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Global Consensus on Keratoconus and Ectatic Diseases

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Background: Despite extensive knowledge regarding the diagnosis and management of keratoconus and ectatic corneal diseases, many controversies still exist. For that reason, there is a need for current guidelines for the diagnosis and management of these conditions.

Purpose: This project aimed to reach consensus of ophthalmology experts from around the world regarding keratoconus and ectatic diseases, focusing on their definition, concepts, clinical management, and surgical treatments.

Methods: The Delphi method was followed with 3 questionnaire rounds and was complemented with a face-to-face meeting. Thirty-six panelists were involved and allocated to 1 of 3 panels: definition/diagnosis, nonsurgical management, or surgical treatment. The level of agreement considered for consensus was two thirds.

Results: Numerous agreements were generated in definitions, methods of diagnosing, and management of keratoconus and other ectatic diseases. Nonsurgical and surgical treatments for these conditions, including the use of corneal cross-linking and corneal transplantations, were presented in a stepwise approach. A flowchart describing a logical management sequence for keratoconus was created.

Conclusions: This project resulted in definitions, statements, and recommendations for the diagnosis and management of keratoconus

and other ectatic diseases. It also provides an insight into the current worldwide treatment of these conditions.

Key Words: keratoconus, corneal ectasia, consensus, corneal cross-linking, corneal transplantation

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Keratoconus and ectatic corneal diseases have been recognized for more than 150 years.^{1,2} Over the last 2 decades, there has been a revolution in the knowledge related to the diagnosis and management of these conditions. In terms of diagnosis, the advent of corneal topography, and more recently corneal tomography, has increased the ability of ophthalmologists to identify corneal ectasia at a much earlier stage than was previously possible.³ As a result, the previously established prevalence of keratoconus of approximately 1/2000 among the general population⁴ has been challenged with much higher prevalence rates found in many parts of the world.^{5,6}

The surgical treatment for keratoconus reflects this evolution.⁷ Alternative procedures, such as the use of intrastromal corneal ring segment(s) (ICRS),^{8,9} corneal cross-linking (CXL),^{10–12} therapeutic excimer laser treatments including phototherapeutic keratectomy¹³ and photorefractive

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keratectomy (PRK),¹⁴ and phakic intraocular lenses (IOL)^{15,16} alone or in combination^{17–19} have been proposed to delay or even prevent the need for corneal transplantation. In addition, new techniques of keratoplasty have been developed such as deep anterior lamellar keratoplasty (DALK)^{20,21} and femto-second laser-assisted corneal transplantation.^{22–24}

Although such advances have significantly improved our ability to diagnose and treat these patients, there remain many controversial aspects including disease definition and diagnosis and also medical and surgical management of these patients. These controversies have led to a need for achieving a consensus to assist practitioners in the management of patients with these conditions.

Formal consensus methods have become important tools to deal with complex problems in health care and medicine and to define levels of agreement on controversial topics.²⁵ They are also a powerful and logical way to generate current guidelines. One such tool is the Delphi method, which has been widely used in research in a variety of disciplines, including telecommunications, social sciences, and health sciences.^{26–28} The goal of this technique is to obtain the most reliable consensus/level of agreement from a group of experts through an iterative process with several rounds of structured questioning.

The Delphi technique has been used in many fields of medicine including respiratory, cardiovascular, and neurological diseases.^{29–31} In ophthalmology, the Delphi method has been used for establishing consensus on dry eye,³² cataract surgery,³³ primary open-angle glaucoma,³⁴ thyroid eye disease,³⁵ infection prophylaxis,³⁶ age-related macular degeneration,³⁷ and ocular allergy.³⁸

The current work presents a consensus regarding the management of keratoconus and other ectatic conditions from a panel of ophthalmology experts from around the world using a modified Delphi method. The consensus covers the most relevant and contentious questions regarding the definition, methods of diagnosis, and the nonsurgical and surgical treatments of these diseases.

METHODS

Design and Organization

We used a modified Delphi technique to obtain a consensus from an expert panel regarding important aspects of keratoconus and other ectatic diseases. One adaptation to this method was to include a face-to-face meeting to address unresolved issues after the initial question rounds (round 3) with a final presentation and approval by all panelists together (designated as Delphi +1).^{32,38,39}

Each of the 4 supranational corneal societies, the Asia Cornea Society (Asia), Cornea Society (USA and international), EuCornea (Europe), and PanCornea (Latin America, the United States, and Canada), assigned 2 coordinators for the project (Asia assigned 1 additional coordinator—a total of 9 coordinators). These coordinators are accomplished cornea specialists with previous experience in the design, conduct, and publication of expert panels. Their role was: (1) literature review and identification of appropriate journal articles to

send to the panelists, (2) design of methodology, (3) development of questionnaires, (4) selection of expert panel members, (5) decision-making process after each round, (6) writing the final manuscript, and (7) project oversight.

A Contract Research Organization (Eurotrials Scientific Consultants S.A., Lisbon, Portugal) provided methodological support during the rounds and was responsible for the data collection and statistical analysis.

Considering the multiplicity of themes, the coordinators formed 3 panels according to the following major topics of interest:

1. Definition/diagnosis: covering the clinical aspects that distinguish keratoconus from other ectatic diseases, diagnostic tests, and risk factors for keratoconus
2. Nonsurgical management: covering medical management and therapeutic approaches based on different scenarios
3. Surgical management: covering the factors or scenarios that lead to a particular surgical approach.

Selection of Expert Panel

Each Cornea Society compiled a list of potential participants complying with the following criteria:

1. Ophthalmologists with experience in the management of keratoconus and ectatic diseases
2. Authorship of scientific publications in high-impact medical journals
3. Wide recognition by the specialized medical community
4. Willing to comply with the initial question rounds, face-to-face meeting, and project timelines.

In addition, the pool of selected experts had to reflect a worldwide geographic distribution and had to equally represent the 4 corneal societies. Each society designated 9 experts, ensuring a total of 36 participants, plus coordinators, for this project.

An invitation e-mail was sent to the experts to explain the aim of the study, the major topic to be covered, the methodology, and to request their participation. In July 2014, the coordinators approved the group of selected experts and allocated 12 experts (3 from each society) to each major topic of interest (Fig. 1). All experts gave their consent to participate in this project.

Steps of the Process

The first 2 rounds of questionnaires were conducted between the August 1 and September 10, 2014. Before the first round, all experts were provided with the current literature regarding the diagnosis and management of ectatic diseases that included peer-reviewed research papers, systematic and narrative reviews, and editorials from recognized experts in the field. The method used to identify publications was to search electronic databases (Medline, EMBASE, and Cochrane Library) with the key words “*keratoconus, ectasia and ectatic corneal disease.*” The selection of articles was based on the relevance of the topic with novel information

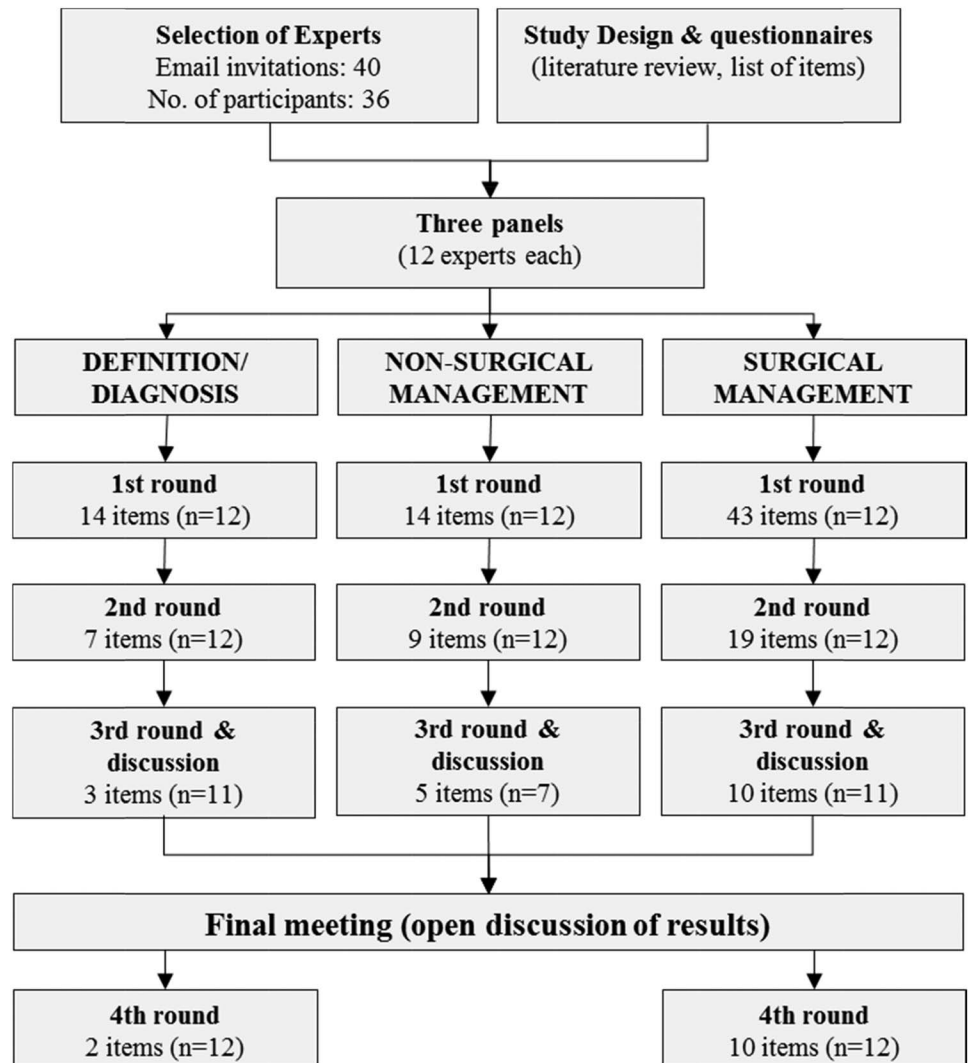


FIGURE 1. Flowchart of the project. No, number; n, number of participants.

that was not originally included in the major reviews by Krachmer et al and Rabinowitz.^{1,2} To reduce attrition, a short turnaround time was selected and close follow-up was implemented, using personalized e-mails and regular reminders to nonresponding experts. To minimize the influence of seniority, presumptions of expertise, and dominant characters, the experts were kept anonymous from each other throughout the first 2 rounds.

A face-to-face meeting was held in Chicago on October 19, 2014, during the American Academy of Ophthalmology annual meeting. This meeting consisted of 3 modules:

1. Explanation of project rationale and methodology to be followed during the face-to-face meeting
2. Three panel sessions, according to the major topic. During these sessions, the results of the previous rounds were presented. In addition, the experts answered a third round of questions. The meeting was open to discussion, and when judged appropriate by all the experts, some items from previous rounds were revisited and subject to discussion. The inputs were registered and compiled.

Each of these sessions was moderated by 3 coordinators who had no interference in the opinions or answers of the experts. One methodologist from Eurotrials ensured that each session complied with the defined procedures.

3. Final Meeting (Delphi +1), with open discussion involving all panelists and coordinators together to present and debate the results of the 3 panel sessions. Technically, this was accomplished by projecting the statements and revising them on screen until no more comments were raised from the participants. When found relevant by the majority of experts, unanswered controversial points were recorded. The coordinators then developed questions for one or more extra questionnaire rounds, which were sent back to the respective panel(s).

After the meeting and additional questionnaire rounds, the coordinators drafted a manuscript describing the results. The manuscript draft was circulated to all coordinators for their review and feedback. The manuscript was then revised incorporating all coordinators' feedback.

Data Collection and Analyses

The list of items generated for each topic was based on the literature review, as well as on suggestions from all the coordinators. Each electronic questionnaire was posted on an access-controlled Web site, and access credentials were distributed among participants. Only analysts had access to responses during the process.

The majority of questions seek a consensus from the experts regarding predefined statements. “Consensus” was considered when at least two thirds of the panel selected the same option. Other questions were aimed at understanding how the experts manage these diseases, considering different case scenarios (consensus was not required). All questions were closed-ended. Still, free text fields after each questions allowed the experts to write any comment if they felt necessary.

After each round, numerical, ordinal, and categorical responses were summarized using descriptive statistics and reviewed by the coordinators. Items on which consensus was not reached were reformulated into a new question. Items that were unclear or confusing based on comments in the free text fields were adjusted and repeated. Suggestions by panel members were incorporated.

Descriptive statistics were computed using percentages for categorical questions and means/medians for numerical/rank questions. The statistical analysis was performed using IBM SPSS Statistics 22.0 (IBM Corp, Chicago, IL).

RESULTS

E-mail invitations were sent to 40 experts, of whom 36 were willing to participate. The country distribution and subspecialties of the experts are shown in Table 1. Four persons declined to participate because of inability to attend the face-to-face meeting in Chicago (3) or because of financial reasons (1).

A 100% response rate was reached in the first 2 rounds in all the 3 panels. Twenty-nine of the 36 experts (80.5%) who answered the previous surveys attended the face-to-face meeting in Chicago: 11/12 in the Definition/diagnosis and Surgical management panels and 7/12 in the Nonsurgical management panel. During the Delphi +1 phase, the experts and coordinators concluded that a fourth round was necessary to rephrase or generate new questions regarding the Definition/diagnosis and Surgical management topics. This postmeeting round was conducted on-line from November 8 to December 18, 2014. The response rate during the fourth round of both Definition/diagnosis and Surgical management panels was 100% (Fig. 1). The items addressed throughout the rounds and during the face-to-face meeting and the consensus obtained are hereby presented by their major topic.

Definition/Diagnosis

“Ectasia” as defined in most medical dictionaries refers to a dilation or distention of a tubular structure.¹ Historically, ophthalmologists, optometrists, and vision scientists have used this term broadly to cover many conditions associated with

TABLE 1. Coordinators and Expert Panel by Major Topic

Definition/Diagnosis	Nonsurgical Management	Surgical Management
Coordinators	Coordinators	Coordinators
Renato Ambrósio (Brazil)	José Gomes (Brazil)	José Guell (Spain)
Michael Belin (United States)	François Malecaze (France)	Christopher Rapuano (United States)
Kohji Nishida (Japan)	Virender Sangwan (India)	Donald Tan (Singapore)
Panelists	Panelists	Panelists
Juan Abad (Colombia)	Penny Asbell (United States)	Alaa El Danasoury (Saudi Arabia)
Roberto Albertazzi (Argentina)	Samar Basak (India)	Richard Davidson (United States)
Mauro Campos (Brazil)	Aldo Caporossi (Italy)	Sheraz Daya (United Kingdom)
Beatrice Cochener (France)	Denise de Freitas (Brazil)	Rajesh Fogla (India)
Christopher Croasdale (United States)	Farhad Hafezi (Switzerland)	Enrique Graue-Hernandez (Mexico)
Harminder Dua (United Kingdom)	Deborah Jacobs (United States)	Luis Izquierdo Jr (Peru)
Friedrich Kruse (Germany)	Choun-Ki Joo (Korea)	George Kymionis (Greece)
Robert Feder (United States)	Stephen Kaufman (United States)	Irving Raber (United States)
Marian Macsai (United States)	Florence Malet (France)	Luis Rodriguez (Venezuela)
Naoyuki Maeda (Japan)	Prema Padmanabhan (India)	Enzo Sarnicola (Italy)
Jodbhir Mehta (Singapore)	Victor Perez (United States)	Shigeto Shimmura (Japan)
Gerard Sutton (Australia)	Daniel Scorsetti (Argentina)	Wolf Wonneberger (Sweden)

changes in the corneal shape. Although most of these ocular conditions do not meet the strict medical definition of ectasia, this panel will define ectasia by identifying which conditions should be classified under the term “ectatic disorder” and contrast these to other conditions that alter the corneal shape, but would not be considered a primary “ectatic disorder.”

The first set of questions for the Definition/diagnosis panel aimed essentially to define and identify distinctive clinical characteristics of keratoconus when compared with other ectatic diseases. The experts agreed that abnormal posterior ectasia, abnormal corneal thickness distribution (eg, as seen with abnormal corneal thickness spatial distribution⁴⁰), and clinical noninflammatory corneal thinning are mandatory findings to diagnose keratoconus. The exact values for any parameter will vary based on the machine being used and, for elevation values, the reference surface. Additionally, the values will vary if one is screening (eg, refractive surgery) where sensitivity is the overriding concern or treating (eg, cross-linking) where specificity assumes greater significance.

As opposed to a “thinning disorder,” keratoconus, pellucid marginal degeneration (PMD), keratoglobus, and postrefractive surgery progressive corneal ectasia should be classified under

“ectatic diseases.” Conditions such as Terrien marginal degeneration, dellen, and inflammatory melts should not be classified as ectatic diseases. Secondary changes (eg, posttrauma) where it is felt that no underlying ectatic propensity existed would be considered a “thinning disorder” as opposed to a primary ectatic disease. Consensus was achieved regarding the statements “keratoglobus and keratoconus are different clinical entities” and “true unilateral keratoconus does not exist.” In addition, the “thinning location and pattern” are aspects that distinguish keratoconus, PMD, and keratoglobus.

The group also agreed that the best way to differentiate keratoconus from PMD is by using a combination of approaches, which includes a full corneal thickness map, slit-lamp examination, anterior curvature map and anterior tomographic elevation map. The group considered central pachymetry the least reliable indicator (or determinant) for diagnosing keratoconus because keratoconus can be present in a cornea of normal central thickness.

This panel also covered the criteria and the tests used to diagnose early or subclinical keratoconus. There was consensus that tomography (eg, Scheimpflug or optical coherence tomography) is currently the best and most widely available test to diagnose early keratoconus. Posterior corneal elevation abnormalities must be present to diagnose mild or subclinical keratoconus.

The group also intended to establish a classification for keratoconus. After 2 rounds and an extensive discussion on the topic, the group agreed that currently there is no clinically adequate classification system for keratoconus and that the historical Amsler–Krumreich classification fails to address current information and technological advances.⁴¹ In the end, the panel felt it was beyond the scope of this project to create an entirely new keratoconus classification system.

The experts felt that there is no primary pathophysiologic explanation for keratoconus. During the face-to-face meeting, the panelists reached the conclusion that the pathophysiology of keratoconus is likely to include environmental, biomechanical, genetic, and biochemical disorders. Secondary induced ectasia may be caused by a purely mechanical process in a predisposed cornea, which may be unilateral. In addition, two relevant aspects were exhaustively debated: definition of ectasia progression and risk factors for keratoconus.

Definition of Ectasia Progression

Currently, there is no consistent or clear definition of ectasia progression. This led the Definition/diagnosis group to use 2 additional questionnaire rounds in an attempt to better define ectasia progression: “Ectasia progression” is defined by a consistent change in at least 2 of the following parameters where the magnitude of the change is above the normal noise of the testing system:

1. Steepening of the anterior corneal surface
2. Steepening of the posterior corneal surface
3. Thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point.”

The changes need to be consistent over time and above the normal variability (ie, noise) of the measurement system

(this will vary by system). Although progression is often accompanied by a decrease in best spectacle-corrected visual acuity (BSCVA), a change in both uncorrected visual acuity and BSCVA is not required to document progression. Although the panel agreed that specific quantitative data are lacking to further define progression and that these data would likely be machine/technology specific, it was agreed that the interval between testing/examinations should be shorter among younger patients and that the same measuring platform, when possible, should be used in sequential examinations.

Risk Factors

During the face-to-face meeting, the experts found it relevant to agree on the most important risk factors for keratoconus (an aspect that was not addressed during the previous rounds). Still, during the face-to-face meeting, no consensus was reached regarding this issue. Therefore, a postmeeting 4th questionnaire round was required involving the Definition/diagnosis panel to identify the relevant risk factors: Down syndrome, relatives of affected patients especially if they are young, ocular allergy, ethnic factors (eg, Asian and Arabian), mechanical factors, eg, eye rubbing, floppy eyelid syndrome, atopy, connective tissue disorders (Marfan syndrome), Ehlers–Danlos syndrome, and Leber congenital amaurosis. The consensuses reached by the Definition/diagnosis panel are summarized in Table 2.

Nonsurgical Management

Initially, the experts ranked the most important goals in the nonsurgical management of ectasia by the order of importance. However, during the face-to-face meeting, panelists agreed that the best approach was to select the 2 most important goals, which were halting disease progression and visual rehabilitation.

The level of importance of several measures used in the nonsurgical management of ectasia was graded by the panel. The most important measures were: verbal guidance to the patient regarding the importance of not rubbing one’s eyes, use of topical antiallergic medication in patients with allergy, and use of topical lubricants (in case of ocular irritation) to decrease the impulse to rub one’s eyes.

Experts agreed that in cases of allergy or if there is any allergic component, patients should be treated with topical antiallergic medication and lubricants. In addition, the group agreed that topical multiple-action antiallergic medications (ie, antihistamines, mast cell stabilizer, antiinflammatory) should be used in patients with keratoconus with atopy or history of eye rubbing.

During the first 2 rounds, there was disagreement about the relationship between keratoconus and dry eye. Therefore, the Nonsurgical management panel discussed the most appropriate way to define this relationship. The group agreed on the statement “There is no direct relationship between keratoconus and dry eye.” Also, when discussing this topic, the group agreed with the statement “Use of eye drops without preservatives is preferable in keratoconus patients.” All panelists recognized that preservative-free agents reduce irritation and epithelial trauma compared with agents with preservatives

TABLE 2. Agreements Reached in the Definition/Diagnosis Panel

- The following findings are mandatory to diagnose keratoconus
 - Abnormal posterior elevation
 - Abnormal corneal thickness distribution
 - Clinical noninflammatory corneal thinning
- Keratoconus and PMD are different clinical presentations of the same disease
- The aspect that distinguishes keratoconus, PMD, and keratoglobus is “thinning location and pattern”
- Keratoconus and PMD are best differentiated by a combination of
 - Full tomographic corneal thickness map
 - Slit-lamp examination
 - Anterior curvature map
 - Anterior tomographic elevation map
- As opposed to “thinning disorders” the following are classified under “ectatic diseases”
 - Keratoconus
 - PMD
 - Keratoglobus
 - Postrefractive surgery progressive corneal ectasia
- Keratoglobus and keratoconus are different clinical entities
- True unilateral keratoconus does not exist
- The best current and widely available diagnostic test to diagnose early keratoconus is tomography (Scheimpflug or optical coherence tomography)
- Currently, there is no clinically adequate classification system for keratoconus
- Posterior corneal elevation abnormalities must be present to diagnose early or subclinical keratoconus
- Secondary induced ectasia may be caused by a pure mechanical process (and can be unilateral)
- Central pachymetry is the least reliable indicator (determinant) for diagnosing keratoconus
- The pathophysiology of keratoconus is likely to include the following components
 - Genetic disorder
 - Biochemical disorder
 - Biomechanical disorder
 - Environmental disorder
- Placido-based topography analyzes the central anterior corneal surface, whereas tomography (Scheimpflug and/or optical coherence tomography) analyzes the anterior and posterior cornea and produces a near full corneal thickness map
- Keratoconus can be present in a cornea of normal central thickness
- Ectasia progression is defined by a consistent change in at least 2 of the following parameters where the magnitude of the change is above the normal noise of the testing system
 - Progressive steepening of the anterior corneal surface
 - Progressive steepening of the posterior corneal surface
 - Progressive thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point
- The changes need to be consistent over time and above the normal | variability (ie, noise) of the measurement system (this will vary by system). Although progression is often accompanied by a decrease in BSCVA, a change in both uncorrected visual acuity and BSCVA is not required to document progression
- Risk factors for keratoconus: Down syndrome, relatives of affected patients especially if they are young, ocular allergy, ethnic factors (Asian and Arabian), mechanical factors, eg, eye rubbing, floppy eyelid syndrome, atopy, connective tissue disorders (Marfan syndrome), Ehlers–Danlos syndrome and Leber congenital amaurosis

(there is evidence that preservatives are associated with irritation, eye rubbing, and epithelial microtrauma).^{42–44}

Regarding refraction and optical correction, subjective refraction should be attempted in all patients with ectasia. In addition, aberrometry may help to determine the optical correction in early disease. Progressive addition glasses are not contraindicated in eyes with keratoconus or other ectasias, but they are rarely successful.

The use of contact lenses in patients with keratoconus and other ectasias was extensively debated during the 2 first rounds and the face-to-face meeting. The group recognized their importance for visual rehabilitation and agreed that their use does not slow or halt progression of corneal ectasias. Still, the use of contact lenses for purely cosmetic reasons should be discouraged in this group of patients because of the difficulty in contact lens fitting and the increased risk of complications from a poorly fit contact lens.

Rigid contact lenses should be used in cases of unsatisfactory vision with glasses or conventional soft contact lenses. Among the rigid contact lenses, gas-permeable lenses are preferred and should be tried initially in patients with keratoconus. Moreover, in a patient with keratoconus who has failed a trial of conventional corneal rigid gas-permeable lenses, the alternative contact lens options would be: hybrid lens (rigid center, soft skirt); toric, bitoric, and keratoconus design soft contact lens; keratoconus design corneal rigid gas-permeable contact lens; piggy-back; corneoscleral, miniscleral, and semiscleral contact lens; and scleral lens.

During the face-to-face discussion, the group felt that it was important to identify special situations where keratoconus evaluation should be considered/recommended. A careful evaluation is strongly recommended in patients with Down syndrome and should be considered in patients with known risk factors for developing keratoconus (see Definition/diagnosis risk factors above). The panel also agreed that pregnancy could contribute to acceleration of the progression of ectasia.

It was also agreed that in acute hydrops, nonsurgical or less invasive surgical management such as intracameral gas injection should be attempted before keratoplasty. The consensus reached by the Nonsurgical management panel are summarized in Table 3.

Surgical Management

In the first 2 rounds and during the face-to-face discussion of surgical management, the question of when to proceed to surgery was debated. Overall, experts have good access to experienced practitioners or experts in contact lens fitting, inside or outside their institution. The consensus was that surgery should be considered when patients were not fully satisfied with nonsurgical treatments. In general, panelists preferred the term “*satisfactory best-corrected*” rather than “*best-corrected*” vision because it differentiates patients who may be able to achieve good corrected vision, for example, with lenses, but are unable to tolerate them or wear them comfortably for long periods of time.

CXL is currently available and is performed by the majority of the panelists (83.3%) for keratoconus, using

TABLE 3. Agreements Reached in the Nonsurgical Management Panel**Statements**

- The 2 most important goals of management are halting disease progression and visual rehabilitation. Verbal guidance should be given to patients regarding the importance of not rubbing one's eyes, use of topical antiallergic medication in patients with allergy, and use of topical lubricants (in the case of ocular irritation) to decrease the impulse to eye rub
- In cases of allergy or if there is any allergic component, patients should be treated with topical antiallergic medication and lubricants. Topical multiple-action antiallergic medications (ie, antihistamines, mast cell stabilizer, antiinflammatory) should be used in patients with keratoconus with atopy or history of eye rubbing
- There is no direct relationship between keratoconus and dry eye
- Preservative-free agents are preferred as they are associated with less irritation and epithelial trauma compared with agents with preservatives
- Subjective refraction should be attempted in all patients with corneal ectasia. Aberrometry may help to determine the optical correction in early disease
- Progressive-type glasses are not contraindicated in eyes with keratoconus or other ectasias, but they are rarely successful
- Contact and scleral lenses are extremely important for visual rehabilitation in patients with keratoconus and other corneal ectasias
- Contact lens use does not slow or halt progression of corneal ectasias
- Rigid contact lenses should be used in cases of unsatisfactory vision with glasses or conventional soft contact lenses. Among the rigid contact lenses, gas-permeable lenses are preferred and should be tried initially in patients with keratoconus. In a patient with keratoconus who has failed conventional corneal gas-permeable lenses, alternative contact lens options would be: hybrid lens (rigid center, soft skirt); toric, bitoric, and keratoconus design soft contact lens; keratoconus design corneal rigid gas-permeable contact lens; piggy-back; corneoscleral, miniscleral, and semiscleral contact lens; and scleral lens
- A careful evaluation for keratoconus is strongly recommended in patients with Down syndrome and should be considered in patients with known risk factors for developing keratoconus (Table 2)
- Pregnancy could contribute to acceleration of the progression of ectasia
- In acute hydrops, nonsurgical management should be attempted before keratoplasty

a variety of techniques. The panelists who do not have current access to CXL were willing to use this technique once it becomes available. In addition, it was recognized that *the term "collagen cross-linking" is not currently considered correct and should be replaced by "corneal cross-linking."*

Regarding the indication for CXL, the panelists found that CXL is extremely important in the treatment of keratoconus with documented clinical progression; it is very important for the treatment of postrefractive surgery keratectasia; it is important for the treatment of keratoconus with a perceived risk of progression (ie, clinical progression has not been confirmed) and for eyes with keratoconus that have previously received other forms of corneal surgery (such as ICRS or PRK). There was no consensus about the use of CXL in subclinical keratoconus. The surgical management of keratoglobus is typically quite different from keratoconus and was not considered in the treatment questionnaires.

In terms of restrictions for CXL, the panelists agreed that there is no age below or above which CXL should be restricted in keratoconic eyes with evidence of progression. As for keratoconic eyes without evidence of progression, there was no consensus on whether there is an age below which CXL should

be restricted, but it is rarely indicated in patients older than 40 years. There was no consensus on an uncorrected vision better than which CXL should be restricted in either keratoconic eyes with or without evidence of progression.

Besides CXL, anterior lamellar keratoplasty (ALK), more specifically descemet deep ALK (dDALK), and penetrating keratoplasty (PK) are the most frequent surgical modalities used in the surgical treatment of keratoconus. ICRS are also used, but to a lesser degree. However, superficial keratectomy (manual or PTK), PRK, conductive keratoplasty, incisional keratotomy (arcuate/parallel incisions), microwave corneal remodeling, and clear lens extraction with spherical/toric IOL are uncommonly used by the expert panel.

Experts who currently use DALK agreed that the most important patient-related factor in determining the need for this type of surgery is contact lens intolerance. As for PK, the most important factor in considering keratoplasty in keratoconus is when significant corneal scarring (eg, posthydrops) is present. Other important factors included the following: the patient is contact lens intolerant or is not keen on wearing contact lenses; other surgical strategies fail, or are contraindicated; the cornea is very thin (<200 μm); and the keratoconus is deemed to be severe and at a potential risk of acute hydrops. In this context, there was no consensus regarding the importance of apparent rapid progression of keratoconus.

According to the expert panel, any form of corneal transplant is offered to 21% to 60% of patients with keratoconus who are eligible for surgery. Among all keratoplasties, some form of ALK (at least attempted) is currently performed in more than 60% of patients. In the absence of previous hydrops (ie, no previous compromise of Descemet membrane), some form of ALK (at least attempted) is performed in more than 60% of the patients, whereas in cases with previous hydrops and deep scarring (ie, previous compromise of Descemet membrane), some form of ALK is performed (at least attempted) in 0% to 20% of patients.

Regarding ALK techniques used by the panelists in keratoconus with no previous evidence of acute hydrops, dDALK with big bubble technique is the most common technique (more than 51% of the cases). Microkeratome-assisted ALK is never performed and other ALK techniques such as manual layer-by-layer predescemet DALK (pdDALK), dDALK with viscodissection, pdDALK with the Melles technique, and femtosecond laser-assisted DALK are performed in less than 25% of the patients. Regarding the ALK techniques used by the panelists in keratoconus with previous evidence of acute hydrops, microkeratome-assisted ALK is never performed and the remaining techniques are performed in less than 25% of the patients.

Although half of the panel have performed femtosecond laser-assisted PK for keratoconus, the majority of PKs are performed with a standard (nonlaser) technique. Of those surgeons performing femtosecond laser-assisted surgery, the percentage of cases varies from 1% to 20%.

The panelists concluded that the most important surgical techniques to restore the best uncorrected visual acuity possible in keratoconus are (in the order of importance): dDALK, PK, and ICRS. The most important surgical techniques to restore the best rigid gas-permeable contact lens

(RGP-CL) corrected visual acuity possible are (in the order of importance): dDALK and PK.

The most common approaches were pooled and are presented in Table 4, which describes which treatment practices are considered in specific case scenarios in which age, stage of disease, and visual acuity are varying factors. A flowchart describing a logical management sequence for a patient with keratoconus is presented in Figure 2.

DISCUSSION

Based on the literature and positive previous experience with dry eye, allergy, and infection prophylaxis, we chose a modified Delphi technique to achieve consensus regarding the most important topics in keratoconus and other corneal ectasias.^{32,36,38} Before this project, we undertook a successful pilot of this specific consensus with Latin-American corneal specialists as a test-run that was approved by the 4 cornea

societies.⁴⁵ One of the advantages of the Delphi method is that information can be gathered from a geographically diverse panel of participants while keeping their anonymity, which reduces the halo effects associated with the opinions of prominent participants.^{46,47} It also allows the panelists adequate time to carefully consider their responses before replying.^{46,47} The reliability of this method increases with the number of participants and rounds.

To achieve a global representation of experts in corneal ectasias, we decided that all 4 of the main active recognized supranational cornea societies would be responsible for the selection of coordinators (9) and panelists (36). This panel size is in line with most Delphi studies and assured sufficient worldwide expertise, even if attrition occurred.⁴⁰ The international representation of the panel strengthens our findings, reflecting a broad range of clinical opinions from diverse geographical regions of the world and a variety of clinical practices.

We achieved a 100% response rate in the first 2 rounds in all 3 panels. Possible reasons for the high response rate achieved could be attributed to the high motivation from the panel of experts who recognized the relevance of the project. In addition, the quick turnaround time, the clear time frame, and the personalized reminders might have also contributed to these high rates. The number of panelists who attended the face-to-face meeting in Chicago and responded to the third round questionnaire was somewhat smaller (29/36 or 80.5%). Considering the logistical difficulties for some of the panelists from outside the United States and the lack of direct funding, we thought it was an excellent attendance.

Although extensively used in the health and technology fields, Delphi and other consensus methods have some limitations. Delphi can pose some difficulties in keeping the interest of the panelists after 2 or more rounds and the costs involving each additional round. Also, if personal contact among participants is desirable, then Delphi is not appropriate. That was the reason we decided to use the modified Delphi method that included a third face-to-face round. Sackman, in his critical analysis of conventional Delphi, pointed out other limitations including the possibility of a crude questionnaire design, vulnerability with respect to who is an “expert,” and obliviousness to reliability measurement and scientific validation of findings.^{46,48} Despite these limitations, we found that the modified Delphi was the best technique for this project. The fact that it was funded by a grant from the Asia Cornea Foundation, without the participation of any company with a possible conflict of interest in the topic, strengthens the importance of this consensus and makes it even more representative of what cornea specialists think about keratoconus and corneal ectasias today.

Definition/Diagnosis

The last decade has seen a dramatic change in the management of ectatic disease. Newer treatment modalities such as CXL have moved the timing of intervention to much earlier in the disease process. No longer are we delaying invasive treatments until there is significant loss of vision. Earlier intervention, however, imposes greater diagnostic challenges, as accurately identifying early ectatic change is

TABLE 4. Panel Consensus to Surgical Approaches Based on Different Case Scenarios

- Young (eg, 15-year-old) patient with stable KCN with satisfactory vision with glasses
Prescribe glasses only or in combination with contact lenses or CXL
- Young (eg, 15-year-old) patient with progressive KCN with satisfactory vision with glasses
Perform CXL and prescribe glasses ± contact lenses
- Older (eg, 55-year-old) patient with stable KCN with satisfactory vision with glasses
Prescribe glasses only or with contact lenses
- Older (eg, 55-year-old) patient with progressive KCN with satisfactory vision with glasses?
Perform corneal cross-linking only or with prescription of glasses/contact lenses
- Patient with stable KCN with unsatisfactory vision with glasses but satisfactory vision with rigid contact lenses and tolerates them well? This patient has a spherical equivalent of moderate myopia [eg, −5 diopters (D)]
Prescribe contact lenses (including scleral lenses)
- Patient with stable KCN with unsatisfactory vision with glasses but good vision with rigid contact lenses, and tolerates them well? This patient has a spherical equivalent of high myopia (eg, −15 D)
Prescribe contact lenses (including scleral lenses)
- Patient with stable KCN with unsatisfactory vision with glasses and contact and scleral lenses, or who does not tolerate contact or scleral lenses? This patient has a spherical equivalent of moderate myopia (eg, −5 D)
Perform dDALK. Consider ICRS in eyes with adequate corneal thickness and minimal to no scarring
- Patient with stable KCN with unsatisfactory vision with glasses and contact and scleral lenses, or who does not tolerate contact or scleral lenses? This patient has a spherical equivalent of high myopia (eg, −15 D)
Perform dDALK
- Patient with stable severe KCN with unsatisfactory vision with glasses and contact and scleral lenses? This patient has moderate anterior corneal scarring but no evidence of previous corneal hydrops
Perform dDALK
- Patient with stable severe KCN with unsatisfactory vision with glasses and contact and scleral lenses? This patient has moderate anterior and deep corneal scarring with evidence of previous corneal hydrops
PK alone or attempt pdDALK

KCN indicates keratoconus.

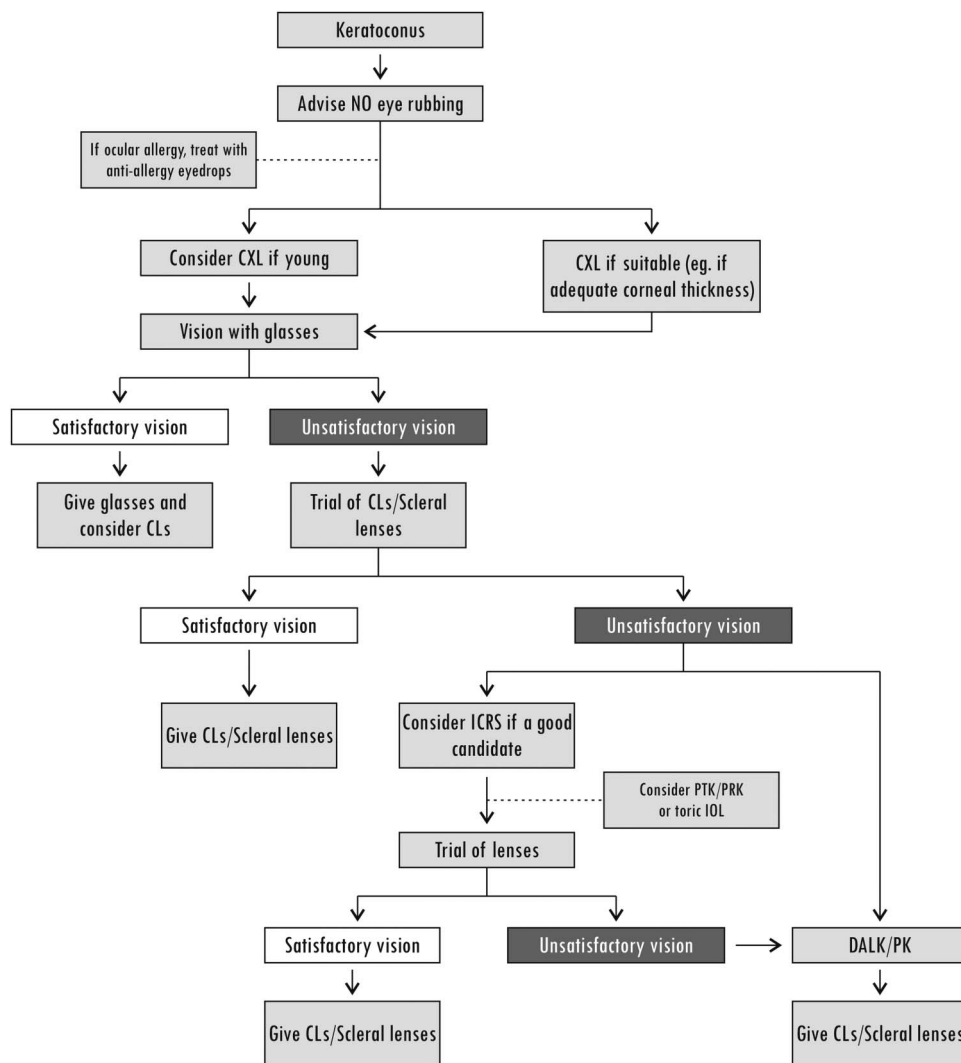


FIGURE 2. Keratoconus treatment flowchart. CLs, contact lenses; CXL, corneal cross-linking; PTK, phototherapeutic keratectomy.

more problematic than the identification of moderate to advanced disease. These greater diagnostic demands have fortunately been accompanied by significant improvements in corneal imaging with the emergence of both Scheimpflug imaging and optical coherence tomography. These devices can measure both anterior and posterior corneal surfaces, produce a corneal thickness map, and reconstruct the anterior segment. This advanced imaging is called corneal tomography to separate it from Placido disc-based videokeratographs that can only image the anterior corneal surface (topography).

The panel acknowledged the limitations of the often used, but dated, keratoconus classifications/staging systems [both Amsler–Krumeich⁴¹ and CLEK (Collaborative Longitudinal Evaluation of Keratoconus⁴⁹)]. And, while the group recognized tomography as a critical diagnostic component, the panel also agreed that a suitable classification system using this additional information currently does not exist. Therefore, studies that correlate clinical findings such as visual performance (ie, BSCVA) with corneal topometric and tomographic parameters are needed. Additionally, the

group agreed that documenting ectasia progression requires changes in at least 2 of the following; steepening of the anterior surface, steepening of the posterior surface, and/or thinning or changes in the pachymetric rate of change. Although these changes were noted as a requisite for documenting progression, the absolute magnitude of the changes is currently unknown. It was recognized, however, that younger patients should be examined for change at shorter time intervals as ectatic change can progress rapidly in this group.

The emergence of corneal/anterior segment tomography and the realization of the importance of the posterior cornea as an early indicator of ectatic change are reflected in the expert panel’s opinion that both changes on the posterior corneal surface and alteration in the corneal thickness progression are necessary to diagnose keratoconus. Additionally, the importance of tomography is reflected in the group’s view that the corneal thickness map, in addition to slit-lamp examination and anterior measurements, is necessary to properly differentiate PMD from keratoconus.

Other areas of consensus were that keratoconus and PMD are different clinical presentations of the same basic disease process and that the term “ectatic” diseases should be reserved for keratoconus, PMD, postrefractive surgery ectasia, and keratoglobus. Other “thinning” conditions, such as Terrien marginal degeneration, dellen, rheumatoid/autoimmune melts, etc, should be classified under the general term “corneal thinning disorders.”

Finally, the pathophysiology of keratoconus was discussed. Keratoconus (and other ectatic disorders) was recognized as a multifactorial disease with genetic, biochemical, biomechanical, and environmental components. And, although it was felt that true unilateral keratoconus does not exist, it was appreciated that a unilateral clinical presentation may occur in a predisposed individual because of asymmetric environmental factors, such as eye rubbing. The findings are summarized in Table 2.

Nonsurgical Treatment

Corneal ectasias can be treated by nonsurgical approaches. Usually used in the initial stages, this form of treatment is often very successful. It is crucial to first define the goals for these less invasive therapeutic strategies. The panelists found that the most important objective of nonsurgical treatment is to halt progression; the second one is visual rehabilitation. Of course, these 2 goals are related and might be extrapolated to the surgical management as well. But together they represent the most important goals for successful treatment of corneal ectasia by ophthalmologists.

The most important nonsurgical treatment measures were patients’ verbal guidance regarding the importance of not rubbing one’s eyes. There is no evidence that a particular medication can halt the progression of ectatic corneal diseases. The majority of this research focuses on new antiinflammatory molecules or innovative technologies to induce transepithelial CXL.^{50,51} It is possible that in the future, the researchers will find a topical medication that could directly influence the progression of keratoconus and other corneal ectasias.

The use of contact lenses in patients with keratoconus was extensively explored. The panelists agreed that although extremely beneficial to correct vision in a many patients, it does not slow or halt the progression of ectasia.⁵² Rigid contact lenses should be tried first in patients with keratoconus. Numerous alternative contact and scleral lens options are available. The options varied according to regional access to some of these lenses and whether the corneal panelists do or do not fit contact lenses in their practices. The findings are summarized in Table 3.

Surgical Treatment

Determining the best surgical approach for keratoconus and other ectasias turned out to be a difficult task for a variety of reasons. For one, there are a large number of surgical procedures that are used to treat these conditions, some quite frequently and others much less frequently, and we included essentially all of these options as possible answers for the

panelists. The wide geographic distribution of the panelists and the fact that some surgical options are more readily available in some countries than others made achieving a consensus difficult. Additionally, just keratoconus (not to mention the other ectasias) comes in a wide range of severity. The irregular astigmatism may be mild to severe. The corneal thinning may be mild to severe. There may or may not be associated high myopia. There may be severe scarring or a history of acute hydrops. In the end, we felt that it was most useful to present a wide variety of patient scenarios attempting to encompass the majority of patients with keratoconus we encounter in clinical practice and see whether we could get a consensus on management of these specific patients.

As a rule, the panelists felt that anyone with progressive ectasia should undergo CXL no matter what age or level of vision (assuming the eye was an appropriate candidate). Panelists also felt it was best not to proceed with surgery (other than CXL) if patients were satisfied with their vision with glasses or contact lenses. ICRS were routinely performed by some panelists and rarely or never performed by other panelists. The situation with phakic IOLs was similar, although they were performed less commonly than ICRS. There was a strong preference for DALK when a corneal transplant was needed, unless the eye had previous compromise of Descemet membrane (most commonly from acute hydrops), at which point the preference was for a PK. A minority of panelists strongly preferred pdDALK even in the presence of previous hydrops. The findings are summarized in Table 4.

CONCLUSIONS

Practice patterns in medicine certainly vary throughout the world. However, with increased international travel and improved communications, among other reasons, these differences seem to be diminishing. This global consensus using a modified Delphi technique resulted in definitions, statements, and recommendations for the diagnosis and management of keratoconus and other ectatic diseases. It should help eye care providers around the world to adopt best practices for these often visually debilitating conditions.

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