Diagnosing the severity of dry eye: a clear and practical algorithm

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ABSTRACT
Dry eye disease (DED) is a distressing ocular condition. Due to its multifactorial nature, clinical and biological signs of DED can be inconsistent and sometimes discordant with symptomatology. Consequently, no gold-standard model for determining DED severity exists. This can impact treatment decisions and complicate evaluation of disease progression, particularly within the stringent context of clinical trials. The multinational ODISSEY European Consensus Group is comprised of ophthalmologists who contend with ocular surface disease issues on a daily basis. This group convened to establish a clear and practical algorithm for evaluation and diagnosis of severe DED. Using a consensus-based approach, they assessed 14 commonly used DED severity criteria. The panel agreed that following confirmed DED diagnosis, just two criteria, symptom-based assessment and corneal fluorescein staining were sufficient to diagnose the presence of severe DED in the majority of patients. In the event of discordance between signs and symptoms, further evaluation using additional determinantal criteria was recommended. This report presents the ODISSEY European Consensus Group recommended algorithm for DED evaluation, which facilitates diagnosis of severe disease even in the event of discordance between signs and symptoms. It is intended that this algorithm will be useful in a clinical and developmental setting.

INTRODUCTION
Dry eye disease (DED) is a common ocular condition which significantly reduces quality of life, and affects 6–34% of the global adult population.1–2

Pathological dry eye was first described as keratoconjunctivitis sicca (KCS) over 70 years ago,3–5 and although DED and KCS are not strictly synonymous (as DED can present without keratitis6), this report will follow accepted dogma by assuming that the terms DED and KCS are interchangeable, and adopt the following 2007 International Dry Eye Workshop (DEWS) definition:

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolality of the tear film and inflammation of the ocular surface.5

There are relatively few effective treatments for DED, especially for severe disease.7 Clinical development of new DED treatments is slow, partly because of problematic diagnosis and classification.8 DED pathogenesis and presentation is multifarious, and symptomatology and signs of DED can be inconsistent. Many disease severity criteria currently used by ophthalmologists are confounded by complex disease subtypes and a lack of standardisation, and the selection of single criteria for assessment of disease severity is therefore fraught with difficulties.9–11 This lack of dependable diagnostic criteria for disease progression and therapeutic response can undermine clinical trial success and complicate clinical decision making.8,11–13

The vicious circle of disease progression
Numerous extrinsic and intrinsic factors can trigger DED by negatively impacting tear film stability and tear hyperosmolality; activating osmotic/mechanical stress mechanisms.14–17 This leads to apoptosis, ocular cell damage, and release of inflammatory mediators, increasing ocular surface stress and leading to potential epithelial damage.18–19 Chronic inflammatory response is now thought to be one of the most important mechanisms in DED pathogenesis.20

In the early stages of mild or moderate DED, the eye can adapt and introduce compensatory mechanisms, and the condition will respond to treatment.21 However, if initial damage is prolonged or too severe, goblet cell repair mechanisms can falter and mucin production becomes dysregulated. Altered mucin production can reduce tear-film stability, and a deadly feedback loop of escalating inflammation can manifest. This cycle has been termed the ‘vicious circle’ (figure 122). No matter how the cycle starts, once it establishes it can lead to severe treatment-refractory disease and permanent damage if no corrective treatment is given.22 23

Discordance between DED signs and symptoms
Many DED pathophysiological mechanisms stimulate sensory neurons of the cornea, and DED has sometimes been described as a ‘symptomatic disease’.24–26 For the majority of DED patients, there is some relation between symptoms and clinical signs. However, it is also well established that perceived symptom severity may not equate to clinical signs of disease, and there exists a significant proportion of patients who have seemingly conflicting symptoms and signs.25 27 Indeed, one study showed that up to 40% of patients had symptom and clinical sign discordance.12 Another study showed meibomian gland disease was more commonly asymptomatic than symptomatic (21.9% vs 8.6%, respectively), and symptom presentation did not correlate with severity of ocular surface damage.28 Physiological mechanisms can partly account for these discrepancies.22 29

In early or mild DED, the presence of hyperalgesia can cause significant ocular discomfort without any signs of tissue damage. Yet in more severe or chronic disease, decreased corneal sensation due to compensatory reflex mechanisms can actually reduce discomfort. Corneal sensory neurons can sometimes also be permanently damaged by very severe DED, or by the underlying causal disease leading to DED.

In addition to the physiological explanation of discordance, the variable specificity, sensitivity and reproducibility of some clinical/biological marker evaluations can introduce the potential for false results. This may also confound severity assessments and contribute to supposed symptom and sign discordance. In one study, over 60% of patients remained poorly classified in terms of disease severity even when a combination of clinical markers was applied.

This apparent paradoxical disconnect between signs, symptoms and severity makes symptomatology alone a relatively poor indicator of severity in some patients, and also a confounding variable in clinical trials.

Evaluation of DED severity

There is still no gold-standard model for determining DED severity. In 2006, a Delphi panel of DED specialists agreed that disease severity is one of the most relevant factors when considering therapeutic options for DED. They subsequently recommended a DED severity grading which was later adopted by the DEWS. Severity was categorised into four levels, based on increasing frequency and intensity of various signs and symptoms. Patient-reported symptoms included requirement of tear substitute, ocular discomfort and visual disturbance. Clinical signs included conjunctival injection, conjunctival and corneal staining, corneal/tear signs (ie, filamentary keratitis), lid/meibomian glands, tear break-up time (TBUT; fluorescein based), and Schirmer score. This system is advantageous in terms of simplicity and practicality, but requires severe symptoms AND severe signs before severe disease is diagnosed. Therefore, this algorithm may not be suitable for patients whose signs and symptoms do not concur. The aim of this consensus group was to build on the DEWS methodology and optimise tailored diagnostic methods specifically for severe DED.

THE ODISSEY EUROPEAN CONSENSUS GROUP

An algorithm that identifies the criteria most relevant to the patient will allow for targeted evaluation of the ocular surface and facilitate assessment of disease severity. This ‘bespoke’ approach to evaluation of severe DED will help to define the most appropriate treatment in the clinical setting, and will also allow for better designed clinical trials. With this aim in mind, the ODISSEY European Consensus Group, comprising 10 ophthalmologists (including one American) who all contend with ocular surface disease issues on a daily basis, was formed.

Members were first asked to complete an electronic questionnaire aimed at finding out which clinical and biological criteria they thought were important for diagnosing severe DED. They then attended a day-long meeting in September 2012. The aim of this meeting was to review clinical and scientific challenges in diagnosis and management of severe DED, and to achieve consensus agreement on a simplified approach to severe DED evaluation. A total of 14 criteria for DED severity were discussed. Advantages and issues were addressed, and also their specificity and sensitivity for diagnosing severe DED. Appropriate scales of assessment and reference values for each criterion were also suggested, based on clinical judgement and the literature.

The following markers and evaluations were discussed:

- Corneal fluorescein staining (CFS)
- Tear hyperosmolarity
- Schirmer test
- Impression cytology
- Filamentary keratitis
- Conjunctival staining
- Impaired visual function
- Meibomian gland disease or eyelid inflammation
- Blepharospasm
- TBUT
- Aberrometry
- In vivo corneal confocal microscopy
Inflammatory biomarkers (ie, HLA-DR (human leukocyte antigen-DR), MMP9 (matrix metalloproteinase 9), cytokines, tear proteomics)

- Refractory to standard disease treatments

### A SIMPLIFIED AND PRACTICAL APPROACH TO EVALUATING DED SEVERITY

Following extensive review of current knowledge, questionnaire results analysis and discussion, the ODISSEY European Consensus Group defined a two-step scoring algorithm for diagnosing severe DED (figure 2). The algorithm addresses the challenge of symptom and sign discordance in some cases of severe DED, and describes specific criteria relevant to evaluating DED severity in three different patient scenarios.

#### Step 1: fundamentals of severe DED diagnosis

The first step of the scoring algorithm evaluates the minimum number of fundamental criteria required for severe DED diagnosis. It was recommended by the panel that just two criteria, a symptomatic assessment and an evaluation of ocular surface damage by CFS would be sufficient to adequately evaluate severity for the majority of patients. These two criteria are discussed below.

Symptomatology and CFS as the primary assessment criteria

DED symptoms of ocular discomfort and visual disturbance can seriously impact patients’ quality of life. The Food and Drug Administration (FDA) has emphasised the importance of patient-reported outcomes as clinical endpoints in ophthalmological trials, and a number of validated questionnaires have been developed to assess symptoms of dry eye. These tools are generally economically viable, correlate well with quality of life, have good sensitivity for DED diagnosis, and can be easily quantified. However, the panel also acknowledged that symptom assessments may not be easily reproducible, are not necessarily specific for DED, and their use may carry a risk of overtreatment. The Ocular Surface Disease Index (OSDI) is one of the most widely used questionnaires. The OSDI and similar tools have been shown to correlate moderately well with disease severity, and to a similar degree as corneal staining (eg, $r^2=0.41$ vs $r^2=0.43$, respectively). However, other studies show poor correlation. Nevertheless, it is generally accepted that an OSDI score of around 30 or over is necessary for diagnosis of severe DED.

CFS is a widely used diagnostic test useful for assessing the health of the cornea. CFS was considered by the panel to be the single most appropriate test of DED signs. It is easy to perform, inexpensive, reproducible and can correlate with visual acuity and disease severity. CFS requires a standardised assessment procedure; also no method of objective quantification is available. However, a score $\geq 3$ on the Oxford Scheme generally indicates severe DED. It must also be remembered that CFS will stain all corneal damage non-specifically, irrespective of cause (eg, refractive laser surgery and drug toxicity). Ambiguous, asymmetrical and artefact staining patterns can also be an issue, as can sensitivity in mild disease (similar to all known markers of DED).

Following discussion, ODISSEY members decided that combined use of CFS and symptom-based assessment can provide a reliable ‘frontline’ diagnostic approach for evaluation of DED severity, and that an OSDI score $\geq 33$ and CFS score $\geq 3$ on the Oxford scheme is enough to clearly establish a diagnosis of severe DED in those patients whose signs and symptoms of disease associate well. Thus, it was recommended that these criteria should be adopted for Step 1 of the diagnostic algorithm (figure 2). However, in cases of discordance, it was recommended that further additional evaluations are needed in order to improve diagnostic specificity.

#### Step 2: additional criteria for severe DED diagnosis

The panel agreed that when there is discordance between DED signs and symptoms, that is, when OSDI and CFS severity scores are not in agreement, additional criteria are necessary to establish severe DED. Three possible outcomes after CFS and OSDI assessment in Step 1 were defined:

- **Scenario A**: if OSDI $<33$ and CFS $\geq 3$.
- **Scenario B**: if OSDI $\geq 33$ and CFS $=2$.
- **Scenario C**: if OSDI $\geq 33$ and CFS $\leq 1$.

#### Diagram

![Consensus derived scoring algorithm for severe DED diagnosis. DED, dry eye disease, TIBUT, tear break-up time, sec, second, CFS, corneal fluorescein staining, OSDI, Ocular Surface Disease Index.](http://bjo.bmj.com/fig2)

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<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Advantages</th>
<th>Issues</th>
<th>Assessment parameters</th>
<th>Severe disease criteria</th>
</tr>
</thead>
</table>
| Conjunctival staining (including conjunctivochalasis/conjunctival folds) | ▶ Staining is related to epithelial damage.  
▶ Easy to perform.  
▶ Good reproducibility (once examiner is fully trained).  
▶ Already existing grading scales.  
▶ Standard method is cost and time effective. | ▶ Epithelial damage is not correlated with subjective signs and improvement.  
▶ Easy to overestimate or underestimate findings.  
▶ Potential interexaminer variability.  
▶ Many assessment scales available.  
▶ Yellow filter may be expensive (and red filter is often not easily available).  
▶ May need 2–3 min time window before correct assessment can be made. | Yes/no for presence of severe disease, as determined on any standardised scale (ie, Oxford Scheme) | Yes, has severe disease as measured on scale |
| Schirmer Test Quantitative test for tear fluid availability. Measures maximal tear secretion capacity without anaesthesia. | ▶ Well established.  
▶ Easy to use.  
▶ Commonly accepted and available.  
▶ Safe and efficient.  
▶ Well tolerated (except with severe DED). | ▶ There is discussion regarding specificity and sensitivity.  
▶ Dependent on corneo-conjunctival sensitivity, normal reflex regulations, uneven wetting of paper.  
▶ Issues with reproducibility (ie, environmental factors).  
▶ Issues with interpretation (ie, cut-off point).  
▶ Issue with comparability (ie, variation of size, colour code, paper).  
▶ Unknown effects of tear fluid composition (lipid layer alterations). | Continuous measurement—cut-off criteria for severe disease | <3 mm |
| Impaired visual function | ▶ Non-invasive technique.  
▶ Information is easy to obtain from the patient.  
▶ Can be self-administered by the patient.  
▶ Non-expensive.  
▶ Can easily be part of standard patient work-up.  
▶ Easily repeatable in controlled conditions.  
▶ Can be used to monitor progression. | ▶ Subjective.  
▶ External bias and confounding factors.  
▶ Non-specific.  
▶ Global tear film stability index.  
▶ Cannot distinguish tear instability effects from cornea surface damage. | Yes/no | Yes |
| Filamentary keratitis | ▶ Highly symptomatic.  
▶ Good correlation with severity.  
▶ Diagnosis is easy for general ophthalmologist.  
▶ Small number of patients for clinical trials and brief course of treatment may allow a fast evaluation of results. | ▶ Not yet widely available.  
▶ Must distinguish between the subtypes of DED with other tests.  
▶ Symptom improvement may lag behind tear osmolarity improvement.  
▶ Needs an external laboratory experienced in cytology and an observer trained in conjunctival pathologies.  
▶ Assessment of squamous metaplasia only | Continuous measurement—cut-off criteria for severe disease | >328 mOsm/L |
| Tear hyperosmolarity | ▶ The most valuable single metric for diagnosis and disease management.  
▶ A global marker for DED.  
▶ Parallels disease severity.  
▶ Responds to effective therapy. | Nelson scale—cut-off criteria for severe disease | ≥Grade 3 |
| Impression cytology | ▶ Minimally invasive.  
▶ Well validated with published scoring systems.  
▶ Goblet cell count as an objective marker. | | | |

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### Table 1 Continued

<table>
<thead>
<tr>
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<th>Issues</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Specimens can be stored for a long period of time before processing.</td>
<td>Semiquantitative.</td>
<td>Impression cytology provides only a small amount of possible information from biological specimens.</td>
<td>Yes/no</td>
<td>Yes</td>
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<tr>
<td>No major technical issue with standard cytological techniques.</td>
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<td>Good marker for severe DED.</td>
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<td>Yes/no to a severe degree</td>
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<td>Has serious consequences for visual function.</td>
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<td>Easy to diagnose (only if more severe/significant).</td>
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<tr>
<td>Accessible to documentation.</td>
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<td>Standardised tools available.</td>
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<td>Few additional basic investigational tools required.</td>
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<td>A condition of chronic inflammation of the eyelid.</td>
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#### Continued

**Blepharospasm**
- Secondary to ocular irritation.
- Good marker for severe DED.
- Has serious consequences for visual function.
- Easy to diagnose (only if more severe/significant).
- Accessible to documentation.
- Standardised tools available.
- Few additional basic investigational tools required.
- Yes/no to a severe degree
- Yes

**Meibomian gland disease or eyelid inflammation**
- A condition of chronic inflammation of the eyelid.
- Easy to diagnose (only if more severe/significant).
- Accessible to documentation.
- Standardised tools available.
- Few additional basic investigational tools required.
- Yes/no to a severe degree
- Yes

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These are clinical and biological markers or evaluations considered by the ODOSSEY consensus panel as being sufficiently validated to establish diagnosis of severe DED. DED, dry eye disease; DEWS, dry eye workshop; KCS, keratoconjunctivitis sicca; mOsm, milliosmole; TBUT, tear break-up time.
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| Refractory to standard disease treatments | - Apparently a clinical indicator of severity.  
- Might indicate ocular surface inflammation.  
- May distinguish between mild and severe cases of DED.  
- Might be used as an indication to initiate long term anti-inflammatory treatment (ie, topical cyclosporine). | - Definition of ‘standard treatment’ is critical.  
- Not all the patients receive the same standard treatment.  
- Refractoriness could be the consequence of inappropriate standard treatments.  
- Severity staging is needed.  
- Discordance of symptoms and signs may be a pitfall.  
- Long-term anti-inflammatory therapies, topical and systemic, may induce adverse events. | Not established | – |
| Confocal microscopy                   | - High resolution in vivo tissue examination.  
- Minimally invasive.  
- Useful for counting inflammatory cells and investigating corneal nerves.  
- Provides overview of the whole ocular surface, including cornea, conjunctiva and limbus. | - Time-consuming.  
- Expensive device not widely available.  
- Needs an expert observer for specific diagnoses.  
- Lack of scoring systems and quantitative methods.  
- Nerve reconstruction software not available (images of narrow areas with limited value). | Not established in clinical setting | – |
| Aberrometry                           | - Non-invasive system.  
- Gives rapid information about patient’s visual problems.  
- Useful for global definition of tear film conditions as a good indicator of tear film instability.  
- Easily repeatable, can be used to monitor therapy efficacy.  
- High sensitivity. | - Expensive instrument not easily available in all offices.  
- Lack of specificity for the disease.  
- Influenced by environmental conditions, quality of the last blink.  
- Influenced by eye drops instillation.  
- Unable to help characterise the disease.  
- There is no objective way to extrapolate results and to predict real visual acuity of the patient. | Not well established | – |
| Inflammatory markers HLA-DR expression | - Minimally invasive sample collection of conjunctival imprints.  
- Expressed by the most important cell population of the conjunctiva, that is, epithelial cells.  
- Large range of values; normal to severe dry eye.  
- Highly expressed in inflammatory and immune diseases.  
- Technique validated in several international multicentre trials with a central reading centre. | - Technique time-consuming: needs appropriate staff and expensive material  
- Strict rules for collecting and sending specimens.  
- Limited time before sample examination.  
- Mainly designed for research and clinical trials. | Used as a biomarker in clinical trials, not established in clinical setting | – |
| Other inflammatory markers MMP9, cytokines, proteomics and Luminex assays. | - Study disease pathogenesis at the molecular level.  
- Minimal tear sample volumes needed.  
- Possible multiple determinations for cytokines and MMPs.  
- Precise/objective determination of molecular quantity.  
- Easy collection: possible to analyse eluate from Schirmer’s strips, cytology specimens, tear samples. | - Not definitely established correlation with severity of the disease.  
- Not well defined role in specific dry eye pathogenic subgroups.  
- Methods not yet very feasible for diagnostic purposes.  
- Labs not available in all clinical centres (useful only for smaller phase 2 or phase 3 trials). | Not well established | – |
panel recommended that if reported symptoms are severe, but there is no immediate correlation with clinical signs as assessed by CFS grade, the diagnosis of DED should be reconsidered (but not necessarily discarded). Use of the TBUT test in this scenario is, therefore, a prerequisite as a preliminary step (see figure 2) to evaluate tear film instability and confirm the original diagnosis of DED. A more comprehensive understanding of the patient case is also necessary (eg, use of an in-depth patient questionnaire to further determine quality of life, mood evaluation, etc.).

It is of note that filamentary keratitis is not considered as an additional determinant criteria in the case of Scenario C, as objective ocular symptoms determined by CFS have already been confirmed as mild (table 3). Similar to Scenario B, corneal sensitivity testing is not required, as the OSDI score is satisfactory.

CONCLUSIONS
The ophthalmological field requires a reliable algorithm for patient-tailored evaluation of ocular surface damage, enabling definitive diagnosis of severe DED. However, reliable assessment of DED severity can be problematic due to several issues, including poorly standardised evaluation methods, non-correlation between disease severity and clinical/biological disease markers, and individual variability in symptomatology and disease signs. The vicious circle of DED pathogenesis, which can exacerbate the condition and facilitate merging or development of mechanistically distinct DED subtypes can further hinder accurate evaluation.

The ODISSEY scoring algorithm for severe DED diagnosis is a simple, easy-to-use and practical tool, which facilitates assessment of ocular surface damage and evaluation of disease severity. For the majority of DED patients who have a good symptom and sign correlation, OSDI and CFS are adequate to establish DED severity. For patients with symptom and sign dissociation, the evaluation of additional specific criteria are recommended to ascertain disease severity. It is hoped that use of this ‘bespoke’ diagnostic algorithm for evaluating severe DED will allow for targeted disease monitoring and treatment, and will also improve clinical trial outcome assessment.

Several systems for classifying DED severity already exist. The Triple Classification System bases severity on the continuing presence of symptoms, along with increasing signs of disease. The DEWS approach ranks DED severity on four levels, centred around simultaneous exacerbation of signs and symptoms. New Japanese DED diagnostic criteria now include symptomatology, and the presence of symptoms and signs is required for a diagnosis of ‘definite dry eye’, which correlates with more severe disease. All these classification systems require severe signs and severe symptoms for a diagnosis of severe disease. However, the ODISSEY scoring algorithm provides diagnostic pathways for patients with more complex discordant DED.

There are several limitations to the use of this model. The method of panel-based consensus is by its very nature not necessarily evidence based. The paucity of ‘gold-standard’ DED biomarkers with well-established criteria also impacts any attempt to standardise DED severity evaluation. Furthermore, the use of specific recommended assessments will heavily depend on local availability, training and cost. There is also an issue of pre-existing differences in definitions of dry eye. For example, the Japanese recognise a short break-up time, dry eye condition, characterised by very short TBUT and severe symptoms, but with minimal surface damage. This scenario is very similar to Scenario C of the algorithm presented in this paper. The
Japanese do not consider this condition severe, however, following the DEWS approach and the algorithm presented here, it would satisfy criteria for diagnosis as severe DED.

Nevertheless, by using a hierarchical approach to provide a range of acceptable marker options relevant for each patient it is hoped that, after extensive validation, this algorithm can be broadly applied across a range of clinical and geographical settings.

The next stage is to test the validity of the ODISSEY scoring algorithm in the context of clinical trials. It is hoped implementation of this tool will help to better define trial outcomes and accelerate clinical development of new treatments. Once validated, this algorithm will also aid the ophthalmologist in patient follow-up and treatment optimisation.

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Review


