^[94] The graft tissue is obtained from the oral labial mucosa and transplanted onto the posterior eyelid lamella or the conjunctival fornix. It has been reported to improve Schirmer values by an average of 2–4 mm. Clinical tests can be helpful while selecting the donor site of the graft tissue. Fluorescein strip is applied to assess the number of functional openings and the secretory rate of the glands. This can be done preoperatively while selecting the graft site and postoperatively in the transplanted graft on the ocular surface.^[95,96] Minor salivary gland transplantation (MSGT) is not recommended in Sjögren's type of DED, since the underlying disease process affects both the salivary and the lacrimal glands and hence would not be beneficial in these patients.^[94]

ADDE with NK

Treatment varies based on the stage of the disease: stage 1 (punctate keratopathy) mainly needs lubricants and eyelid taping; stage 2 (persistent epithelial defects with rolled edges) requires a bandage contact lens, aggressive topical lubricants and steroids, autologous serum eye drops, and tarsorrhaphy; and stage 3 (ulcer) is difficult to treat and requires surgical interventions such as amniotic membrane transplantation (AMT), conjunctival flap, or corneal neurotization.^[96] Recent studies show the efficacy of topical formulation of recombinant nerve growth factor cenegermin (Oxervate; Dompé Farmaceutici SpA, Milan, Italy) with faster healing rates and reduced recurrences of epithelial defects compared to placebo. As such, it is now a preferred treatment in the USA for stage 2 and 3 NK.^[94]

ADDE with neuropathic component to pain

Treatment of neuropathic ocular pain is evolving, but topical, periocular, and oral neuromodulatory agents can all be considered. Topically, autologous serum eye drops are often used in individuals with a suspected peripheral component of pain. A transient receptor potential vanilloid subtype 1 antagonist is being studied as a treatment for

persistent postoperative pain. Scleral contact lenses can be considered as they may help decrease firing in sensitizing nerves.^[97] Periocular neuromodulatory strategies include botulinum toxin injections and nerve stimulators. Oral approaches are those used for neuropathic pain outside the eye, including pregabalin, nortriptyline, and topiramate, to name a few. These agents are often coupled with mood stabilizers such as duloxetine (a serotonin- and norepinephrine-reuptake inhibitor). Vitamin deficiencies should also be investigated, such as Vitamin B12 deficiency.^[98] Vitamin B12 promotes reinnervation and re-epithelialization of the corneal surface by hindering the nociceptive activity.^[99-102]

Unmet Needs and Future Directions

Gut microbiome modulation in SS

Altered gut microbiome has been implicated in the pathophysiology of autoimmune conditions such as SS and associated DED.^[103] As such, supplementation with probiotics or metabolites of commensal bacteria have been discussed as an approach for the treatment of DED. Another approach is the transplant of healthy fecal flora, a therapy known as fecal microbial transplant. However, this treatment modality is still in its initial stages, and further trials are needed to prove its efficacy and safety and to establish the effective route of microbiome transfer.^[91,104-106]

Mesenchymal stem cell therapy for lacrimal gland regeneration

Mesenchymal stem cells (MSCs) possess immunomodulatory properties, are easily available, and have multilineage differentiation abilities. They also have anti-inflammatory properties by inhibiting the activation and proliferation of T cells and upregulating anti-inflammatory cytokines. Hence, they are useful in treating patients with autoimmune DED. Injection of MSCs into the lacrimal gland has shown to decrease infiltration of CD4⁺ cells. It has a potential role in treating patients with severe, refractory ADDE and steroid-resistant GVHD.^[80,107,108]

Bioengineered lacrimal gland

Lacrimal gland regeneration using MSCs is one of the main focuses of current research, which is gaining popularity.^[109-111] Further advances include the development of bioengineered lacrimal glands producing tears mimicking human tears in composition.^[112] Researchers have also established 3D organoids of the human lacrimal gland, which can engraft and produce mature tear products after orthotopic transplantation in mice.^[113] Organoids can be expanded over multiple months and recapitulate morphological and transcriptional features of lacrimal ducts. These breath-taking novel approaches are awaiting clinical translation.

Conclusion

ADDE, although less common than EDE, is the more serious clinical form of DED as it may cause long-term ocular morbidity and impair vision. Therefore, timely diagnosis and initiation of treatment is key in preventing chronic complications of ADDE. This requires a high index of suspicion in patients with complaints of dryness associated with dry mouth, dry skin, and joint pains and a history of associated systemic diseases or of allogeneic HSCT. In autoimmune conditions like SS,

ADDE may be the first manifestation of the systemic disease, even before antibody positivity,^[62] which emphasizes the important role of ophthalmologist in caring for these patients. It is also imperative to understand that some ADDE patients will have an underlying systemic disease, and therefore, multidisciplinary care with a rheumatologist, dermatologist, and/or hemato-oncologist may be required. It is also equally important to rule out clinical masquerades, especially patients with EDE, to avoid unnecessary systemic evaluation or medication. Sometimes, the underlying cause can be the use of topical or systemic medications, and their simple withdrawal can reverse symptoms. Once the diagnosis of ADDE has been confirmed clinically, it is best for a general ophthalmologist to refer these patients to an ocular surface clinic, where the necessary systemic evaluation and consultation with other medical specialists, if required, is possible. It is critical to understand that adequate care of many cases of ADDE is not possible through symptomatic or palliative treatment with topical lubricants and anti-inflammatory medications alone. This is particularly true for conjunctival cicatrizing diseases like MMP that can progress relentlessly without systemic therapy and lead to devastating keratopathy and blindness. This review summarizes the elements that the authors feel are key to confirming the diagnosis of ADDE, identifying the underlying cause, and initiating appropriate therapy to improve the lives of patients afflicted with this condition.

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Conflicts of interest

There are no conflicts of interest.

References

- Donthineni PR, Kammari P, Shanbhag SS, Singh V, Das AV, Basu S. Incidence, demographics, types and risk factors of dry eye disease in India: Electronic medical records driven big data analytics report I. *Ocul Surf* 2019;17:250-6.
- Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II epidemiology report. *Ocul Surf* 2017;15:334-65.
- Galor A, Levitt RC, Felix ER, Sarantopoulos CD. Understanding the true burden of dry eye disease. *Expert Rev Ophthalmol* 2015;10:403-5.
- Craig JP, Nelson JD, Azar DT, Belmonte C, Bron AJ, Chauhan SK, et al. TFOS DEWS II report executive summary. *Ocul Surf* 2017;15:802-12.
- Negrini S, Emmi G, Greco M, Borro M, Sardanelli F, Murdaca G, et al. Sjögren's syndrome: A systemic autoimmune disease. *Clin Exp Med* 2022;22:9-25.
- Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: A revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554-8.
- Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/ European League against rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol* 2017;69:35-45.

8. Wang J, Zhou L, Liu B. Update on disease pathogenesis, diagnosis, and management of primary Sjögren's syndrome. *Int J Rheum Dis* 2020;23:723-7.
9. Tian Y, Yang H, Liu N, Li Y, Chen J. Advances in pathogenesis of Sjögren's syndrome. *J Immunol Res* 2021;2021:5928232.
10. Carreno-Galeano JT, Dohlman TH, Kim S, Yin J, Dana R. A review of ocular graft-versus-host disease: Pathophysiology, clinical presentation and management. *Ocul Immunol Inflamm* 2021;29:1190-9.
11. Nair S, Vanathi M, Mukhija R, Tandon R, Jain S, Ogawa Y. Update on ocular graft-versus-host disease. *Indian J Ophthalmol* 2021;69:1038-50.
12. Ogawa Y, Kim SK, Dana R, Clayton J, Jain S, Rosenblatt MI, *et al.* International chronic ocular graft-vs-host-disease (GVHD) consensus group: Proposed diagnostic criteria for chronic GVHD (Part I). *Sci Rep* 2013;3:3419.
13. Vazirani J, Donthineni PR, Goel S, Sane SS, Mahuvakar S, Narang P, *et al.* Chronic cicatrizing conjunctivitis: A review of the differential diagnosis and an algorithmic approach to management. *Indian J Ophthalmol* 2020;68:2349-55.
14. Kohanim S, Palioura S, Saeed HN, Akpek EK, Amescua G, Basu S, *et al.* Stevens-Johnson syndrome/toxic epidermal necrolysis--A comprehensive review and guide to therapy. I. Systemic disease. *Ocul Surf* 2016;14:2-19.
15. Patel TK, Barvaliya MJ, Sharma D, Tripathi C. A systematic review of the drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Indian population. *Indian J Dermatol Venereol Leprol* 2013;79:389-98.
16. Charlton OA, Harris V, Phan K, Mewton E, Jackson C, Cooper A. Toxic epidermal necrolysis and Steven-Johnson syndrome: A comprehensive review. *Adv Wound Care (New Rochelle)* 2020;9:426-39.
17. Kohanim S, Palioura S, Saeed HN, Akpek EK, Amescua G, Basu S, *et al.* Acute and chronic ophthalmic involvement in Stevens-Johnson syndrome/toxic epidermal necrolysis - A comprehensive review and guide to therapy. II. Ophthalmic disease. *Ocul Surf* 2016;14:168-88.
18. Shanbhag SS, Chanda S, Donthineni PR, Sane SS, Priyadarshini SR, Basu S. Clinical clues predictive of Stevens-Johnson syndrome as the cause of chronic cicatrizing conjunctivitis. *Br J Ophthalmol* 2020;104:1005-9.
19. Singh S, Mishra DK, Shanbhag S, Vemuganti G, Singh V, Ali MJ, *et al.* Lacrimal gland involvement in severe dry eyes after Stevens-Johnson syndrome. *Ophthalmology* 2021;128:621-4.
20. Singh S, Donthineni PR, Shanbhag SS, Senthil S, Ong HS, Dart JK, *et al.* Drug induced cicatrizing conjunctivitis: A case series with review of etiopathogenesis, diagnosis and management. *Ocul Surf* 2022;24:83-92.
21. Dua HS, Said DG, Messmer EM, Rolando M, Benitez-Del-Castillo JM, Hossain PN, *et al.* Neurotrophic keratopathy. *Prog Retin Eye Res* 2018;66:107-31.
22. Singh S, Das AV, Ali MH. Ocular involvement in facial nerve paralysis: Risk factors for severe visual impairment and ocular surface exposure in 1870 patients. *Orbit* 2022;1-6. doi: 10.1080/01676830.2022.2090013.
23. Yoo TK, Oh E. Diabetes mellitus is associated with dry eye syndrome: A meta-analysis. *Int Ophthalmol* 2019;39:2611-20.
24. Rosenthal P, Borsook D. Ocular neuropathic pain. *Br J Ophthalmol* 2016;100:128-34.
25. Singh S. Congenital alacrimia with lacrimal gland hypoplasia. *Orbit* 2021;1. doi: 10.1080/01676830.2021.1942503.
26. Gupta N, Farooqui JH, Agni M, Kumar A, Sharma M, Mathur U. Alacrima, a rare cause of pediatric dry eye. *J AAPOS* 2018;22:233-5.
27. Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, *et al.* TFOS DEWS II diagnostic methodology report. *Ocul Surf* 2017;15:539-74.
28. Singh A, Vanathi M, Kishore A, Gupta N, Tandon R. Evaluation of strip meniscometry, tear meniscus height and depth in the diagnosis of dry eye disease in asian Indian eyes. *Ocul Surf* 2019;17:747-52.
29. Akiyama R, Usui T, Yamagami S. Diagnosis of dry eye by tear meniscus measurements using anterior segment swept source optical coherence tomography. *Cornea* 2015;34(Suppl 11):S115-20.
30. Qiu X, Gong L, Lu Y, Jin H, Robitaille M. The diagnostic significance of Fourier-domain optical coherence tomography in Sjögren syndrome, aqueous tear deficiency and lipid tear deficiency patients. *Acta Ophthalmol* 2012;90:e359-66.
31. Nichols KK, Mitchell GL, Zadnik K. The repeatability of clinical measurements of dry eye. *Cornea* 2004;23:272-85.
32. Dogru M, Ishida K, Matsumoto Y, Goto E, Ishioka M, Kojima T, *et al.* Strip meniscometry: A new and simple method of tear meniscus evaluation. *Invest Ophthalmol Vis Sci* 2006;47:1895-901.
33. Ibrahim OM, Dogru M, Ward SK, Matsumoto Y, Wakamatsu TH, Ishida K, *et al.* The efficacy, sensitivity, and specificity of strip meniscometry in conjunction with tear function tests in the assessment of tear meniscus. *Invest Ophthalmol Vis Sci* 2011;52:2194-8.
34. Singh S, Shanbhag SS, Basu S. Palpebral lobe of the human lacrimal gland: Morphometric analysis in normal versus dry eyes. *Br J Ophthalmol* 2021;105:1352-7.
35. Singh S, Shanbhag SS, Basu S. Tear secretion from the lacrimal gland: Variations in normal versus dry eyes. *Br J Ophthalmol* 2022;106:772-6.
36. Begley C, Caffery B, Chalmers R, Situ P, Simpson T, Nelson JD. Review and analysis of grading scales for ocular surface staining. *Ocul Surf* 2019;17:208-20.
37. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea* 2003;22:640-50.
38. Gonzales JA, Shiboski SC, Bunya VY, Akpek EK, Rose-Nussbaumer J, Seitzman GD, *et al.* Ocular clinical signs and diagnostic tests most compatible with keratoconjunctivitis sicca: A latent class approach. *Cornea* 2020;39:1013-6.
39. Lemp MA, Hamill JR Jr. Factors affecting tear film breakup in normal eyes. *Arch Ophthalmol* 1973;89:103-5.
40. Tsubota K. Short tear film breakup time-type dry eye. *Invest Ophthalmol Vis Sci* 2018;59:DES64-70.
41. Yokoi N, Georgiev GA, Kato H, Komuro A, Sonomura Y, Sotozono C, *et al.* Classification of fluorescein breakup patterns: A novel method of differential diagnosis for dry eye. *Am J Ophthalmol* 2017;180:72-85.
42. Hong J, Sun X, Wei A, Cui X, Li Y, Qian T, *et al.* Assessment of tear film stability in dry eye with a newly developed keratograph. *Cornea* 2013;32:716-21.
43. Fuller DG, Potts K, Kim J. Noninvasive tear breakup times and ocular surface disease. *Optom Vis Sci* 2013;90:1086-91.
44. Cho P, Douthwaite W. The relation between invasive and noninvasive tear break-up time. *Optom Vis Sci* 1995;72:17-22.
45. Zhao S, Le Q. Analysis of the first tear film break-up point in Sjögren's syndrome and non-Sjögren's syndrome dry eye patients. *BMC Ophthalmol* 2022;22:1.
46. Spurr-Michaud S, Argüeso P, Gipson I. Assay of mucins in human tear fluid. *Exp Eye Res* 2007;84:939-50.
47. Hwang J, Dermer H, Galor A. Can *in vivo* confocal microscopy differentiate between sub-types of dry eye disease? A review. *Clin Exp Ophthalmol* 2021;49:373-87.
48. Mercado C, Muñoz-Ortiz J, Godin F, Galor A. Confocal microscopy abnormalities preceding antibody positivity and manifestations

- of Sjogren's syndrome. *Ocul Immunol Inflamm* 2022;1-5. doi: 10.1080/09273948.2022.2103713.
49. Tashbayev B, Utheim TP, Utheim ØA, Ræder S, Jensen JL, Yazdani M, *et al.* Utility of tear osmolarity measurement in diagnosis of dry eye disease. *Sci Rep* 2020;10:5542.
50. Lemp MA, Bron AJ, Baudouin C, Benítez Del Castillo JM, Geffen D, Tauber J, *et al.* Tear osmolarity in the diagnosis and management of dry eye disease. *Am J Ophthalmol* 2011;151:792-8.e1.
51. Soifer M, Mousa HM, Stinnett SS, Galor A, Perez VL. Matrix metalloproteinase 9 positivity predicts long term decreased tear production. *Ocul Surf* 2021;19:270-4.
52. Lanza NL, McClellan AL, Batawi H, Felix ER, Sarantopoulos KD, Levitt RC, *et al.* Dry eye profiles in patients with a positive elevated surface matrix metalloproteinase 9 point-of-care test versus negative patients. *Ocul Surf* 2016;14:216-23.
53. Messmer EM, von Lindenfels V, Garbe A, Kampik A. Matrix Metalloproteinase 9 testing in dry eye disease using a commercially available point-of-care immunoassay. *Ophthalmology* 2016;123:2300-8.
54. Sivak JM, Fini ME. MMPs in the eye: Emerging roles for matrix metalloproteinases in ocular physiology. *Prog Retin Eye Res* 2002;21:1-14.
55. Pinto-Fraga J, Enríquez-de-Salamanca A, Calonge M, González-García MJ, López-Miguel A, López-de la Rosa A, *et al.* Severity, therapeutic, and activity tear biomarkers in dry eye disease: An analysis from a phase III clinical trial. *Ocul Surf* 2018;16:368-76.
56. Flanagan JL, Willcox MD. Role of lactoferrin in the tear film. *Biochimie* 2009;91:35-43.
57. Danjo Y, Lee M, Horimoto K, Hamano T. Ocular surface damage and tear lactoferrin in dry eye syndrome. *Acta Ophthalmol (Copenh)* 1994;72:433-7.
58. Sonobe H, Ogawa Y, Yamada K, Shimizu E, Uchino Y, Kamoi M, *et al.* A novel and innovative paper-based analytical device for assessing tear lactoferrin of dry eye patients. *Ocul Surf* 2019;17:160-6.
59. Taurone S, Spoletini M, Ralli M, Gobbi P, Artico M, Imre L, *et al.* Ocular mucous membrane pemphigoid: A review. *Immunol Res* 2019;67:280-9.
60. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet* 2016;388:2023-38.
61. Lemp MA. Management of dry eye disease. *Am J Manag Care* 2008;14 (3 Suppl):S88-101.
62. Pucker AD, Ng SM, Nichols JJ. Over the counter (OTC) artificial tear drops for dry eye syndrome. *Cochrane Database syst Rev* 2016;2:Cd009729.
63. Periman LM, Perez VL, Saban DR, Lin MC, Neri P. The immunological basis of dry eye disease and current topical treatment options. *J Ocul Pharmacol Ther* 2020;36:137-46.
64. Tuan HI, Chi SC, Kang YN. An updated systematic review with meta-analysis of randomized trials on topical cyclosporin A for dry-eye disease. *Drug Des Devel Ther* 2020;14:265-74.
65. Mandal A, Gote V, Pal D, Ogundele A, Mitra AK. Ocular pharmacokinetics of a topical ophthalmic nanomicellar solution of cyclosporine (Cequa®) for dry eye disease. *Pharm Res* 2019;36:36.
66. Abidi A, Shukla P, Ahmad A. Lifitegrast: A novel drug for treatment of dry eye disease. *J Pharmacol Pharmacother* 2016;7:194-8.
67. Hsueh PY, Ju Y, Vega A, Edman MC, MacKay JA, Hamm-Alvarez SF. A multivalent ICAM-1 binding nanoparticle which Inhibits ICAM-1 and LFA-1 interaction represents a new tool for the investigation of autoimmune-mediated dry eye. *Int J Mol Sci* 2020;21:2758.
68. Semba CP, Gadek TR. Development of lifitegrast: A novel T-cell inhibitor for the treatment of dry eye disease. *Clin Ophthalmol* 2016;10:1083-94.
69. Donnenfeld ED, Karpecki PM, Majmudar PA, Nichols KK, Raychaudhuri A, Roy M, *et al.* Safety of lifitegrast ophthalmic solution 5.0% in patients with dry eye disease: A 1-year, multicenter, randomized, placebo-controlled study. *Cornea* 2016;35:741-8.
70. Sheppard JD Jr, Singh R, McClellan AJ, Weikert MP, Scoper SV, Joly TJ, *et al.* Long-term supplementation With n-6 and n-3 PUFAs improves moderate-to-severe keratoconjunctivitis sicca: A randomized double-blind clinical trial. *Cornea* 2013;32:1297-304.
71. Rogers NM, Kireta S, Coates PT. Curcumin induces maturation-arrested dendritic cells that expand regulatory T cells *in vitro* and *in vivo*. *Clin Exp Immunol* 2010;162:460-73.
72. Keating GM. Diquafosol ophthalmic solution 3%: A review of its use in dry eye. *Drugs* 2015;75:911-22.
73. Koh S, Ikeda C, Takai Y, Watanabe H, Maeda N, Nishida K. Long-term results of treatment with diquafosol ophthalmic solution for aqueous-deficient dry eye. *Jpn J Ophthalmol* 2013;57:440-6.
74. Kashima T, Itakura H, Akiyama H, Kishi S. Rebamipide ophthalmic suspension for the treatment of dry eye syndrome: A critical appraisal. *Clin Ophthalmol* 2014;8:1003-10.
75. Kinoshita S, Awamura S, Oshiden K, Nakamichi N, Suzuki H, Yokoi N. Rebamipide (OPC-12759) in the treatment of dry eye: A randomized, double-masked, multicenter, placebo-controlled phase II study. *Ophthalmology* 2012;119:2471-8.
76. Tajima K, Hattori T, Takahashi H, Katahira H, Narimatsu A, Kumakura S, *et al.* Rebamipide suppresses TNF- α production and macrophage infiltration in the conjunctiva. *Vet Ophthalmol* 2018;21:347-52.
77. Itoh S, Itoh K, Shinohara H. Regulation of human corneal epithelial mucins by rebamipide. *Curr Eye Res* 2014;39:133-41.
78. Fox RI. Use of cevimeline, a muscarinic M1 and M3 agonist, in the treatment of Sjögren's syndrome. *Adv Exp Med Biol* 2002;506:1107-16.
79. Ono M, Takamura E, Shinozaki K, Tsumura T, Hamano T, Yagi Y, *et al.* Therapeutic effect of cevimeline on dry eye in patients with Sjögren's syndrome: A randomized, double-blind clinical study. *Am J Ophthalmol* 2004;138:6-17.
80. Vivino FB, Al-Hashimi I, Khan Z, LeVeque FG, Salisbury PL 3rd, Tran-Johnson TK, *et al.* Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: A randomized, placebo-controlled, fixed-dose, multicenter trial. P92-01 Study Group. *Arch Intern Med* 1999;159:174-81.
81. Wirta D, Vollmer P, Paauw J, Chiu KH, Henry E, Striffler K, *et al.* Efficacy and safety of OC-01 (Varenicline Solution) nasal spray on signs and symptoms of dry eye disease: The ONSET-2 phase 3 randomized trial. *Ophthalmology* 2022;129:379-87.
82. Kojima T, Higuchi A, Goto E, Matsumoto Y, Dogru M, Tsubota K. Autologous serum eye drops for the treatment of dry eye diseases. *Cornea* 2008;27(Suppl 1):S25-30.
83. Sheppard JD, Torkildsen GL, Geffin JA, Dao J, Evans DG, Ousler GW, *et al.* Characterization of tear production in subjects with dry eye disease during intranasal tear neurostimulation: Results from two pivotal clinical trials. *Ocul Surf* 2019;17:142-50.
84. Ji MH, Moshfeghi DM, Periman L, Kading D, Matossian C, Walman G, *et al.* Novel extranasal tear stimulation: Pivotal study results. *Transl Vis Sci Technol* 2020;9:23.
85. Panigrahi T, Shivakumar S, Shetty R, D'souza S, Nelson EJR, Sethu S, *et al.* Trehalose augments autophagy to mitigate stress induced inflammation in human corneal cells. *Ocul Surf* 2019;17:699-713.
86. Mittal R, Patel S, Galor A. Alternative therapies for dry eye disease. *Curr Opin Ophthalmol* 2021;32:348-61.
87. Diel RJ, Kroeger ZA, Levitt RC, Sarantopoulos C, Sered H, Martinez-Barrizonte J, *et al.* Botulinum toxin A for the treatment

- of photophobia and dry eye. *Ophthalmology* 2018;125:139-40.
88. Wang Y, Carreno-Galeano JT, Singh RB, Dana R, Yin J. Long-term outcomes of punctal cauterization in the management of ocular surface diseases. *Cornea* 2021;40:168-71.
 89. Ervin AM, Law A, Pucker AD. Punctal occlusion for dry eye syndrome. *Cochrane Database Syst Rev* 2017;6:Cd006775.
 90. Kate A, Basu S. Systemic immunosuppression in cornea and ocular surface disorders: A ready reckoner for ophthalmologists. *Semin Ophthalmol* 2022;37:330-44.
 91. Ruiz-Irastorza G, Bertsias G. Treating systemic lupus erythematosus in the 21st century: New drugs and new perspectives on old drugs. *Rheumatology (Oxford)* 2020;59(Suppl 5):v69-81.
 92. Branisteanu DC, Stoleriu G, Branisteanu DE, Boda D, Branisteanu CI, Maranduca MA, *et al.* Ocular cicatricial pemphigoid (Review). *Exp Ther Med* 2020;20:3379-82.
 93. Hingorani M, Lightman S. Ocular cicatricial pemphigoid. *Curr Opin Allergy Clin Immunol* 2006;6:373-8.
 94. Vazirani J, Bhalekar S, Amescua G, Singh S, Basu S. Minor salivary gland transplantation for severe dry eye disease due to cicatrizing conjunctivitis: Multicentre long-term outcomes of a modified technique. *Br J Ophthalmol* 2021;105:1485-90.
 95. Singh S, Basu S. A novel diagnostic technique of measuring labial minor salivary gland secretions using sodium fluorescein dye: Implications for patients with dry eyes. *Semin Ophthalmol* 2022;37:111-6.
 96. Singh S, Basu S. Functional assessment of transplanted minor salivary glands. *Cornea* 2020;39:e21-2.
 97. Harthan JS, Shorter E. Therapeutic uses of scleral contact lenses for ocular surface disease: Patient selection and special considerations. *Clin Optom (Auckl)* 2018;10:65-74.
 98. Dermer H, Lent-Schochet D, Theotoka D, Paba C, Cheema AA, Kim RS, *et al.* A Review of management strategies for nociceptive and neuropathic ocular surface pain. *Drugs* 2020;80:547-71.
 99. Goyal S, Hamrah P. Understanding neuropathic corneal pain—gaps and current therapeutic approaches. *Semin Ophthalmol* 2016;31:59-70.
 100. Ongun N, Ongun GT. Is gabapentin effective in dry eye disease and neuropathic ocular pain? *Acta Neurol Belg* 2021;121:397-401.
 101. Patel S, Mittal R, Felix ER, Sarantopoulos KD, Levitt RC, Galor A. Differential effects of treatment strategies in individuals with chronic ocular surface pain with a neuropathic component. *Front Pharmacol* 2021;12:788524.
 102. Aggarwal S, Kheirkhah A, Cavalcanti BM, Cruzat A, Colon C, Brown E, *et al.* Autologous serum tears for treatment of photoallodynia in patients with corneal neuropathy: Efficacy and evaluation with *in vivo* confocal microscopy. *Ocul Surf* 2015;13:250-62.
 103. Cavuoto KM, Banerjee S, Galor A. Relationship between the microbiome and ocular health. *Ocul Surf* 2019;17:384-92.
 104. Pflugfelder SC, de Paiva CS. The pathophysiology of dry eye disease: What we know and future directions for research. *Ophthalmology* 2017;124:S4-13.
 105. Trujillo-Vargas CM, Schaefer L, Alam J, Pflugfelder SC, Britton RA, de Paiva CS. The gut-eye-lacrimal gland-microbiome axis in Sjögren Syndrome. *Ocul Surf* 2020;18:335-44.
 106. Mendez R, Watane A, Farhangi M, Cavuoto KM, Leith T, Budree S, *et al.* Gut microbial dysbiosis in individuals with Sjögren's syndrome. *Microb Cell Fact* 2020;19:90.
 107. Møller-Hansen M, Larsen AC, Toft PB, Lynggaard CD, Schwartz C, Bruunsgaard H, *et al.* Safety and feasibility of mesenchymal stem cell therapy in patients with aqueous deficient dry eye disease. *Ocul Surf* 2021;19:43-52.
 108. Weng J, He C, Lai P, Luo C, Guo R, Wu S, *et al.* Mesenchymal stromal cells treatment attenuates dry eye in patients with chronic graft-versus-host disease. *Mol Ther* 2012;20:2347-54.
 109. Kawakita T. Regeneration of lacrimal gland function to maintain the health of the ocular surface. *Invest Ophthalmol Vis Sci* 2018;59:DES169-73.
 110. Liu CY, Hirayama M, Ali M, Shah D, Aakalu VK. Strategies for regenerating the lacrimal gland. *Curr Ophthalmol Rep* 2017;5:193-8.
 111. Dietrich J, Schrader S. Towards lacrimal gland regeneration: Current concepts and experimental approaches. *Curr Eye Res* 2020;45:230-40.
 112. Hirayama M, Tsubota K, Tsuji T. Generation of a bioengineered lacrimal gland by using the organ germ method. *Methods Mol Biol* 2017;1597:153-65.
 113. Hayashi R, Okubo T, Kudo Y, Ishikawa Y, Imaizumi T, Suzuki K, *et al.* Generation of 3D lacrimal gland organoids from human pluripotent stem cells. *Nature* 2022;605:126-31.