

Title: Standardization of Nomenclature for Ocular Tuberculosis – Results of Collaborative Ocular Tuberculosis Study (COTS) workshop

Authors: Rupesh Agrawal,^{1,2,3*} Aniruddha Agarwal,^{4*} Douglas A. Jabs,^{5,6} Aera Kee,¹ Ilaria Testi,² Sarakshi Mahajan,⁷ Peter J. McCluskey,⁸ Amod Gupta⁴, Quan Dong Nguyen,⁷ Carlos Pavesio,² and Vishali Gupta⁴ for the Collaborative Ocular Tuberculosis Study (COTS) Group

* Both the authors have contributed equally to the manuscript and share first authorship

COTS, IOIS, IUSG Nomenclature Working Group Investigators: Please see at the end of the manuscript

Author affiliation:

¹National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore

²Moorfields Eye Hospital, Department of Ophthalmology, NHS Foundation Trust, London, United Kingdom

³School of Material Science and Engineering, Nanyang Technological University, Singapore

⁴Advanced Eye Center, Department of Ophthalmology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

⁵Department of Epidemiology, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA

⁶Wilmer Eye Institute, Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

⁷Byers Eye Institute, Department of Ophthalmology, Stanford University, Palo Alto, California, United States of America

⁸Discipline of Ophthalmology, Save Sight Institute, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

Corresponding author:

Prof. Vishali Gupta, MS

Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, 160012, India

Tel: +91-172-2747837

Fax: +91-172-2747837

Email: vishalisara@yahoo.co.in;

vishalisara@gmail.com

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Abstract:

Purpose: To standardize a nomenclature system for defining clinical phenotypes, and outcome measures for reporting clinical and research data in patients with ocular tuberculosis (OTB).

Methods: Uveitis experts initially administered and further deliberated the survey in an open meeting to determine and propose the preferred nomenclature for terms related to the OTB, terms describing the clinical phenotypes and treatment and reporting outcomes.

Results: The group of experts reached a consensus on terming uveitis attributable to tuberculosis (TB) as tubercular uveitis. The working group introduced a SUN-compatible nomenclature that also defines disease “remission” and “cure”, both of which are relevant for reporting treatment outcomes.

Conclusion: A consensus nomenclature system has been adopted by a large group of international uveitis experts for OTB. The working group recommends use of standardized nomenclature to prevent ambiguity in communication and to achieve the goal of spreading awareness of this blinding uveitis entity.

Introduction

In 2015, uveitis experts around the world recognized the urgent need for a strong collaboration to tackle the challenges faced by uveitis related to tuberculosis (TB) and as a result, formed the Collaborative Ocular Tuberculosis Study (COTS) group with 76 experts from 25 centers globally. Despite the many advances in imaging, laboratory medicine, therapeutics and molecular engineering, TB uveitis still remains a difficult entity to diagnose and treat.¹⁻⁷ One of the reasons for this is the protean clinical manifestations of the disease and its ability to affect all the anatomical compartments of the globe, as well as the sclera, orbit and adnexa. Isolation and culture of the causative organism, *Mycobacterium tuberculosis*, is also challenging due to difficulty in obtaining an adequate sample and the low bacterial load often associated with the disease.^{4,6-9} Furthermore, the high prevalence of latent TB in many countries sometimes makes it difficult to distinguish between disease due to infection with TB and uveitis coincident with unrelated latent TB.

Thus far, the COTS group members have identified several differences in the management of TB uveitis in different centers of the world.¹ There is no single gold standard diagnostic test, and the clinical phenotypes are highly variable, depending upon the immigrant status, geographic conditions, ethnicity, as well as the local prevalence of the disease. The COTS group has aimed to increase the awareness of TB uveitis as a distinct extra-pulmonary manifestation of systemic infection, so that ophthalmologists across the globe can work closely with pulmonologists and infectious disease colleagues to initiate anti-tubercular therapy (ATT). One of the challenges recognized by the experts in the COTS was the use of non-standardized terms and names for ocular manifestations associated with TB uveitis resulting in ambiguity among clinicians and researchers. For instance, retinal vasculitis in TB has been referred to as Eales' disease, presumed TB retinal vasculitis, tubercular retinal vasculitis, TB-associated retinal vasculitis, among others, in the literature.¹⁰⁻¹⁶ The use of such non-standardized heterogeneous terminology reflects the lack of a general consensus among uveitis experts regarding this condition and the cause-effect relationship of the organism, which is the major limitation in convincing infectious disease specialists to initiate ATT.

In order to create a general agreement among ophthalmologists, including uveitis experts, and bridge the gap between ophthalmologists, scientists and colleagues in other specialties, the COTS, International Uveitis Study Group (IUSG) and International Ocular Inflammation Society (IOIS) together initiated the process, by creating a platform and inviting experts from all over the world, to work together to achieve a consensus nomenclature for ocular TB. Such an effort would standardize terminology, facilitate communication amongst clinicians and unify the reporting of outcomes after therapy in clinical studies and translational research related to ocular TB.

Materials and Methods

Study Planning and Participants

The COTS Nomenclature working group was conceived during the meeting of the COTS CON, IUSG and IOIS, held in Chandigarh, India, in November 2018. The core group, consisting of international uveitis experts (V.G., R.A., D.A.J., Q.D.N., and C.P.), conceptualized the format of the consensus guidelines. A coordinating and writing committee consisting of uveitis fellows (A.A., A.K., I.T., and S.M.) was formed to conduct the proceedings of the study. In order to ensure maximum inclusivity, diversity of opinion

and acceptability of the proposed nomenclature system, members of the COTS working group and all the members of IOIS and IUSG were invited to participate in a pre-meeting online survey for building the nomenclature (**Supplementary 1**). The experts who responded and completed the questionnaire were further invited to attend an international meeting, to develop and adopt the consensus nomenclature. The international meeting was held in Vancouver, Canada, in May 2019. The participants and their countries of practice are listed in **Appendix 1**.

International Pre-meeting Survey

Prior to the international meeting of experts, the coordinating and writing committee thoroughly reviewed the literature including manuscripts on ocular TB, using diverse key words from published literature. Various terms used to describe the anatomical location of the disease, clinical morphology, phenotype and treatment/failure or healing response, and anatomical/functional outcomes were identified and collected. In addition, a thorough review of the SUN Working Group Classification,¹⁷ International Statistical Classification of Diseases (ICD)-10 criteria and World Health Organization (WHO) criteria were studied. Before the meeting, the core group identified the knowledge gaps in the terminology for uveitis and TB and designed an online survey to determine the diversity of opinion and generate consensus from global experts. The survey was critically reviewed and approved by the core committee. The survey was modified based on the responses from the core committee, before it was circulated to the all the members of COTS Group, IOIS, and IUSG (**Supplementary 1**).

Eighty-eight experts administered the survey. The responses recorded by the members were categorized as following: a. Agreement >80% (good agreement); b. Agreement <80% (needs further discussion). For all the terms that had agreement less than 80%, an open “dialogue” was planned till the consensus could be reached. The participants were also asked to suggest new nomenclature, if they deemed appropriate, to describe the feature/entity. This process permitted identification of terms that needed greater clarification compared to others, for which a straightforward consensus was present.

Consensus Workshop for Adopting Nomenclature

The working group met for the workshop after the results of the online survey were obtained and analyzed. The consensus meeting for nomenclature was divided into four segments for the benefit of those attending, using a prepared presentation:

- a. Terms that are disease defining/describe anatomical location of inflammation;
- b. Terms that define phenotypes of the disease;
- c. Terms that can be used for reporting disease outcomes, healing and response to therapy;
- d. Terms from the literature that need clarification.

The terms for which consensus was achieved on the online survey were shown to the attendees initially without the results of the survey. The term was adopted if the attendees provided a unanimous answer which matched with the survey results. For terms where there was a disagreement, discussion continued till a consensus was achieved. On the other hand, for terms where a consensus was not achieved during the online survey,

the most preferred terms selected by the responders were used as proposed terms for discussion and dialogue was continued till consensus was achieved.

Results

Pre-meeting Survey: Broad Results

In the online survey, a total of 75 uveitis experts responded and completed the survey. The details of the participants and their countries are provided in **Appendix 1**. There was a general consensus to use a simplified terminology in order to facilitate a standardized nomenclature for reporting the disease in the literature. The responders agreed that the nomenclature should be “SUN-compatible” and reflect our current understanding of the disease pathophysiology and natural course. The responders also agreed to retain terminologies that have a widespread use in the literature and especially pertain to the typical phenotypes of TB, such as “serpiginous-like choroiditis”, and “paradoxical worsening”.

1. Consensus Nomenclature for Disease Defining Terms:

The first part of the nomenclature workshop pertained to the broad term that must be used for uveitis *attributable* to TB (indicating that the ocular inflammation is considered to be tubercular in origin by the treating ophthalmologist based on positive immunological tests (such as Mantoux/interferon gamma release assay) and radiological tests (such as chest computerized tomography indicative of old/healed tuberculosis) and *not necessarily* a confirmed test such as histopathology or polymerase chain reaction). The attendees in the workshop deemed correct, the use of a broad, umbrella term “*ocular tuberculosis (OTB)*” to define the disease. This was based on the premise that as per the SUN working group, a direct infection caused by a specific pathogen in the body requiring specific antimicrobial therapy is termed as “name of the pathogen” followed by “anatomical structure involved” (for example: cytomegalovirus retinitis, toxoplasma retinochoroiditis and syphilitic uveitis). There was consensus that the term “*associated*” should *not* be applied to OTB since it is used to indicate uveitis in the presence of a systemic risk factor such as juvenile idiopathic arthritis (JIA)-associated uveitis and human leucocyte antigen (HLA) B27-associated uveitis.

Terms that describe the anatomical segment of the eye involved were further discussed. It was decided that under the umbrella term of *OTB*, *intraocular inflammation* should be termed as “*tubercular uveitis (TBU)*”. Extraocular manifestations should be termed accordingly; for instance: *tubercular scleritis*. Based on this argument, all the attendees agreed that for different anatomical structures affected (based on the SUN classification), the terms that must be adopted include: *tubercular anterior uveitis (TAU)*, *tubercular intermediate uveitis (TIU)*, *tubercular posterior uveitis (TPU)*, *tubercular panuveitis (TBP)*, and *tubercular retinal vasculitis (TRV)*.

Table 1 represents consensus nomenclature for disease defining terms.

2. Consensus Nomenclature for Terms Defining Disease Morphology and Phenotype

This section pertains to names that denote the choroidal lesions commonly observed in patients with OTB (“choroiditis”). Since choroiditis among patients with OTB

can have protean clinical manifestations and can affect primarily the choriocapillaris or the choroidal stroma, it was decided to provide a broad term “*tubercular choroiditis (TBC)*”, which will encompass all the conditions characterized by choroidal inflammation in TB. Under the umbrella term of *TBC*, the attendees agreed that 4 distinct phenotypes must be identified and named:

a. *Tubercular serpiginous-like choroiditis (TB SLC)*: This term was proposed to describe the phenotype, which presents as discreet yellowish-white fuzzy choroidal lesions with slightly raised edges, that show wave-like progression over a few weeks with an active serpiginous-like edge, and characterized by central healing. On autofluorescence imaging, the active edge shows hyper-autofluorescence and central healed areas show hypo-autofluorescence. TB SLC lesions can further be *multifocal or placoid*. The lesions of multifocal SLC are $\frac{1}{4}$ – 1 disc diameter in size with well-defined margins and slightly raised edges. The edges of these lesions are non-contiguous initially and gradually become confluent. Placoid lesions are diffuse plaque-like and have characteristic amoeboid pattern and active edge.^{18–20}

b. *Tubercular multifocal choroiditis (TB MC)*: this term was proposed for *multifocal* choroiditis lesions with a phenotype similar to idiopathic multifocal choroiditis, acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and other phenotypes that *do not* resemble TB SLC.²¹

c. *Tubercular focal choroiditis (TB FC)*: this term was proposed for unifocal choroiditis lesions that *do not* resemble TB SLC.²¹

d. *Tuberculoma*: a unique phenotype of OTB is a yellowish subretinal lesion with indistinct borders and surrounding exudative fluid, along with presence of a hyporeflective oval/round lesion in the choroidal stroma on optical coherence tomography, and hypocyanescence in the early (and possibly late) phase of the indocyanine green angiography (choroidal granuloma).^{22,23} These may be single or multiple in the posterior pole or in the mid-periphery. The attendees agreed that the term “choroidal granuloma” is incorrect since a granuloma is a histological term. However, this entity must be differentiated from *TB SLC*, *TB MC* and *TB FC* because it has a different anatomical location of inflammation, course and outcomes, and must be differentiated from sarcoid granulomas.

Choroidal tubercles are typically defined in the literature to occur among individuals with disseminated or miliary TB as unilateral/ bilateral, usually multiple (but may be single), ≤ 0.5 disc diameter, discreet greyish-white lesions with a central core and surrounding rim of inflammation (in the active stage), followed by an oval/rounded appearance of a scar with variable pigmentation and resolution (in healed stage). On optical coherence tomography they may show elevation of the retinal pigment epithelium-Bruchs’ complex, due to their location in the choroid in the active stage.^{24–26} Since this term is very commonly used in published literature and is in sync with tubercles seen in other parts of the body, it was decided to retain this term *but as a part of TB MC*.

Tubercular subretinal abscess was determined to be a severe form of tuberculoma characterized by subretinal, yellowish lesion surrounded with exudation, associated with rapid necrosis and tissue destruction, often associated with presence of overlying retinal hemorrhages. It was decided to not give a separate term for this entity.²⁷

A table simplifying the terms related to choroiditis is provided in **Table 2**.

3. Consensus Nomenclature for Terms Related to Treatment/Healing and Reporting Outcomes

This section pertains to names that denote outcomes in patients with OTB after initiation of antitubercular therapy (ATT). The experts agreed that OTB merits special consideration for standardized nomenclature for reporting treatment and outcome. According to the SUN working group, *remission* denotes inactive disease for ≥ 3 months after discontinuing all treatments for eye disease.¹⁷ In the context of OTB, the experts agreed that “*remission*” must be used when the disease is inactive (grade 0 cells/no inflammation) for at least 3 months after a complete course of ATT. In line with the terminology for pulmonary TB,^{28–30} the experts also agreed to denote disease inactivity 24 months after a complete course of ATT as “*cure*”.

During the course of ATT, it is often observed that certain patients develop worsening of inflammation in the eye (ocular Jarisch-Herxheimer reaction). In the context of choroiditis, it consists of clinical or angiographic progression of the lesion(s) or development of new lesion(s) (in at least one eye) in patients who were started on treatment with ATT (with concomitant corticosteroids). This also includes lesions that seem to respond initially but show worsening during the course of therapy. The experts agreed to denote this as “*paradoxical worsening*” of the disease. This term is the most preferred in the existing literature as well.^{27,31–35}

4. Consensus Nomenclature for Terms Needing Clarification

Based on the pre-meeting literature search, the coordinating and working committee came across the term “Eales’ disease”, that has been often attributed to TB. Eales’ disease is predominantly encountered in the Indian subcontinent and is characterized by occlusive retinal vasculitis (primarily retinal periphlebitis) with high risk of retinal neovascularization. This condition has a strong immunological link to TB.^{10–12,36} Morphologically, there is no pathological feature that allows distinction from TRV. Therefore, the experts agreed upon using the term TRV and *avoid* Eales’ disease in cases where TB is determined to be the etiology of inflammation.

Table 3 provides a short summary of the novel and existing terms adopted by the COTS Nomenclature workshop.

Discussion

A scientific field's (including ocular TB, clinical trials and translational research) terminology is not satisfactory unless there is a specific definition for each lesion/term; i.e., there should be one-to-one relationship between the clinical condition and term. There should not be any condition, which can be described by multiple terms, and likewise, no term should characterize more than a single clinical condition. It is imperative that a logical system using consensus approach be created, incorporating all of the disease and outcome defining individual terms.

The COTS Nomenclature working group, initiated by COTS and supported by IUSG and IOIS, have provided the first standardized international consensus nomenclature on OTB. This nomenclature will provide an enhanced understanding of the disease among

ophthalmologists as well as physicians from other specialties. In addition, such an effort by international experts in the field of uveitis will allow recognition of OTB as a specific form of extra-pulmonary TB which requires ATT *even when mycobacteria cannot be isolated/cultured from the sample* and diagnosis is based on the clinical disease phenotype, supportive laboratory tests (Mantoux or interferon gamma release assay) and radiological investigations (chest X-ray or computerized tomography, indicative of old/healed tuberculosis).

The SUN working group has already provided nomenclature guidelines on various aspects such as onset of inflammation, grading of severity, disease activity, anatomical classification of uveitis, as well as documenting complications.^{17,37-39} These are widely acceptable and applicable for all types of uveitis. Therefore, the COTS Nomenclature working group attempted to prepare a SUN-compatible nomenclature system for various features of OTB. The major breakthrough from the COTS Nomenclature workshop was shedding of the term “associated” (ie. tubercular-“associated” uveitis), since most experts agreed that by naming the disease as “tubercular uveitis” causality is suggested. This will make it easier for uveitis colleagues world over to co-manage their patients with infectious disease specialists, encouraging them to proceed with systemic investigations such as: endobronchial/ transbronchial biopsies, lymph node aspiration, bronchoalveolar/gastric lavage, and to initiate ATT when directed by ophthalmologists. Such a nomenclature will make TB at par with other conditions such as syphilitic uveitis and cytomegalovirus retinitis for which specific anti-microbial therapy is indicated.

Another major consensus issue discussed and agreed upon by the COTS Nomenclature working group was the classification of choroiditis lesions in TB. The four major groups of TB choroiditis include TB SLC (which may be multifocal or placoid), TB multifocal choroiditis, TB focal choroiditis (both of which do not resemble SLC) and tuberculoma. This classification aims to simplify the description of phenotypic expression, as well as segregate them based on their morphological appearance.

One of the highlights of the COTS Nomenclature working group guidelines was the introduction of the terms “remission” and “cure” in the context of OTB. These terms will help in reporting outcomes of treatment with ATT among patients with various phenotypes of OTB. Reporting “remission” and “cure” will also demonstrate the efficacy of ATT in the context of tubercular uveitis. Long-term outcome analysis of patients with OTB will help in further clarifying the relevance of these terms.

In conclusion, it is clear from the literature review and expert opinions, that there are significant discrepancies and ambiguity in the current terminology related to OTB. This new consensus nomenclature will eliminate the current discrepancies in terminology related to OTB. The COTS Nomenclature working group advocates widespread application of the new nomenclature system for reporting OTB to further understanding of this enigmatic disease. Besides IUSG and IOIS, as additional major ophthalmological organizations, scientific journals, infectious disease specialist and organizations endorses this system and mandates its adoption in scientific submissions. This new classification will gradually disseminate across the field of OTB and become the common language amongst uveitis specialists, infectious disease specialists and researchers.

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Appendix 1: COTS Nomenclature Working Group Collaborators

1. Alan Palestine (USA)
2. Alastair Denniston (UK)
3. Alay Banker (India)
4. Alessandro Invernizzi (Italy)
5. Alex Fonollosa (Spain)
6. Aman Sharma (India)
7. Amitabh Kumar (India)
8. Andre Curi (Brazil)
9. Annabelle Okada (Japan)
10. Ariel Schlaen (Argentina)
11. Arnd Heiligenhaus (Germany)
12. John Kempen (Africa)
13. Atul Kumar (India)
14. Avinash Gurbaxani (UAE)
15. Bahram Bodaghi (France)
16. Bulbul Islam Shah (Bangladesh)
17. Careen Lowder (USA)
18. Christoph Tappeiner (Switzerland)
19. Cristina Muccioli (Brazil)
20. Daniel Vitor Vasconcelos-Santos (Brazil)
21. Debra Goldstein (USA)
22. Digambar Behra (India)
23. Dipankar Das (India)
24. Dorine Makhoul (Belgium)
25. Edoardo Baglivo (Switzerland)
26. Ekaterina Denisova (Russia)
27. Elisabetta Misericocchi (Italy)
28. Ester Carreno (Spain)
29. Fatma Asyari (Indonesia)
30. Francesco Pichi (UAE)
31. H. Nida Sen (USA)
32. Harvey Uy (Philippines)
33. Heloisa Nascimento (Brazil)
34. Ilknur Tugal-Tutkun (Turkey)
35. J Fernando Arevalo (USA)
36. Janet Davis (USA)
37. Jennifer Thorne (USA)
38. Joyce Hisae Yamamoto (Brazil)
39. Justine Smith (Australia)
40. Justus G. Garweg (Switzerland)
41. Jyotirmay Biswas (India)
42. Kalpana Babu (India)
43. Kanika Aggarwal (India)
44. Luca Cimino (Italy)
45. Lucia Kuffova (UK)
46. Mamta Agarwal (India)
47. Manfred Zierhut (Germany)
48. Manisha Agarwal (India)

49. Marc De Smet (Switzerland)
50. Maria Sofia Tognon (Italy)
51. Marie-Helene Errera (France)
52. Marion Munk (Switzerland)
53. Mark Westcott (UK)
54. Masoud Soheilian (Iran)
55. Massimo Accorinti (Italy)
56. Moncef Khairallah (Tunisia)
57. Myhanh Nguyen (Vietnam)
58. Onn Minn Kon (UK)
59. Padmamalini Mahendradas (India)
60. Peizeng Yang (China)
61. Piergiorgio Neri (UAE)
62. Pinar Ozdal (Turkey)
63. Radgonde Amer (Israel)
64. Richard Lee (UK)
65. Rina La Distia Nora (Indonesia)
66. Romi Chhabra (UK)
67. Rubens Belfort (Brazil)
68. Salil Mehta (India)
69. Samir Shoughy (UAE)
70. Saurabh Luthra (India)
71. Shelina Oli Mohamed (Malaysia)
72. Soon-Phaik Chee (Singapore)
73. Soumyava Basu (India)
74. Stephen Teoh (Singapore)
75. Sudha Ganesh (India)
76. Talin Barisani-Asenbauer (Austria)
77. Yan Guex-Crosier (Switzerland)
78. Yilmaz Ozyazgan (Turkey)
79. Yonca Akova (Turkey)
80. Zohar Habot-Wilner (Israel)

1. University of Colorado, Denver, USA
2. Department of Ophthalmology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; Moorfields Eye Hospital, NHS Foundation Trust, London, United Kingdom
3. Banker's Retina Clinic and Laser Centre, 5 Subhash Society, Ahmedabad, India
4. Eye Clinic, Department of Biomedical and Clinical Science "L. Sacco", Luigi Sacco Hospital, University of Milan, Milan, Italy
5. Hospital Universitario Cruces, Cruces-Barakaldo, Bilbao, Vizcaya (Spain)
6. Department of Rheumatology , PGIMER , Chandigarh, India.
7. Department of Uvea , Aditya Birla Sankara Nethralaya , Kolkata , India
8. Instituto Nacional de Infectologia Evandro Chagas, Fiocruz, Brazil
9. Department of Ophthalmology, Kyorin University School of Medicine, Tokyo, Japan
10. Hospital Universitario Austral, Hospital de Clinicas "Jose de San Martín", Universidad de Buenos Aires
11. Augenabteilung und Ophtha Lab am St. Franziskus-Hospital, Münster.

12. Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts
13. Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India
14. Moorfields Eye Hospital, NHS Foundation Trust, London, United Kingdom
15. Department of Ophthalmology, Sorbonne University, Paris, France
16. Ibn Sina Hospital, Dhaka, Bangladesh
17. Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA.
18. Department of Ophthalmology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
19. Instituto da Visão, Hospital São Paulo, Universidade Federal de São Paulo, SP, Brazil
20. Uveitis Unit, Hospital São Geraldo / Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
21. Feinberg School of Medicine, Department of Ophthalmology, Northwestern University, Chicago, Illinois, USA
22. Department of Pulmonary Medicine, Advanced Eye Centre, Postgraduate Institute of Medical Education & Research, Chandigarh, India
23. Department of Ocular Pathology, Uveitis & Neuro-Ophthalmology Services; Sankaradeva Nethralaya, Guwahati, India
24. Department of Ophthalmology, CHU Saint-Pierre, Université Libre de Bruxelles (ULB), Brussels, Belgium
25. Department of Ophthalmology, Clinique de l'oeil, Geneva, Switzerland
26. Helmholtz research institute of eye diseases, Moscow, Russia
27. Ophthalmology Department, San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy
28. Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
29. INOIS, Department of Ophthalmology University of Indonesia, Indonesia
30. Eye Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
31. The Laboratory of Immunology, National Eye Institute, Bethesda, Maryland
32. Ocular Immunology and Uveitis Service, Asian Eye Institute, Makati, Philippines
33. Instituto da Visão, Hospital São Paulo, Universidade Federal de São Paulo (UNIFESP), SP, Brazil
34. Istanbul Faculty of Medicine, Department of Ophthalmology, Istanbul University, Turkey
35. Vitreoretinal Division, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia; Retina Division, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
36. Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, USA.
37. Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, USA
38. Department of Ophthalmology, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.
39. Flinders University College of Medicine and Public Health, Adelaide, Australia
40. Swiss Eye Institute and Berner Augenklinik am Lindenhofspital, Bern, Switzerland; University of Bern, Bern, Switzerland.
41. Sankara Nethralaya, Chennai, India
42. Vittala International Institute of Ophthalmology, Bangalore, India
43. Advanced Eye Centre, Postgraduate Institute of Medical Education & Research, Chandigarh, India

44. Ocular Immunology Unit, Azienda USL IRCCS, Reggio Emilia, Italy
45. Section of Immunity, Infection and Inflammation, Division of Applied Medicine, University of Aberdeen, School of Medicine and Dentistry, Aberdeen
46. Sankara Nethralaya, Chennai, India
47. Centre of Ophthalmology, University of Tuebingen, Tuebingen, Germany
48. Dr Shroff's Charity Eye Hospital Daryaganj, New Delhi, India
49. Department of Ophthalmology ZNA Middelheim, Antwerp, Belgium
50. Ocular Immunology Unit, Department of Ophthalmology, S. Antonio Hospital, Padova, Italy
51. Centre National d'Ophthalmologie des 15-20, Paris, Sorbonne-Universités, Paris 6, France
52. Department of Ophthalmology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
53. Moorfields Eye Hospital, NHS Foundation Trust, London, United Kingdom
54. Shahid Beheshti University of Medical Sciences, Tehran, Iran
55. Department of Ophthalmology, Sapienza University of Rome, Rome, Italy.
56. Department of Ophthalmology, Fattouma Bourguiba University Hospital, Faculty of Medicine, University of Monastir, Monastir, Tunisia
57. Cao Thang Eye Hospital, Ho Chi Minh City, Vietnam
58. Chest and Allergy Clinic, St Mary's Hospital, Imperial College Healthcare Service trust, London, United Kingdom
59. Department of Uveitis and Ocular Immunology, Narayana Nethralaya, Bangalore, India
60. The First Affiliated Hospital of Chongqing Medical University, Chongqing Key Laboratory of Ophthalmology and Chongqing Eye Institute, Chongqing, China
61. Eye Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
62. Department of Ophthalmology, Ulucanlar Eye Education and Research Hospital, University of Health Sciences, Ankara, Turkey
63. Department of Ophthalmology, Hadassah Medical Center, Jerusalem, Israel.
64. Moorfields Eye Hospital, NHS Foundation Trust, London, United Kingdom
65. INOIS, Department of Ophthalmology University of Indonesia, Indonesia
66. Department of Ophthalmology, University of Manchester, Manchester, United Kingdom
67. Department of Ophthalmology and Visual Sciences, Federal University of São Paulo, São Paulo, Brazil.
68. Department of Ophthalmology, Lilavati Hospital and Research Center, Bandra Reclamation, Mumbai, India
69. The Eye Center and The Eye Foundation for Research in Ophthalmology, Riyadh, Saudi Arabia
70. Drishti Eye Centre, Dehradun, Uttaranchal, India.
71. Hospital Shah Alam, Shah Alam, Selangor, Malaysia
72. Singapore Eye Research Institute, Singapore; Yong Loo Lin School of Medicine, National University of Singapore, Singapore
73. LV Prasad Eye Institute, Bhubaneswar, India
74. Eagle Eye Centre, Singapore
75. Department of Uvea, Medical Research Foundation, Sankara Nethralaya, Chennai, 600006, India.
76. OCUVAC - Centre of Ocular Inflammation and Infection, Laura Bassi Centre of Expertise, Center of Pathophysiology, Infectiology & Immunology, Medical University of Vienna, Vienna
77. Jules Gonin Eye Hospital, FAA, University of Lausanne, Switzerland

78. Department of Ophthalmology, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey.
79. Department of Ophthalmology , Bayindir Kavaklidere Hospital , Ankara , Turkey.
80. Ophthalmology Division, Tel Aviv Medical Center, Tel Aviv, Israel; The Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.