Chapter

Examination for Dry Eyes

Tri Wahyu

Abstract

Dry eye disease (DED) is a multifactorial disease of tears and ocular surface that results in various symptoms with the potential damage to the ocular surface. It can range from mild to severe signs and symptoms and may affect patient's quality of life. Various techniques and methods have been developed to evaluate DED for initial examination or regular follow up. The simple evaluations that can be performed in clinic include eyelid examination, tear break-up time, and ocular surface stainings; while the advanced ones may require certain devices or laboratory equipment. Careful and thorough examinations are important to guide the clinician to assess and evaluate dry eye.

Keywords: dry eye examination, ocular surface staining, tear film stability, tear volume, laboratory test

1. Introduction

Dry eye disease is one of the most commonly encountered problem in daily practice. It is the reason why a patient visits the eye care professional. Dry eye—as it was defined by the National Eye Institute (NEI)/Industry Workshop on Clinical Trials in Dry Eyes—is a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort [1]. In 2007, the International Dry Eye Workshop updated the original definition and classified dry eye as "multi-factorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" [2]. In 2017, the definition was revised, which centered on the clinical effects and associated signs as "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" [3].

Based on those definitions, dry eye symptoms can change from day to day and they may vary in every patient, from mild to severe ocular discomfort and visual disturbance. Dry eye disease can affect patients' quality of life. It is important for eye care professionals to recognize, diagnose, and treat DED; but, somehow DED can be puzzling since there is no consistent, well accepted, diagnostic test that is both readily available and reproducible [4]. When a patient comes in due to the symptoms that may suggest DED or for a routine examination, an eye care professional should do history taking comprehensively. Various diagnostic tests may be required to determine if the patient has DED due to aqueous deficient, evaporative, or both. In daily practice, tear-film and dry eye assessment are often performed in

symptomatic patients. However, it must be kept in mind that dry eye symptoms and signs may be not well associated, as reported in previous studies [5–7].

2. History taking

A careful history taking is an important thing to perform in the first place to help the eye care professional in assessing dry eye correctly, including history of previous medication, long-term contact lens wear, ocular surface surgery, or systemic condition(s). Patients with dry eye often complain of eye discomfort or irritation, gritty or foreign body sensation, burning, tearing, stinging, intermittent sharp pain, redness, or/and photophobia. Visual disturbance may occur. Dry eye patients may have all, some, or none of these symptoms.

A clinician should also understand that dry eye symptoms increase with age, menopausal status, hormonal diseases, current smoking history, certain medications, and presence of pterygium are a few factors result in dry eye [4, 5, 8–10]. Noor et al. [7] found that there was a likelihood of shifting from preclinical dry eye towards DED and from normal towards predisposition to dry eye in older age.

There are many questionnaires available that can be used to utilize in assessing DED, such as National Eye Institute Visual Function Questionnaire-25 (NEV-VFQ-25) [11], Ocular Surface Disease Index (OSDI) [12], Standard Patient Evaluation of Dry Eye Questionnaire (DEQ-5) [13], and some others more. Every clinicians have their own preferences of questionniare.

3. Staining grading system

Visual acuity assessment (including best-corrected acuity), thorough eyelid and slit-lamp of anterior segment examinations are mandatory. Patients with dry eye often complain of blurred vision which improves with blinking or instillation of artificial tear.

Whilst taking patient's history, a clinician can examine the eyelids macroscopically. It can guide the clinician to evaluate if the patient has dry eye. Lagophthalmous, lid laxity, decreased frequency of blinking, and size of palpebral aperture. Malpositions of the eyelid have to be recognized (such as involutional or cicatrical ectropion, eversion of lacrimal punctum, dermatochalasis, full-thickness defects, inadequate lid closure due to previous eyelid surgical reconstruction) because these conditions can influence the tear turnover. Patient's history can guide the clinician to perform identify certain ocular manifestations under careful and focused slit-lamp examination.

3.1 Slit-lamp biomicroscopy

Under the slit-lamp biomicroscopy, a clinician should evaluate anatomical structures of the lid, including the alterations of lid margins and eyelashes. The alterations of the lid margins include hyperaemia, telangiectasia, thickening, scarring, keratinization, ulceration, tear debris, abnormalities of the meibomian orifices, metaplasia, character of expressed meibomian secretions; while for the eyelashes, the alterations include misdirection (trichiasis), malposition (dystichiasis), encrustations, collarettes [14–16]. Careful evaluation of meibomian gland is important since its dysfunction is the most frequent cause of evaportive DED and is often symtomatic [17–19]. Evaluate if the meibomian gland orifices are plugged or obstructed and/or change in its secretion.

Tear film should be evaluated for mucus, debris, or meibomian foam. Decreased tear meniscus is often a sign of dry eye. Normally, a patient with normal tear production has tear meniscus height of 0.2–0.5 mm; but in patient with dry eye, it is usually less than 0.25 mm or absent [4, 14, 15, 20, 21].

Ocular manifestations in mild to moderate dry eye may conjunctival hyperaermia, with or without corneal epithelial erosions; or these signs may not present in some mild cases. In severe forms of the disease, conjunctival scarring or conjunctivochalasis and/or corneal complications may occur. Filamentary keratitis, persistent epithelial defects, ulceration, and even corneal perforation can complicate the course [14, 15, 22]. Corneal staining may be required to evaluate the severity of its defects.

There are several tests that can be performed to confirm the diagnosis of dry eye and to evaluate the severity of the disease. The tests can measure the following parameters: (1) stability of the tear film as related to its break-up time (TBUT); (2) tear production (Schirmer, fluorescein clearance, and tear osmolarity); and (3) ocular surface disease (corneal stains and impression cytology). There is no clinical test to confirm the diagnosis of evaporative dry eye [21, 23].

3.2 Staining of the ocular surface

Epithelial damage to the exposed ocular surface can be evaluated with vital stainings. Staining of the cornea occurs commonly in inferior part, often more in nasal and temporal areas. Corneal epithelial defect, erosions, filaments, or punctuates can be seen in dry eye. Staining of the bulbar conjunctiva occurs over a wedge-shaped zone nasally and temporally, and in advanced dry eye may become confluent; but in milder forms of dry eye, it may be present in the absence of corneal stain [23].

3.2.1 Fluorscein

Fluorscein staining is a basic and standard method to evaluate ocular surface damage. Commonly, every clinician is able to perform this examination in daily practice. The orange-dyed fluorescein strip is wetted with a sterile drop of saline and then is applied to tarsal or bulbar conjunctiva. Excess fluid is shaken from the strip prior to application. The dye will distribute over ocular surface after blinking. Under slit-lamp examination using cobalt-blue filter, the orange dye will turn into fluoresces green in the damaged area. Common characteristic distribution of this test is confined to the exposed intrapalpebral area of the ocular surface, but the staining may extend to unexposed area in severe case.

In the case of perforation, aqueous from the anterior chamber will leak out of the eye and mix with the tear film. The fluorescein dye around the perforated area will be diluted by this leak and the leak will appear bright green (Seidel test).

3.2.2 Rose bengal

Rose bengal is a synthetic fluorescein derivative, also perhaps referred to as bengal rose and also known as a Chemical Index (C.I.) Acid Red 94 [24]. It has the ability to bind to epithelial cells that are uncoated by certain proteins (mainly mucin) and presents high cell toxicity [25]. The instillation of this dye causes stinging or pain, particularly in DED patients, and it may be disliked by some patients; thus topical anesthesia is best instilled first to limit stinging sensation. Although rose bengal had been thought to be a vital dye, staining dead or degenerating cells, it is known that rose bengal normally stains healthy cells [26, 27].

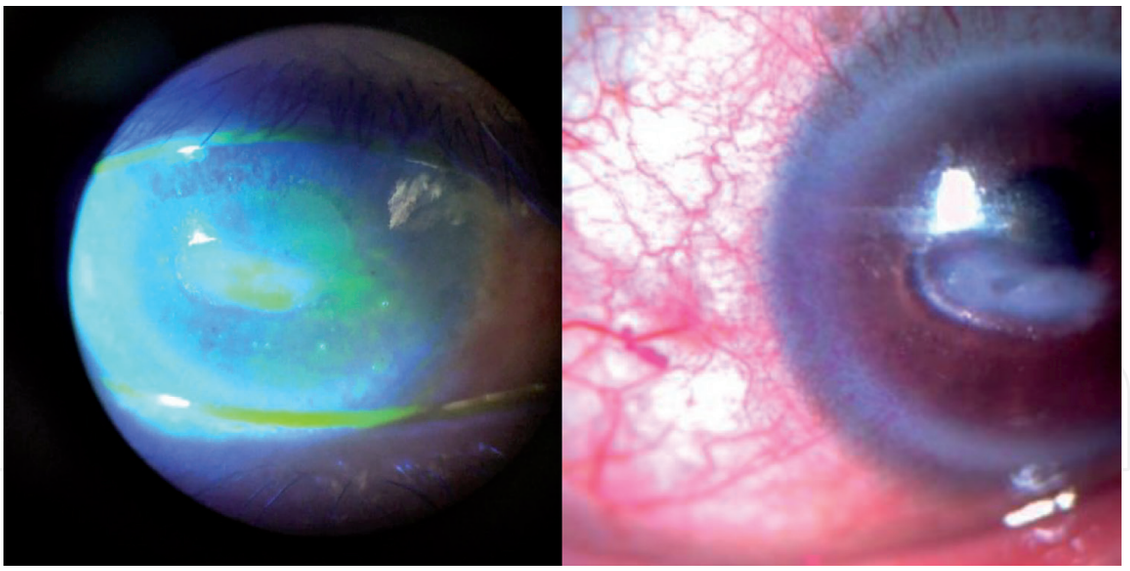


Figure 1.
Left: Fluorescein staining shows large defect in central cornea with discrete punctate staining all over cornea; right: Rose bengal staining in the same patient.

Under slit-lamp with a white light, rose bengal staining can revealed discrete or confluent punctuate in damaged area of cornea and visible bulbar conjunctiva which can be seen as red dots (**Figure 1**). But there are disadvantages in using rose bengal in addition to pain on instillation. Although bulbar conjunctival staining is demonstrated well against the white background provided by the sclera, the dye is difficult to see on the cornea against the background of a dark iris [23]. Another disadvantage of rose bengal is its toxicity, including decreasing the chance to recover herpes viruses in human cell cultures [25].

3.2.3 Lissamine green

Lissamine green is a synthetically produced organic acid dye with two aminophenyl group and it has been used as a substitute for rose bengal since it has similar laboratory and clinical staining properties, also it is a less toxic stain and less stinging upon instillation [25, 28].

	Fluorescein	**Rose Bengal**	**Lissamine Green**
Discomfort (pain/ stinging)	No	Yes	No
Staining normal/ healthy cells	No	Yes	No
Staining dead or degenerated cells	No	Yes	Yes
Clinical means	Disruption of cellular junctions and increased membrane permeability	Loss of insufficient protection by ocular surface mucin	Cell degeneration and death (unprotected by ocular mucin or glyco-calyx)
Slit-lamp filter	Cobalt-blue	White light or green barrier filter	Red barrier filter

Adapted from [29].

Table 1.
Comparison of ocular surface stainings.

Lissamine green is a vital dye that stains ocular surface epithelial cells that are unprotected by mucin or glycocalyx, as well as cells that have been damaged, and it does not stain healthy cells or damage them [28–30]. In patient with red eyes, lissamine green could provide better staining visualization than rose bengal.

The use of ocular staining mentioned above is helpful in assessing the integrity of the ocular surface epithelium. These tests are easy to perform in daily clinical practice in-office setting. The clinician can choose one of these staining to assess dry eye based on the availability of the equipment in the clinic. Fluorescein impregnated strips are preferred due to their availability and simplicity of use; while rose bengal and/or lissamine may not always be available in some eye care facilities. **Table 1** helps the clinician to compare these three stainings. Significant staining of the conjunctiva with rose bengal or lissamine green is most common in severe dry eye to Sjögren's syndrome [29].

4. Staining grading systems

Staining grading systems remain an essential element of ocular examination and allow the clinician to record the level of ocular surface staining and evaluate the severity of dry eye. The three most common grading systems are: (1) the van Bijsterveld grading system (uses rose bengal staining of the conjunctiva and cornea); (2) the Oxford grading scheme (uses fluorescein, rose bengal, or lissamine green of the conjunctiva and cornea); and (3) and the NEI Workshop system (uses fluorescein staining to grade the cornea and rose bengal to grade the conjunctiva) [29].

The van Bijstervel grading system is the first proposed system to grade three areas in each eye: the nasal and temporal bulbar conjunctiva and the cornea (**Figure 2**). The intensity of the staining is graded on scale 0 (no staining), 1 (sparsely scattered staining), 2 (densely scattered), and 3 (confluent staining). The maximum score for each eye is 9. Staining score of 3 or higher is considered abnormal.

The Oxford grading scheme uses a chart consisting of a series of panels labeled A to E in order of increasing severity of staining (**Figure 3**). Staining is represented by punctate dots and increases by 1 log unit between panel A and B and by ½ log unit between each subsequent panel (B to E).

The NEI Workshop grading system divides cornea into five areas and conjunctiva into six areas for each eye (**Figure 4**). The scale of 0 to 3 is used for the grading, according to the intensity of fluorescein staining. The maximum staining score for the cornea is 15, and for conjunctiva, the maximum score is 18. The values above 3 is considered abnormal for cornea or conjunctiva in each eye.

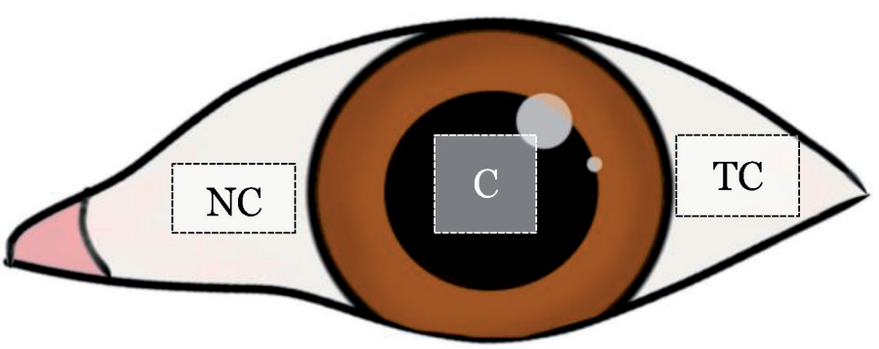


Figure 2.
The van Bijsterveld grading system. The exposed nasal and temporal conjunctiva (NC and NT, respectively) and cornea (C) are graded on scale: 0 (no staining) to 3 (confluent staining), with maximum score is 9.

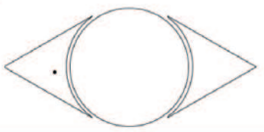
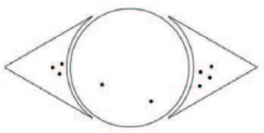
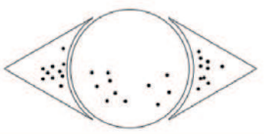
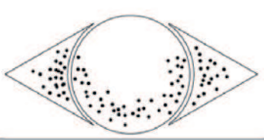
A 	Equal to or less than picture A	Log: 0	Grade 0 (absent)
B 	Equal to or less than picture B, greater than A	Log: 1	Grade 1 (minimal)
C 	Equal to or less than picture C, greater than B	Log: 1.5	Grade 2 (mild)
D 	Equal to or less than picture D, greater than C	Log: 2.0	Grade 3 (moderate)
E 	Equal to or less than picture E, greater than D	Log: 2.5	Grade 4 (marked)
>E	Greater than picture E	Log: >2.5	Grade 5 (severe)

Figure 3.
The Oxford grading scheme. Staining is represented by punctate dots. (adapted from Bron AJ, Evan VE, smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 2003;22(7):640–650).

4.1 Laboratory tests

Lack of stability in the tear film can be seen in aqueous deficient, evaporative, or both type of dry eye. It may also occur in the setting of a poor blink rate or epithelial irregularity [30]. There are several numbers of tools designed to evaluate tear film stability to help clinician or researcher to assess and support the diagnosis of DED.

4.1.1 Tear break-up time (TBUT)

Tear break-up time was first introduced by Norn in 1969 and remains the most frequently used diagnostic test to evaluate tear film stability [31]. It measures the time between a complete blink and the first appearance of a dry spot on the ocular surface using fluorscein. Right after applying the fluorescein strip on to the ocular surface, and under cobalt blue filter in slit-lamp biomicroscopy, patient is asked to blink completely and hold the eye open (avoid blinking). The clinician should observe the first dry spots appear on his/her ocular surface. Normally, dry spot(s) will appear after 10 seconds.

The TBUT less than 10 seconds is considered as a cut-off score for the diagnosis of dry eye, with values of 5–10 seconds are considered marginal and less than 5 seconds indicate the dry eye symptoms [31–34]. But, the threshold for Asian patients may be set much lower as many Asians with TBUT between about 7–10 seconds do not have dry eye symptoms [35]. Some studies suggest that healthy Asian subjects

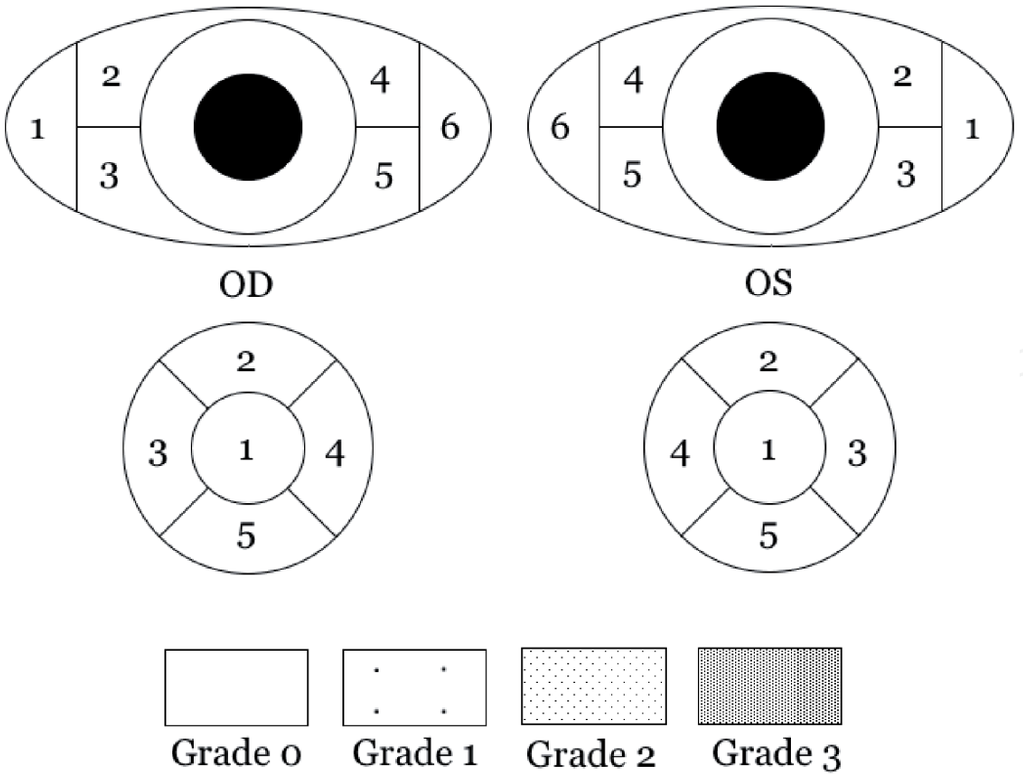


Figure 4.
The NEI scale system for grading fluorescein staining which divides the corneal and conjunctival surfaces. The conjunctival surface is divided into 6 areas and the corneal surface is divided into 5 areas. A standardized grading system of 0 to 3 is used for each of areas on cornea and conjunctiva.

have an 11–24% shorter TBUT than non-Asians [35, 36]. It hypothesized that the tear lipid layer is not able to efficiently perform its usual expansion and compression during a blink in an eye with a small palpebral aperture size (Asian), resulting in a less stable tear film [37].

4.1.2 Non-invasive break-up time (NIBUT)

This technique was first introduced by Mengher et al. in 1983 and is defined as 'the time taken in seconds between the last complete blink and the appearance of the first random disturbance of a grid' [38, 39]. The NIBUT test can be performed using several device options, such as topography, keratography, or Placido disc video-keratography. Tear break-up time is considered when the reflected mires become distorted.

Mengher et al. [38] reported a NIBUT value of 47.9 seconds (range of four to 214 seconds), but Mohidin et al [36] reported lower NIBUT value (15.8 ± 9.4 seconds, range of 4.2 to 48.6 seconds). Sharanjeet-Kaur et al. [40] reported that NIBUT values for normal Malays and Chinese were 7.74 ± 3.34 seconds and 7.15 ± 3.38 seconds respectively. Generally, in normal population, NIBUT is longer than TBUT, with range of four to 214 seconds (median 4–19 seconds); and in patients with DED, NIBUT and TBUT values are almost the same (the cut-off values for positive finding can be as low as 2.7 seconds for automated algorithms and up to 10 seconds for subjective observation techniques) [41].

4.2 Tear volume

The aim of tear volume assessment is to measure the quantity of tear film produced by lacrimal gland and conjunctiva.

4.2.1 Schirmer's test

The Schirmer's test is the most common examination performed whenever there is a suspicion of inadequate tear secretion. The test was named after Schirmer who brought the test forward for the first time in 1903 [42]. Basically, without anesthesia, the test measures total (basic and reflex) tear secretion, as with anesthesia it measures basic tear secretion devoid of reflex component [43, 44]. This test remains as the most common test used for tear quantity assessment [45]. It can be divided into Schirmer I and Schirmer II test.

The Schirmer I test is performed using strip that is folded from one end and inserted into the lower conjunctival sac at the junction of lateral and middle thirds, avoiding touching the cornea. After five minutes, the length of wetted strip is recorded. Fifteen minutes later, after instillation of topical anesthesia, the strip is placed again over the same point in the same patient for five minutes. The Schirmer II test measure reflex secretion of lacrimal gland. The procedure of this test is as the same as Schirmer I test with topical anesthesia and nasal mucosa is irritated with a cotton-tiped applicator prior to measuring tear production. The result is recorded after 5 minutes. Normally, the length of wetted strip is around 10 mm or greater and if the length is less than 5 mm, it indicates symptomatic tear deficient; but Schirmer's test values less or equal to 10 mm have greater diagnostic value and indicate hyposecretion [22, 46–50].

4.2.2 Phenol red thread test

The phenol red thread (PRT) test was invented by Hamano in 1982 and developed to overcome the disadvantage of Schirmer's test including variable results, poor repeatibility, and low sensitivity in detecting dry eyes [44, 51–53]. The test uses a special cotton thread impregnated with phenol red (a pH-sensitive indicator). The procedure is performed in the similar manners to Schirmer test, which the thread is folded at the end and inserted into the lower conjunctival sac and it will absorb the tears that contact with it. The color of this thread will change from yellow to red over the pH range of normal tears. The result is recorded after 15 seconds, much shorter than Schirmer's test. The PRT is almost comparable with Schirmer's test and it has advantages including simpler and more comfortable to the patient and can also be performed in children [54].

4.3 Laboratory tests

Conjunctival biopsy may be one of the best methods to investigate and evaluate the ocular surface condition, which offers specimens of epithelial layers and conjunctival stroma to be examined under light or electron microscopy, cytology, and immunohistochemical analyses. These techniques may allow identification and counting of inflammatory cells and analysis of cell membrane markers, intracyto-plasmic cells, or extracellular matrix components [55]. But, of all methods mentioned above, conjunctival biopsy is an invasive technique that may cause discomfort to the patient.

4.3.1 Impression cytology

Impression cytology (IC) refers to the application of cellulose acetate filter to the ocular surface to remove the superficial layers of the ocular surface epithelium [56]. The analysis techniques used in this method vary, depend on the purpose and the equipment availability in eye care facility. The simplest analysis technique remains

light microscopy, in which epithelial and goblet cells can be well visualized through hemtoxylin and periodic acid Schiff (PAS) staining. Other techniques include electron microscopy, immunohistochemistry, flow cytometry, and RT-PCR/PCR.

The RT-PCR was used in IC specimens as early as 1994 and identified inflammatory cytokins in conjunctival specimens from Sjögren's syndrome eyes [57].

4.3.2 Tear osmolarity

Tear osmolarity is the most accurate method to diagnose DED. Tear hyperosmolarity is considered as pathogenic factor causing ocular surface inflammation, symptoms, and tissue damage which can lead to DED. This condition can occur in many situations including insufficient tear production, meibomian gland dysfunction, and exposure. There is a commercially available objective point of care test (TearLab Osmolarity System; TearLab, San Diego, California) that can measure the osmolarity of a 50-nL tear sample and is easier to use [30, 58, 59]. A reading of 308 mOsms/L or greater indicates tear osmolarity disruption. This test must be completed quickly to avoid any evaporation of tear sample. Although reproducible, this test is difficult to perform in clinic setting.

4.3.3 Ferning test

Tear ferning test is a simple test for tear film quality. This test requires capillary tubes, spatula, or glass rods to collect tear from the lower tear meniscus (about 5–20 μl). The collected tear is applied to a glass slide and evaluated under light or digital microscope with various magnifications (40-100x). In DED, the delicate fronded pattern becomes fragmented or broken up and irregular and the appearances can be graded into type I and II (healthy tear film) and type III and IV (increasing degrees of dry eye) [14, 60].

5. Assessing the dry eye

The diagnosis of dry eye depends on the results of several of tests mentioned above, which ideally could be performed at a single clinic visit. It is important to keep in mind that a clinician should carry out the test in an appropriate order. **Table 2** suggests a suitable order for diagnostic test, although there are various and informal data to justify a particular sequence of the tests. Some of the standard tests are specific for subgroup of the disease (**Table 3**). **Table 4** helps the clinician to grade the severity of the DED.

1. Patient history (a symptom-oriented questionnaire may be needed).
2. Measure UCVA and BCVA.
3. Observe eyelid and its skin appearance, including upper and lower lid positions.
4. Measure blink rate.
5. Tear-film break-up time with fluorescein
6. Ocular surface staining
7. Schirmer test with/without anesthesia
8. Slit lamp xamination of the eyelid margins, meibomian gland orifices with expression of meibomian secretion, and anterior segments.

Table 2.
Practical sequence of dry eye tests.

- Schirmer test evaluates the aqueous phase secretion.
- Altered meibomian gland status can be characteristic of evaporative dry eye. Other conditions that can be the signs of evaporative dry eye include:
  - changes in tear composition (lack of lipid content; primary type: lack of gland and distichiasis; secondary type: bleharitis and MGD);
  - abnormalities of eyelids, reduced blinking rate or incomplete blinking (office workers, Parkinsonism, and schizophrenia);
  - ocular surface irregularities;
  - contact lens wear.
- Tear-film hyperosmolarity is considered a key pathological factor, both in aqueous tear-deficient and in evaporative dry eye disease.

Adapted from Módis and Szalai [22].

Table 3.
Practical applications of several test for assessing DED.

	Dry Eye Severity Level			
	1	**2**	**3**	**4**
Discomfort, severity, and frequency	Mild and/or episodic; occurs under enviromental stress	Moderate episodic or chronic, strees or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly dissabling
Conjunctival injection	None to mild	None to mild	Mild or not present	Mild to moderate
Corneal staining (severity/location)	None to mild	Variable	Marked central	N/A
Cornea/tear signs	None to mild	Mild debris, decreased meniscus	Filamentary keratitis, mucus clumping, increased tear debris	Filamentary keratitis, mucus clumping, increased tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	MGD frequent	Trichiasis, keratinization, symblepharon
TBUT (seconds)	Variable	≤ 10	≤ 5	Immediate
Schirmer score (mm/5 minutes)	Variable	≤ 10	≤ 5	≤ 2

Table 4.
The severity grading scheme for dry eye disease.

Despite the wide use in clinical practice, standard tests for assessing DED and ocular surface disorders (including history taking and symptoms recording, TBUT, meibomian gland testing, ocular surface saining, and Schirmer's testing) have shown poor repeatability and lack of efficacy [22, 57]. Moreover, it is well know that subjective symptoms often do not correlate with objective signs. Additional exploratory technique may be required to assess DED and evaluate the severity of the disease. The laboratory test may be required in patient who have subjective complaint

• Subjective description of oral symptoms
• Subjective description of ocular symptoms
• Objective signs of oral dryness, determined by unstimulated salivary flow rate and/or Saxon test
• Objective signs of ocular dryness, diagnosed on the basis of a reduced Schirmer test result, reduced TBUT, and/or positive ocular surface staining
• Histopathological evidence of infiltrating lymphocytes in minor salivary glands
• Evidence of serum autoantibodies, especially antibodies to Ro(SSA) or La(SSB) antigens

Table 5.
Diagnosis criteria for Sjögren's syndrome.

that is not identified as dry eye (such as fluctuating vision) but do not show a lot of ocular finding such as corneal staining or any other marked conditions.

Patient with xerostomia in addition to dry eye must be investigated for the possible presence of Sjögren's syndrome. The revised criteria of the European-American Consensus Group for the diagnosis of Sjögren's syndrome are summarized in **Table 5**. The diagnosis of Sjögren's syndrome is made if four of the six criteria are fulfilled. If SSA/SSB diagnostic testing is negative, a positive ANA (antinuclear antibody) test or positive rheumatoid factors may be indicative [15].

6. Conclusion

Careful and thorough examinations help the clinician to assess and evaluate dry eye disease. Various examinations are available, but the clinicians must adjust the examination to the available tools or equipments in their facilities. Ocular surface staining is the simplest test that can be performed in every clinic. If the case is complicated with or without underlying disease and needs further examniations, a clinician should refer to higher facility or dry eye specialist.

Acknowledgements

Author would like to acknowledge Susi Heryati, Angga Fajriansyah, Arief Mustaram, Patriotika Muslima, and Elfa Ali Idrus as supervisors in Infection and Immunology Division, Department of Ophthalmology, Cicendo National Eye Hospital, Bandung, Indonesia.

Conflict of interest

The author declares that there is no conflict of interest in this work.

Appendices and nomenclature

ANA	antinuclear antibody
BCVA	best-corrected visual acuity
C.I.	chemical index
DED	dry eye disease
DEQ-5	Standard Patient Evaluation for Dry Eye Questionnaire
IC	impression cytology

MGD	meibomian gland dysfunction
mOsm	milliosmole
NEI	National Eye Institute
NEV-VFQ-25	National Eye Institute Function Questionnaire-25
NIBUT	non-invasive break-up time
OSDI	Ocular Surface Disease Index
PAS	periodic acid Schiff
PCR	polymerase chain reaction
pH	power of hydrogen
PRT	phenol red thread
RT-PCR	reverse transcription polymerase chain reaction
SSA	anti-Sjögren's syndrome type A
SSB	anti-Sjögren's syndrome type B
TBUT	tear break-up time
UCVA	uncorrected visual acuity

Author details

Tri Wahyu
Sawangan Eye Clinic Depok, West Java, Indonesia

*Address all correspondence to: tri.why89@gmail.com

References

[1] Lemp MA. Report of the National eye Institute/industry workshop on clinical trials in dry eyes. CLAO J. 1995;21: 221-232

[2] [No author listed]. The definition and classification of dry eye disease: Report of the definition and classification subcommittee of the international dry eye workshop. Ocul Surf. 2007;5(2):75-92

[3] Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15:276-283. DOI: 10.1016/j.jtos.2017.05.008

[4] Zeev MSB, Miller DD, Latkany R. Diagnosis of dry eye disease and emerging technologies. Clin Ophthalmol. 2014;8:581-590 DOI: 10.2147/OPTH.S45444

[5] Schein OD, Tielsch JM, Munõz B, Bandeen-Roche K, West S. Relation between signs and symptoms of dry eye in the elderly. Ophthalmology 1997;104:1395-1401

[6] McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne, Australia. Ophthalmology 1998;105:1114-1119

[7] Noor NA, Rahayu T, Gondhowiardjo TD. Prevalence of dry eye and its subtypes in an elderlu population with cataracts in Indonesia. Clin Ophthalmol. 2020; 14:2143-2150. DOI: 10.1097/00003226-200208000-00009

[8] de Paiva CS. Effects of aging in dry eye. Int Ophthlamol Clin. 2017 Spring;57(2): 47-64. DOI: 10.1097/IIO.0000000000000170

[9] Sharma A, Hindman HB. Aging: A predisposition to dry eyes. J Ophthalmol. 2014;2014:781683. DOI: 10.1155/2014/781683

[10] Lee AJ, Lee J, Saw SM, Gazzard G, Koh D, Widjadja D, et al. Prevalence and risk factors associated with dry eye symptoms: A population based study in Indonesia. Br J Ophthalmol. 2002;86:1347-1351

[11] Nichols KK, Mitchell GL, Zadnik K. Performance and repeatability of the NEI-VFQ-25. Cornea 2002;21(6):578-583. DOI: 10.10970/01.ICO.0000016353.01275.23

[12] Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. Arch Ophthalmol. 2000;18:615-621. DOI: 10.1001/archopht.118.615

[13] Chalmers RL, Begley CG, Caffery B. Validation of the 5-item dry eye questionnaire (DEQ-5): Discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. Contact Lens and Anterior Eye 2010;33:55-60. DOI: 10.1016/j.clae.2009.12.010

[14] Kaercher T, Anthony JB. Classification and diagnosis of dry eye. Dev Ophthalmol. 2008;41:36-53.

[15] Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. Dtsch Arztebl Int. 2015;112:71-82. DOI: 10.3238/arztebl.2015.0071

[16] Chhadva P, Goldhardt R, Galor A. Meibomian gland disease: The role of gland dysfunction in dry eye disease. Ophthalmology 2017;124(11):S20-S26. DOI: 10.1016/j.ophtha.2017.05.031

[17] Yokoi N, Mossa F, Tiffany JM, Bron AJ. Assessment of meibomian gland function in dry eye using meibometry. Arch Ophthalmol.

1999;117:723-729. DOI: 10.1001/archopht.117.6.723

[18] Boudouin C, Messmer EM, Aragona P, Geerling G, Akova YA, Benítez-del-Castillo J, et al. Revisiting the vicious circle of dry eye disease: A focus on the pathophysiology of meibomian gland dysfunction. Br J Ophthalmol. 2016;100: 300-306. DOI: 10.1136/ojophthalmol-2015-307415

[19] Dell SJ, Gaster RN, Barbarino SC, Cunningham DN. Prospective evaluation of intense pulsed light and meibomian gland expression efficacy on relieving signs and symptoms of dry eye disease due to meibomian gland dysfunction. Clin Ophthalmol. 2017;11:817-827. DOI: 10.2147/OPTH.S130706

[20] Mainstone JC, Bruce AS, Golding TR. Tear meniscus measurement in the diagnosis of dry eye. Curr Eye Res. 1996;15:653-661. DOI: 10.3109/02713689609008906

[21] Salmon JF. Kanski's Clinical Ophthalmology. 9th ed. Edinburgh: Elsevier; 2020. p. 156-165. DOI: 9780702077135

[22] Módis L, Szalai E. Dry eye diagnosis and management. Expert Rev Ophthalmol. 2011;6(1):67-79. DOI: 10.1586/eop.10.89

[23] Bron AJ. Diagnosis of dry eye. Surv Ophthalmol. 2001;45(Suppl 2):S221-S226. DOI: 10.1016/s0039-6257(00)00201-0

[24] Doughty MJ. Rose bengal staining as an assessment of ocular surface damage and recovery in dry eye disease—a review. Contact Lens and Anterior Eye 2013; 36:272-280. DOI: 10.106/j.clae.2013.07.008

[25] Machado LM, Castro RS, Fontes BM. Staining patterns in dry eye syndrome: Rose bengal versus lissamine green. Cornea 2009;28:732-734. DOI: 10.1097/ICO.0b013e3181930c03

[26] Feenstra RP, Tseng SC. Comparison of fluorescein and rose bengal staining. Ophthalmology 1992;99(4):605-617. DOI: 10.106/s0161-6420(92)31947-5

[27] Feenstra RPG, Tseng SCG. What is actually stained by rose bengal?. Arch Ophthalmol 1992;110(7):984-993. DOI: 10.1001/archopht.1992.01080190090035

[28] Hamrah P, Alipour F, Jiang S, Sohn JH, Foulks GN. Optimizing evaluation of lissamine green parameters for ocular surface staining. Eye 2011;25:1429-1434. DOI: 10.1038/eye.2011.184

[29] Nelson JD. In-office diagnostic tests for dry eye disease. In: Asbell PA, Lemp MA, editors. Dry Eye Disease: The Clinician's Guide to Diagnosis and Treatment. New York: Thieme; 2006. p. 34-46. DOI: 10.1055/b-002-51025

[30] Kloosterboer A, Dermer HI, Galor A. Diagnostic tests in dry eye. Expert Rev Ophthalmol. 2019;14(4-5):237-246. DOI: 10.1080/17469899.2019.1657833

[31] Sweeney DF, Millar TJ, Raju SR. Tear film stability. Experimental Eye Research 2013;117:28-38. DOI: 10.106/j.exer.2013.08.010

[32] Wang MTM, Murphy PJ, Blades KJ, Craing JP. Comparison of non-invasive tear film stability measurement techniques. Clin Exp Optom. 2018;101:13-17. DOI: 10.1111/cxo.12546

[33] Plugfelder SC, Tseng SCG, Sanabria O, Kell H, Garcia CG, Felix C, et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. Cornea 1998;17(1):38-56. DOI: 10.1097/00003226-199801000-00007

[34] O'Brien PD, Collum LMT. Dry eye: Diagnosis and current treatment strategies. Current Allergy and Asthma Reports 2004;4:314-319. DOI: 10.1007/s11882-004-0077-2

[35] Mohidin N, Bay TC, Yap M. Non-invasive tear break-up time in normal Malays. Clin Exp Optom. 2002;85(1):37-41. DOI: 10.1111/j.1444-0938.2002.tb03070.x

[36] Yeh TN, Graham AD, Lin MC. Relationships among tear film stability, osmolarity, and dryness symptoms. Optom Vis Sci. 2015;92(9):e264-e272. DOI: 10.1097/OPX.0000000000000649

[37] Wang H, Seger KR, Yang S, Xing X. The role of ethnicity versus environment in tear film stability: a pilot study. Contact Lens and Anterior Eye 2019;42:553-556. DOI: 10.106/j.clae.2019.04.015

[38] Mengher LS, Bron AJ, Tonge SR, Gilbert DJ. A non-invasive instrument for clinical assessment of the pre-corneal tear film stability. Curr Eye Res. 1985; 4(1):1-7. DOI: 10.3109/02713688508999960

[39] Mengher LS, Pandher KS, Bron AJ. Non-invasive tear film break-up time: sensitivity and specificty. Acta Ophthalmol. 1986;64:441-444. DOI: 10.111/j.1755-3768.1986.tb06950.x

[40] Sharanjeet-Kaur, Ho CY, Mutalib HA, Ghazali AR. The relationship between tear ferning patterns and non-invasive tear break-up time in normal Asian population. Journal of Optometry 2016;9:175-181. DOI: 10.106/j.optom.2015.10.004

[41] Pauk SV, Petriček I, Jukić T, Popović-Suić S, Tomić M, Kalauz M, et al. Noninvasive tear film break-up time assessment using handheld lipid layer examination instrument. Acta Clin Croat. 2019;58:63-71. DOI: 10.20471/acc.2019.58.01.09

[42] Li N, Deng X, He M. Comparison of the Schirmer I test with and without topical anesthesia for diagnosis dry eye. Int J Ophthalmol 2012;5(4):478-481. DOI: 10.3980/j.issn.2222-3959.2012.04.14

[43] Clinch TE, Benedetto DA, Felberg NT, Laibson PR. Schirmer's test: A closer look. Arch Ophthalmol. 1983;101:1383-1386. DOI: 10.1001/archopht.1983.01040020385009

[44] Senchyna M, Wax MB. Quantitative assessment of tear production: A review of methods and utility in dry eye drug discovery. J Ocul Biol Dis Inform. 2008;1:1-6. DOI: 10.1007/s12177-008-9006-2

[45] Ibrahim OMA, Dogru M, Ward SK, Matsumo Y, Wakamatsu TH, Ishida K, et al. The efficacy, sensitivity, and specificty of strip meniscometry in conjunction with tear function tests in the assessment of tear meniscus. Invest Ophthalmol Vis Sci. 2011;52:2194-2198. DOI: 10.1167/iovs.10-5986

[46] Wright JC, Meger GE. A review of the Schirmer test for tear production. Arch Ophthalmol. 1962;67:564-565. DOI: 10.1001/archopht.1962.00960020564008

[47] Jones LT. The lacrimal secretory system and its treatment. Am J Ophthalmol. 1966;62(1):47-60. DOI: 10.1016/0002-9394(66)91676-x

[48] [No author listed]. Methodologies to diagnose and monitor dry eye disease: Report of the definition and classification subcommittee of the international dry eye workshop (2007). Ocul Surf. 2007;5(2):108-152. DOI: 10.1016/s1542-0124(12)70083-6

[49] Wood SD, Mian SI. Diagnostic tools for dry eye disease. European Ophthalmic Review 2016;10(2):101-107. DOI: 10.17925/EOR.2016.10.02.101

[50] Makateb A, Torabifard H. Dry eye signs and symptoms in night-time workers. J Curr Ophthalmol. 2017;29(4):270-273. DOI: 10.106/j.joco.2017.05.003

[51] Sakamoto R, Bennet ES, Henry VA, Paragina S, Narumi T, Izumi Y, et al. The phenol red thread tear test: A cross-cultural study. Invest Ophth Vis Sci. 1993; 34:3510-3513.

[52] Saleh TA, McDermott B, Bates AK, Ewings P. Phenol red thread test vs Schirmer's test: A comparative study. Eye 2006;20:913-915. DOI: 10.1038/sj.eye.6702052

[53] Tomlinson A, Blades KJ, Pearce EI. What does the phenol red thread test actually measure?. Optometry and Vision Science 2001;78(3):142-146.

[54] Vashisht S, Singh S. Evaluation of phenol red thread test versus Schirmer test in dry eyes: A comparative study. Int J Appl Basic Med Res. 2011;1(1):40-42. DOI: 10.4103/2229-516X.81979

[55] Baudouin C, Brignole F, Becquet F, Pisella P, Gogue A. Flow cytometry in impression cytology specimens. Invest Ophth Vis Sci. 1997;38(7):1458-1464.

[56] Singh R, Joseph A, Umapathy T, Tint NL, Dua HS. Impression cytology of the ocular surface. Br J Ophthalmol. 2005;89:1655-1659. DOI: 10.1136/bjo.2005.073916

[57] Baoudoin C. Nonroutine tests for dry eye disease. In: Asbell PA, Lemp MA, editors. Dry Eye Disease: The Clinician's Guide to Diagnosis and Treatment. New York: Thieme; 2006. p. 47-62. DOI: 10.1055/b-002-51025

[58] Lemp MA, Bron AJ, Baoudouin C, del Castillo JMB, Geffen D, Tauber J, et al. Tear osmolarity in the diagnosis and management of dry eye disease. Am J Ophthalmol. 2010;151(5):792-798. DOI: 10.1016/j.ajo.2010.10.032

[59] Schargus M, Wolf F, Tony HP, Meyer-ter-Vehn T, Geerling G. Correlaion between tear film osmolarity, dry eye disease, and rheumatoid arthritis. Cornea 2014; 33:1258-1261. DOI: 10.1097/ico.0000000000000257

[60] Masmali AM, Purslow C, Murphy PJ. The tear ferning test: A simple clinical technique to evaluate the ocular tear film. Clin Exp Optom. 2014;97:399-406. DOI: 10.1111/cxo.12160