Agreement of Physician Treatment Practices With the International Task Force Guidelines for Diagnosis and Treatment of Dry Eye Disease

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Purpose: To evaluate the clinical implementation of guidelines for the treatment of dysfunctional tear syndrome (DTS) developed by the International Task Force (ITF) of dry eye disease experts.

Methods: Nine physicians implemented the ITF guidelines for 3 months. Newly diagnosed patients with DTS rated their ocular symptoms and were clinically examined. Using the guidelines, physicians determined the DTS severity level (0–4, where 4 is most severe) and made their therapeutic choices.

Results: Of 183 patients enrolled (mean age, 65.1 years; range, 25–91 years), 67% presented without lid margin disease, and 68% had no apparent ocular surface inflammation. Symptoms were significantly more severe in patients with altered tear distribution or evident inflammation ($P < 0.05$). Most patients diagnosed at severity level 1 did not have lid margin disease (56/61, 92%), and inflammation was not apparent (53/58, 91%); 43% of severity level 1 patients (27/63) were treated at level 2 (therapeutic choices include unpreserved tears or topical cyclosporine). Most patients presenting with inflammation were diagnosed at severity level 2 (74%, 32/43). More than 9 in 10 severity level 2 patients were treated at level 2 (100/106; 94%). Physicians reported that 96% of their treatment recommendations were consistent with management they would have recommended if they had not consulted the ITF guidelines. They spent an average of 4.5 minutes per patient applying the guidelines.

Conclusions: Implementation of the ITF guidelines was simple and not time consuming. Many practitioners chose to treat patients diagnosed at severity level 1 with treatments at level 2 that include unpreserved tears and topical cyclosporine.

Key Words: dry eye disease, dysfunctional tear syndrome, treatment guidelines, Delphi panel

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Dry eye disease is a common condition estimated to afflict more than 7 million Americans over the age of 40.[1–5] Risk factors include older age, female sex, postmenopausal status, and previous laser in situ keratomileusis (LASIK) surgery.[2–4] Common symptoms include ocular discomfort and irritation such as scratchiness, grittiness, foreign body sensation, burning, blurring, and itching.[6] Symptoms can be exacerbated by the use of systemic medications that dry the ocular surface and by environmental factors such as reduced humidity, air conditioning, and prolonged use of video display terminals.[3,6,7] An individual's quality of life can be significantly affected by dry eye symptoms, as documented by several validated survey instruments.[8–10] The psychologic impact of this chronic condition is suggested by utility (patient preference) assessments of patients' willingness to trade years at the end of life for an opportunity to be free of dry eye disease, which found that the utility of moderate dry eye disease was similar to that of moderate angina.[11]

Dry eye disease encompasses diverse etiologies and varies greatly in severity; in addition, correlations between symptoms, clinical signs, and diagnostic test results are variable, making the diagnosis and treatment of this condition challenging.[12] Dry eye treatment patterns are evolving, as our understanding of the condition has evolved from considering it to be that of a tear volume insufficiency to identifying it as a disorder of tear film instability with an underlying inflammatory pathophysiology that results in altered tear composition.[3,13–15] Anti-inflammatory therapies such as topical cyclosporine have been developed to target this root cause of the disease.[16–20] A practice algorithm incorporating the latest knowledge of diagnosis and treatments could lead to more effective therapeutic regimens for patients.

To address this need, an International Task Force (ITF) consisting of 17 dry eye expert clinicians was impaneled to create diagnosis and treatment guidelines for dry eye disease, using a Delphi consensus technique.[21] The panel recommended that the term "dry eye disease" be replaced with "dysfunctional tear syndrome" (DTS) to reflect current understanding of the condition's pathophysiology. Disease severity was considered to be the most important factor in treatment decision-making and was categorized into four levels. The panel agreed that patient symptoms and clinical signs were the key factors in determining DTS severity and guiding treatment decisions, with less reliance on diagnostic tests such as the Schirmer test.

Treatment algorithms were developed for each DTS severity level, taking into account the presence or absence of lid margin disease and disturbances of tear distribution and

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clearance. If the patient failed to respond to the recommended treatments for the diagnosed severity level, the panel recommended moving to the recommendations for the next (higher) level of disease severity. Abbreviated versions of the ITF guidelines for severity level determination and treatment guidelines for each level are presented in Tables 1 and 2, respectively.

A key recommendation in the guidelines was that topical anti-inflammatory therapy should be used even if ocular surface inflammation is not clinically apparent. Research in recent years has shown that the disease involves progressive, self-reinforcing alterations of tear film composition that promote inflammation. These alterations include a reduction in anti-inflammatory tear film components, increases in several proinflammatory cytokines, and an increase in tear osmolarity that is also an inflammatory stimulus.[13,14,18] Furthermore, in dry eye associated with postmenopausal status, the hormonal support that normally maintains the ocular surface in a noninflammatory state is compromised.[22] Although these inflammatory alterations of the ocular surface are usually not apparent in a routine clinical examination, they are now understood to underlie dry eye disease.

The successful use of short courses of topical steroids to reduce the severity of dry eye underscores the inflammatory nature of the disease, but steroids may not be suitable long-term therapies because of safety concerns, and pulses of steroids may be followed by longer-term topical cyclosporine therapy.[18] Anti-inflammatory treatments that normalize the tear film composition early in the disease process and that are safe for chronic use may have the potential to slow, prevent, or reverse DTS progression.

This study reports the implementation of the ITF guidelines in clinical practice. Nine physicians used the guidelines to develop treatment regimens for patients with newly diagnosed DTS seen during a 3-month period. The study was designed to provide a portrait of newly diagnosed DTS patients classified according to the guidelines and to compare treatment recommendations made using the guidelines with physicians' usual clinical practice patterns.

MATERIALS AND METHODS

This nonrandomized, multicenter study was conducted over a 3-month period from January to April 2005. Of 9 investigators, 1 was a corneal transplant specialist, and 7 had cataract and refractive subspecialties. During the study period, they completed a report on each new patient with dry eye presenting in their practices. Physicians determined the clinical category of DTS (without lid margin disease, with lid margin disease, or altered tear distribution/clearance) and whether inflammation was visually apparent during a clinical examination. Physicians asked patients to rate the severity of their ocular discomfort, ocular fatigue, and visual disturbances on the following scale: 0 = none, 1 = mild/moderate, 2 = moderate/severe, 3 = severe, 4 = extremely severe. These symptoms were chosen for study because authors of the ITF guidelines considered them "especially relevant" for DTS severity determination.[21] Clinical signs were also noted (Table 1). Each investigator had the option of performing additional diagnostic tests, if desired, according to his or her own usual clinical practice.

Physicians determined each patient's dry eye severity level by using the ITF guidelines presented in Table 1. The guidelines give primary consideration to symptoms and clinical signs and secondary consideration to the results of any diagnostic tests. After consulting the ITF guideline recommendations for treating each severity level of DTS (Table 2), physicians indicated their choice of treatment for each patient on a survey form similar in appearance to Table 2. They indicated either a general treatment level or specific therapy choices made within a level. Although treatment decisions were made with reference to the guidelines, physicians were free to recommend any therapy to any particular patient from his or her clinical judgment.

Investigators completed a survey comparing their treatment choices made using the ITF guidelines with their previous usual clinical recommendations and recorded the time they spent with each patient to apply the guidelines.

Statistical analyses used unpaired t tests. $P \leq 0.05$ was considered statistically significant.

RESULTS

Nine physicians enrolled 183 patients with dry eye over a 3-month period. Patients were an average of 65.1 ± 14.3 years of age (range, 25–91 years). Investigators used the ITF guidelines to determine the DTS severity level for these patients and to help choose therapeutic options. To apply the guidelines, physicians noted the clinical category of dry eye

TABLE 1. ITF Guidelines for Determining the Severity Level of DTS[21]

	DTS Severity			
	Level 1	**Level 2**	**Level 3**	**Level 4**
Symptoms*	Mild–moderate	Moderate–severe	Severe	Severe
Signs†	Mild–moderate conjunctival signs	Tear film signs Fluctuation of vision/blurred vision	Corneal filamentary keratitis	Corneal erosions Conjunctival scarring
Staining†	None	Mild punctate corneal staining Conjunctival staining	Central corneal staining	Severe corneal staining

*Ocular discomfort, ocular fatigue, and visual disturbance each ranked on a scale of 0 (none) to 4 (extremely severe).
†Graded on a scale of 0 (low) to 4 (high).

TABLE 2. ITF Guidelines for Treatment of DTS at Each Severity Level[21]

	DTS Severity			
	Level 1	**Level 2**	**Level 3**	**Level 4**
Treatment options (without lid margin disease*)	Patient education	Unpreserved tears	Oral tetracyclines	Systemic anti-inflammatory
	Environmental modification	Gels, ointments	Punctal plugs (after inflammation has been controlled)	Acetylcysteine
	Preserved tears	Topical cyclosporin A		Moisture goggles
	Control allergy	Topical steroids		Surgery (tarsorrhaphy)
		Secretagogues		
		Nutritional support		
Treatment algorithm	If no improvement, add level 2 treatment	If no improvement, add level 3 treatment	If no improvement, add level 4 treatment	

*For patients with lid margin disease, the guidelines include the above treatments plus one or all of the following: lid hygiene, thermomassage, oral tetracyclines.

and whether or not inflammation was overtly apparent, assessed ocular surface staining, and asked patients to rate their symptoms of ocular discomfort, ocular fatigue, and visual disturbance.

Clinical Categories and Inflammation

Physicians classified each patient into 1 of 3 dry eye clinical categories: with lid margin disease, without lid margin disease, or having altered tear film distribution/clearance. Most patients (70%, 122/175) presented without lid margin disease. Most patients in this category did not display any apparent ocular surface inflammation (88%; 100/114). The second most common clinical category was altered tear distribution/clearance (17%, 30/175). Slightly more than 1 in 10 patients (13%, 23/175) presented with lid margin disease, making this the least common clinical category (Fig. 1). Inflammation was apparent in 70% (16/23) of these patients. Overall, inflammation was judged not apparent in 74% of the study population (124/167; Fig. 1).

Symptom Severity

Table 3 presents symptoms scored by patients on the following scale: 0 = none; 1 = mild/moderate; 2 = moderate/severe; 3 = severe; 4 = extremely severe. Ocular discomfort was the most severe symptom overall, scoring 2.16 ± 0.97 (SD) that corresponds to moderate/severe. Mean ocular discomfort was significantly more severe than ocular fatigue and visual disturbance (1.74 ± 1.07 and 1.74 ± 1.10, respectively; $P = 0.0001$). Among the 3 clinical categories, the most severe symptoms were seen in patients classified as having altered tear distribution. Ocular discomfort and ocular fatigue were each significantly more severe in these patients than those in the other clinical categories, as was the average score of all 3 symptoms ($P \leq 0.045$).

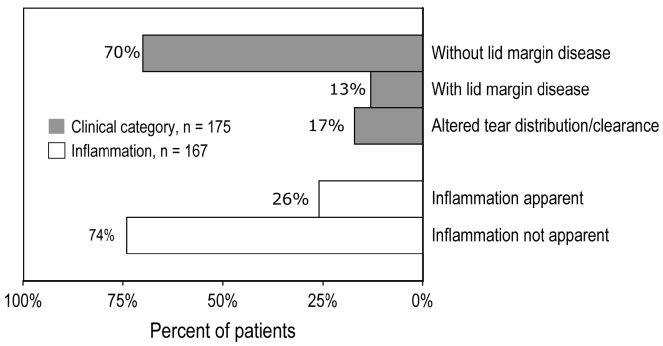

FIGURE 1. Classification of clinical category and inflammation in patients with DTS. Study population N = 183; totals shown in figure are less because of the lack of responses for all patients.

Determination of DTS Severity Level

Severity level diagnosis from the ITF guidelines is shown in Table 4. More than 9 of 10 patients with DTS (93%, 169/181) were diagnosed at either severity level 1 or level 2 (Table 4). Severity level 2 was diagnosed most frequently (59%, 106/181), followed by level 1 (35%, 63/181), level 3 (6%, 11/181), and level 4 (1/181). Most severity level 1 patients (92%, 56/61) presented without lid margin disease. Inflammation was not apparent in 91% of level 1 cases (53/58). Nearly three quarters of patients who presented with apparent inflammation were diagnosed at severity level 2 (74%, 32/43). Most of those diagnosed at severity level 2 presented without lid margin disease (58%, 59/102); however, patients who presented with either lid margin disease or altered tear distribution/clearance were most likely to be diagnosed at level 2 (78% and 83% of those clinical categories, respectively).

Treatment Level Determination

Most patients (57%; 36/63) diagnosed at DTS severity level 1 were prescribed treatments associated with level 1 of the ITF guidelines, whereas 43% (27/63) were prescribed treatments associated with level 2 of the guidelines (Fig. 2). Level 1 treatment options include patient education and preserved artificial tears, whereas level 2 treatment options include unpreserved artificial tears and topical cyclosporine.

Most patients with a severity level 2 diagnosis were prescribed level 2 treatments (94%, 100/106). Level 2 treatments were also prescribed for patients diagnosed at

TABLE 3. Symptoms by Clinical Category and Association With Inflammation

	n	Symptom Scores* (Mean ± SD)			
		Ocular Discomfort	Ocular Fatigue	Visual Disturbance	Average of 3 Symptoms
Overall study population	183	2.16 ± 0.97†	1.74 ± 1.07	1.74 ± 1.10	1.87 ± 0.87
By clinical category:					
Without lid margin disease	122	2.10 ± 0.97	1.52 ± 1.12	1.74 ± 1.16	1.78 ± 0.90
With lid margin disease	23	2.05 ± 1.21	1.84 ± 0.97	1.77 ± 1.06	1.87 ± 0.92
Altered tear distribution	30	2.58 ± 0.66‡,§	2.47 ± 0.97‡,§	1.93 ± 0.90	2.33 ± 0.55‡,§
By inflammation:					
Apparent	43	2.55 ± 0.92‖	2.21 ± 0.88‖	2.05 ± 1.00¶	2.27 ± 0.75‖
Not apparent	124	2.02 ± 0.96	1.54 ± 1.08	1.64 ± 1.11	1.72 ± 0.87

*Graded on 0 to 4 scale; 4, most severe.
†$P = 0.0001$ vs. ocular fatigue and visual disturbance.
‡$P \leq 0.002$ vs. without lid margin disease.
§$P < 0.045$ vs. with lid margin disease.
‖$P \leq 0.002$ vs. not apparent.
¶$P = 0.037$ vs. not apparent.

DTS severity levels 3 and 4, who were primarily patients with central corneal staining and/or severe symptoms. Level 3 or level 4 treatments were not prescribed for this group (Fig. 2). Physicians who identified specific therapies (in addition to treatment levels) on their case report forms chose topical cyclosporine in 66 cases. Other therapies specifically identified were topical steroids, punctal plugs, and oral tetracycline that were chosen for 13, 2, and 3 patients, respectively.

Most patients for whom steroids were prescribed had severe symptoms and corneal staining or lid margin disease. All 3 patients for whom tetracycline was prescribed had lid margin disease and received steroids.

Clinical Practice Alignment and Ease of Implementation

Physicians reported that, in 96% of cases (168 of 176 patients), the treatment choices they made using the ITF guidelines were consistent with the clinical recommendations they would have made before they implemented the guidelines.

For 2 patients, physicians who chose topical cyclosporine in accordance with the ITF guidelines commented that they would have recommended punctal plugs before implementation of the guidelines. For 2 other patients, cyclosporine was chosen, but physicians commented that they would have prescribed artificial tears alone before implementation of the guidelines. On average, physicians spent 4.5 minutes per patient applying the ITF guidelines.

TABLE 4. Severity Level Diagnosis by Clinical Category and Presence of Inflammation

	Severity Level Diagnosed				
	Level 1	Level 2	Level 3	Level 4	Total
Overall study population	63	106	11	1	181
By clinical category					
Without lid margin disease	56	59	5	1	
With lid margin disease	3	18	2	0	
Altered tear distribution	2	25	3	0	
Total	61	102	10	1	174
By inflammation					
Apparent	5	32	6	0	
Not apparent	53	67	2	1	
Total	58	99	8	1	166

Values are numbers of patients. Study N = 183. Totals are less because of the lack of responses for all patients for severity level, clinical category, and/or inflammation.

DISCUSSION

This study investigated implementation of DTS diagnosis and treatment guidelines developed by an ITF of dry eye disease experts. Patient disease severity was graded by ITF guidelines, and the concordance of physician treatment preferences with the ITF guidelines was evaluated. The study population consisted of patients not previously treated for tear

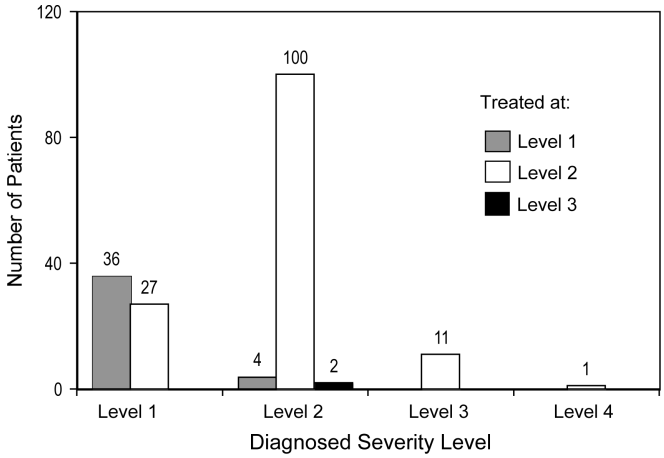

FIGURE 2. Physicians' choices of treatment levels for patients with dry eye by DTS severity level. Study population N = 183; the total number of patients in figure are less because of the lack of responses for all patients.

deficiency. Most of the patients presented without lid margin disease, and ocular surface inflammation was not visually apparent in most. Overt inflammation was most frequently apparent in patients who had lid margin disease. Ocular discomfort was the most severe symptom, consistent with this being a primary symptom of dry eye.[3] Most patients were diagnosed at either severity level 1 or 2, with severity level 2 being the most common diagnostic category.

Nearly all of the patients diagnosed at severity level 2 were treated with therapies that the ITF guidelines recommended for level 2 that include unpreserved artificial tears and topical cyclosporine. Interestingly, level 2 treatments were also prescribed for many patients diagnosed at severity level 1, perhaps as a consequence of physicians' increased awareness that aggressive, early treatment of tear deficiency might slow or prevent disease progression.

Physicians commented that the treatment choices arrived at by application of the ITF guidelines were generally consistent with those they would have made before implementation of the guidelines. They also commented that because of the guidelines, they now relied more on patient symptoms for diagnosis as opposed to diagnostic tests. An unanticipated benefit to giving patient symptoms more weight is that office staff can be trained to be alert to patients' complaints about symptoms that patients might not normally mention to physicians. This increases the probability that a patient with dry eye will receive the proper level of therapy.

Use of the ITF guidelines resulted in greater focus on treatment of the disease at early stages, evidenced by the observations that many level 1 patients were prescribed level 2 treatments. Physicians commented that under the guidelines they were more likely to treat severity level 1 patients. Because the ITF guidelines recommend escalation of treatment to the next level if no improvement occurs, physicians said they were more likely to use topical cyclosporine if artificial tears and patient education did not resolve the complaints of level 1 patients, no longer reserving cyclosporine for patients with severe disease. This shift in the patterns of cyclosporine use is in keeping with the evolving understanding of the pathophysiology of dry eye and the hypothesis that the interruption of self-reinforcing inflammatory cycles might be instrumental in preventing disease progression. However, further study is needed to establish clinical evidence for prevention of dry eye disease progression by early treatment.

Regarding physicians' choices of specific therapies, topical corticosteroids were reported as the treatment choice for 13 patients, 11 of whom also received topical cyclosporine. One possible rationale for this treatment pattern is that, for patients with severe dry eye that may be manifested by severe corneal staining or by lid margin disease, a short course of steroids helps bring acute inflammation under control, whereas cyclosporine safely addresses the long-term pathophysiology.[18]

Punctal plugs were prescribed for only 2 patients. For 2 additional patients, the physician commented that, before implementing the guidelines, he would have prescribed punctal plugs, but instead chose cyclosporine "to avoid keeping inflammatory factors on the ocular surface, as happens with punctal plugs." Reports of specific therapies mentioned in this study are probably underestimates, because physicians had the option to indicate treatment choices by indicating a treatment level or by indicating specific therapies chosen, and not all physicians specified individual therapies on the case report forms.

Several investigators participating in this study now report that they use topical cyclosporine as initial therapy in all patients with dry eye diagnosed at severity level 2 to treat the underlying cause of dry eye that may not be readily clinically apparent and to prevent disease progression. Because symptoms of ocular discomfort and irritation are generally of lower intensity in level 2 patients than in level 3 or 4 patients, level 2 patients may be less likely to experience stinging with cyclosporine eye drops, a side effect that has been previously reported.[19]

In summary, physicians found that implementation of the ITF guidelines for the treatment of dry eye was simple and not time consuming. Many practitioners chose to treat patients diagnosed at severity level 1 with treatments at level 2 that include unpreserved tears and topical cyclosporine, suggesting that they are more likely to use anti-inflammatory agents such as topical cyclosporine early in the disease to prevent progression.

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