Intraocular Inflammation and Uveitis

Last major revision 2015–2016
The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The American Academy of Ophthalmology designates this enduring material for a maximum of 10 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME expiration date: June 1, 2018. AMA PRA Category 1 Credits™ may be claimed only once between June 1, 2015, and the expiration date.

BCSC® volumes are designed to increase the physician's ophthalmic knowledge through study and review. Users of this activity are encouraged to read the text and then answer the study questions provided at the back of the book.

To claim AMA PRA Category 1 Credits™ upon completion of this activity, learners must demonstrate appropriate knowledge and participation in the activity by taking the posttest for Section 9 and achieving a score of 80% or higher. For further details, please see the instructions for requesting CME credit at the back of the book.

The Academy provides this material for educational purposes only. It is not intended to represent the only or best method or procedure in every case, nor to replace a physician's own judgment or give specific advice for case management. Including all indications, contraindications, side effects, and alternative agents for each drug or treatment is beyond the scope of this material. All information and recommendations should be verified, prior to use, with current information included in the manufacturers' package inserts or other independent sources, and considered in light of the patient's condition and history. Reference to certain drugs, instruments, and other products in this course is made for illustrative purposes only and is not intended to constitute an endorsement of such. Some material may include information on applications that are not considered community standard, that reflect indications not included in approved FDA labeling, or that are approved for use only in restricted research settings. The FDA has stated that it is the responsibility of the physician to determine the FDA status of each drug or device he or she wishes to use, and to use them with appropriate, informed patient consent in compliance with applicable law. The Academy specifically disclaims any and all liability for injury or other damages of any kind, from negligence or otherwise, for any and all claims that may arise from the use of any recommendations or other information contained herein.

AAO, AAOE, American Academy of Ophthalmology, Basic and Clinical Science Course, BCSC, EyeCare America, EyeNet, EyeSmart, EyeWiki, Focal Points, IRIS, ISRS, OKAP, ONE, Ophthalmic Technology Assessments, Ophthalmology, Preferred Practice Pattern, ProVision, SmartSight, The Ophthalmic News & Education Network, and the AAO logo (shown on cover) and tagline (Protecting Sight. Empowering Lives.) are, among other marks, the registered trademarks and trademarks of the American Academy of Ophthalmology.

Cover image: From BCSC Section 5, Neuro-Ophthalmology: Fundus photograph showing an arteriovenous malformation (racemose angioma) of the retina in a patient with Wyburn-Mason syndrome. (Courtesy of Mark J. Greenwald, MD.)

Copyright © 2017 American Academy of Ophthalmology. All rights reserved. No part of this publication may be reproduced without written permission.

Printed in the United States of America.
Basic and Clinical Science Course

Louis B. Cantor, MD, Indianapolis, Indiana, Senior Secretary for Clinical Education
Christopher J. Rapuano, MD, Philadelphia, Pennsylvania, Secretary for Lifelong Learning and Assessment
George A. Cioffi, MD, New York, New York, BCSC Course Chair

Section 9

Faculty

Russell W. Read, MD, PhD, Chair, Birmingham, Alabama
Nisha Acharya, MD, San Francisco, California
Ralph D. Levinson, MD, Los Angeles, California
P. Kumar Rao, MD, St Louis, Missouri
H. Nida Sen, MD, MHS, Bethesda, Maryland
Jonathan D. Walker, MD, Fort Wayne, Indiana
Daniel V. Vasconcelos-Santos, MD, Consultant, Belo Horizonte, Brazil

The Academy wishes to acknowledge the American Uveitis Society (AUS) for recommending faculty members to the BCSC Section 9 committee.

The Academy also wishes to acknowledge the following committees for review of this edition:

Committee on Aging: Kelly L. Larkin, MD, Houston, Texas

Vision Rehabilitation Committee: Paul I. Homer, MD, Boca Raton, Florida

Practicing Ophthalmologists Advisory Committee for Education: Dasa V. Gangadhar, MD, Primary Reviewer, Wichita, Kansas; Edward K. Isbey III, MD, Chair, Asheville, North Carolina; Alice L. Bashinsky, MD, Asheville, North Carolina; David J. Browning, MD, PhD, Charlotte, North Carolina; Robert G. Fante, MD, Denver, Colorado; Bradley D. Fouraker, MD, Tampa, Florida; Steven J. Grosser, MD, Golden Valley, Minnesota; James A. Savage, MD, Memphis, Tennessee

European Board of Ophthalmology: Carlos E. Pavesio, MD, EBO Chair, London, United Kingdom; Talin Barisani-Asenbauer, MD, FEBO, EBO Liaison, Vienna, Austria; Bahram Bodaghi, MD, PhD, Paris, France; Marc D. de Smet, MD, PhD, Lausanne, Switzerland; Arnd Heiligenhaus, MD, PhD, Münster, Germany; Richard W. J. Lee, PhD, Bristol, United Kingdom; Elisabetta Misericocchi, MD, Milan, Italy; Philip I. Murray, MBBS, DO (RCS), PhD, Birmingham, United Kingdom; Piergiorgio Neri, MD, PhD, FEBO, Ancona, Italy; Miles Stanford, MD, London, United Kingdom
Financial Disclosures

Academy staff members who contributed to the development of this product state that within the past 12 months, they have had no financial interest in or other relationship with any entity discussed in this course that produces, markets, resells, or distributes ophthalmic health care goods or services consumed by or used in patients, or with any competing commercial product or service.

The authors and reviewers state that within the past 12 months, they have had the following financial relationships.*

Dr Acharya: Santen (C), Xoma (C)

Dr Barisani-Asenbauer: Askin Austria (L), Croma Pharma (S), Laboratoires Thea Austria (L), Novartis Pharmaceuticals (S), Teva Pharmaceutical Industries (C)

Dr Bodaghi: Abbott Medical Optics (C), Allergan (C, S), Bausch + Lomb Surgical (C), Novartis Pharmaceuticals (S), Santen (C), Xoma (C)

Dr Browning: Aerpio Therapeutics (S), Alimera Sciences (C), Diabetic Retinopathy Clinical Research (S), Genentech (S), Novartis Pharmaceuticals (S), Pfizer (S), Regeneron Pharmaceuticals (S)

Dr de Smet: Allergan (C, L, S), Arnhem Ophthalmic Research (O, P), Bayer Pharmaceuticals (C), Centocor Pharmaceuticals (C, S), GlaxoSmithKline (C), Regeneron Pharmaceuticals (C), Sanofi (C), Santen (C), Thrombogenics (C, L, P, S)

Dr Fante: Ophthalmic Mutual Insurance Company (C)

Dr Fouraker: Addition Technology (C), Alcon Laboratories (C), Keravision (C), Ophthalmic Mutual Insurance Company (C)

Dr Grosser: Ivantis (O)

Dr Isbey: Alcon Laboratories (S), Allscripts (C), Bausch + Lomb (S), Medflow (C)

Dr Larkin: AbbVie Humira (C), Xoma Eyeguard Study (C)

Dr Lee: EMD Serono (C), Genentech (C), UK National Institute for Health Research (S), US Patent Application No. 61/919,404 (P)

Dr Miserocchi: Abbott Immunology (C), Allergan (C), Santen (C)

Dr Neri: AbbVie (L), Bausch + Lomb (C, L), Santen Pharma (C)

Dr Pavesio: Alcon (C), Alimera Sciences (C), Bausch + Lomb (C)

Dr Rao: National Eye Institute (S), Regeneron Pharmaceuticals (S), Servier Laboratories (C)

Dr Read: EyeSight Foundation of Alabama (S), Matthew Family Foundation (S), Research to Prevent Blindness (S)

Dr Savage: Allergan (L)

The other authors and reviewers state that within the past 12 months, they have had no financial interest in or other relationship with any entity discussed in this course that pro-
duces, markets, resells, or distributes ophthalmic health care goods or services consumed by or used in patients, or with any competing commercial product or service.

*C = consultant fees, paid advisory boards, or fees for attending a meeting; L = lecture fees (honoraria), travel fees, or reimbursements when speaking at the invitation of a commercial sponsor; O = equity ownership/stock options of publicly or privately traded firms (excluding mutual funds) with manufacturers of commercial ophthalmic products or commercial ophthalmic services; P = patents and/or royalties that might be viewed as creating a potential conflict of interest; S = grant support for the past year (all sources) and all sources used for a specific talk or manuscript with no time limitation

Recent Past Faculty
Bahram Bodaghi, MD, PhD
Ramana S. Moorthy, MD
Russell N. Van Gelder, MD, PhD
Albert T. Vitale, MD

In addition, the Academy gratefully acknowledges the contributions of numerous past faculty and advisory committee members who have played an important role in the development of previous editions of the Basic and Clinical Science Course.

American Academy of Ophthalmology Staff
Dale E. Fajardo, Vice President, Education
Beth Wilson, Director, Continuing Professional Development
Ann McGuire, Acquisitions and Development Manager
Stephanie Tanaka, Publications Manager
D. Jean Ray, Production Manager
Kimberly Torgerson, Publications Editor
Beth Collins, Medical Editor
Naomi Ruiz, Editorial Assistant

American Academy of Ophthalmology
655 Beach Street
Box 7424
San Francisco, CA 94120-7424
Contents

General Introduction ........................................ xiii

Objectives ...................................................... 1
Introduction ................................................... 3

PART I  Ocular Immunology ................................. 5

Introduction to Ocular Immunology and Immune-Mediated Eye Disease .......... 7

1  Basic Concepts in Immunology:
Effector Cells and the Innate Immune Response ............ 9
Definitions .................................................. 9
Components of the Immune System .......................... 9
Leukocytes .................................................. 9
Overview of the Innate Immune System .................. 12
Immunity Versus Inflammation ........................... 12
Triggers of Innate Immunity ............................... 13
Bacteria-Derived Molecules That Trigger Innate Immunity .. 13
Other Triggers or Modulators of Innate Immunity ........ 16
Innate Mechanisms for the Recruitment and Activation of
Neutrophils .............................................. 16
Innate Mechanisms for the Recruitment and Activation of
Macrophages ............................................. 19
Mediator Systems That Amplify Immune Responses ........ 22
Plasma-Derived Enzyme Systems .......................... 22
Lipid Mediators ........................................... 24
Cytokines .................................................. 26
Reactive Oxygen Intermediates ............................ 29
Reactive Nitrogen Products ................................ 29
Neutrophil-Derived Granule Products ..................... 30

2  Immunization and Adaptive Immunity:
The Immune Response Arc and Immune Effectors ........ 31
Overview of the Immune Response Arc .................. 32
Phases of the Immune Response Arc ..................... 33
Afferent Phase ........................................... 33
Processing Phase ......................................... 36
Effector Phase ........................................... 38
Clinical Approach to Uveitis

Animal Models of Human Uveitis

Ocular Immune Responses

HLA Associations and Disease

Immune Responses of the Retina, RPE, Choriocapillaris, and Choroid

Immune Responses of the Cornea

Immune Responses of the Anterior Chamber, Anterior Uvea, and Vitreous

Features of the Immunologic Microenvironment

Immunoregulatory Systems

Immune Responses of the Con junctiva

Features of the Immunologic Microenvironment

Immunoregulatory Systems

Immune Responses of the Cornea

Features of the Immunologic Microenvironment

Immunoregulatory Systems

Immune Responses of the Retina, RPE, Choriocapillaris, and Choroid

Features of the Immunologic Microenvironment

Immunoregulatory Systems

Special Topics in Ocular Immunology

Animal Models of Human Uveitis

Experimental Autoimmune Uveoretinitis

Endotoxin-Induced Uveitis

Equine Recurrent Uveitis

AIRE-Deficient Mice

IRBP-Specific T-Cell Receptor Transgenic Mice

HLA Associations and Disease

Normal Function of HLA Molecules

Allelic Variation

Disease Associations

PART II Intraocular Inflammation and Uveitis

Clinical Approach to Uveitis

Classification of Uveitis

Anterior Uveitis

Intermediate Uveitis

Posterior Uveitis

Panuveitis

Retinal Vasculitis

Categorization by Clinical Course
Symptoms of Uveitis .................................................. 78
Signs of Uveitis . ...................................................... 79
  Anterior Segment ............................................... 79
  Intermediate Segment ........................................ 83
  Posterior Segment ............................................. 84
Review of the Patient’s Health and Other Associated Factors ........... 84
Epidemiology of Uveitis ........................................... 85
Laboratory and Medical Evaluation ................................ 88
Therapy ............................................................. 93
Medical Management of Uveitis ................................... 93
  Mydriatic and Cycloplegic Drugs ............................. 94
  Nonsteroidal Anti-Inflammatory Drugs .................... 94
  Corticosteroids ............................................... 95
  Immunomodulatory Medications .............................. 100
Surgical Management of Uveitis ................................... 109

6 Noninfectious Ocular Inflammatory Diseases . 111
  Noninfectious Scleritis ......................................... 111
    Treatment of Noninfectious Scleritis ...................... 111
  Anterior Uveitis ............................................. 112
    Acute Nongranulomatous Anterior Uveitis ................ 112
    Chronic Anterior Uveitis .................................. 121
  Intermediate Uveitis ......................................... 127
    Pars Planitis .............................................. 128
    Multiple Sclerosis ....................................... 132
  Posterior Uveitis ........................................... 132
    Collagen Vascular Diseases .............................. 132
    Susac Syndrome .......................................... 139
    Inflammatory Chorioretinopathies of Unknown Etiology . 140
  Panuveitis ................................................... 166
    Sarcoidosis .............................................. 166
    Sympathetic Ophthalmia .................................. 171
    Vogt-Koyanagi-Harada Syndrome .......................... 175
    Behçet Disease .......................................... 182

7 Infectious Ocular Inflammatory Diseases . 191
  Viral Uveitis .................................................. 191
    Herpesviridae Family ...................................... 191
    Rubella .................................................... 203
    Lymphocytic Choriomeningitis Virus ...................... 205
    Measles (Rubeola) ....................................... 206
    West Nile Virus .......................................... 208
    Rift Valley Fever ........................................ 210
    Human T-Lymphotropic Virus Type 1 .................... 212
    Dengue Fever ............................................. 213
    Chikungunya Fever ...................................... 213
    Other Viral Diseases ..................................... 214
Fungal Uveitis ............................................. 214
  Ocular Histoplasmosis Syndrome ................. 214
Protozoal Uveitis ........................................ 219
  Toxoplasmosis ......................................... 219
Helminthic Uveitis ....................................... 228
  Toxocariasis ......................................... 228
  Cysticercosis ........................................ 230
  Diffuse Unilateral Subacute Neuroretinitis .... 232
  Onchocerciasis ...................................... 234
Bacterial Uveitis ....................................... 236
  Syphilis ............................................ 236
  Lyme Disease ....................................... 243
  Leptospirosis ....................................... 248
  Ocular Nocardiosis .................................. 249
  Tuberculosis ........................................ 250
  Ocular Bartonellosis ................................ 255
  Whipple Disease .................................... 258
Infectious Scleritis .................................... 259
  Etiology ............................................ 259
  Clinical Features ................................... 259
  Diagnostic Workup .................................. 259
  Treatment ........................................... 260
  Prognosis .......................................... 260

8 Endophthalmitis ...................................... 261
  Chronic Postoperative Endophthalmitis .......... 261
  Endogenous Endophthalmitis ....................... 263
    Endogenous Bacterial Endophthalmitis ........ 263
    Endogenous Fungal Endophthalmitis ............ 265

9 Masquerade Syndromes ............................... 273
  Neoplastic Masquerade Syndromes ................ 273
    Primary Central Nervous System Lymphoma .... 273
    Neoplastic Masquerade Syndromes Secondary to Systemic Lymphoma ....... 276
    Neoplastic Masquerade Syndromes Secondary to Leukemia ...... 276
    Neoplastic Masquerade Syndromes Secondary to Uveal Lymphoid Proliferations ........ 276
    Nonlymphoid Malignancies ....................... 277
    Metastatic Tumors ................................ 278
    Bilateral Diffuse Uveal Melanocytic Proliferation ........ 278
  Nonneoplastic Masquerade Syndromes ............. 278
    Retinitis Pigmentosa. ............................ 278
    Ocular Ischemic Syndrome ......................... 278
    Chronic Peripheral Rheumatogenous Retinal Detachment ........ 279
    Intraocular Foreign Bodies ....................... 279
    Pigment Dispersion Syndrome .................... 280
    Other Syndromes .................................. 280
10 Complications of Uveitis .......................................................... 281
  Calcific Band Keratopathy ...................................................... 281
  Cataracts .................................................................................. 281
    Management ......................................................................... 282
  Complications ........................................................................ 284
  Glaucoma ................................................................................. 284
    Uveitic Ocular Hypertension ................................................... 285
    Uveitic Glaucoma .................................................................. 285
    Corticosteroid-Induced Ocular Hypertension and Glaucoma ... 286
    Management ......................................................................... 287
  Hypotony ................................................................................... 288
  Cystoid Macular Edema .............................................................. 289
  Vitreous Opacification and Vitritis ........................................... 290
  Rhegmatogenous Retinal Detachment ...................................... 291
  Retinal and Choroidal Neovascularization .............................. 291
  Vision Rehabilitation ................................................................. 292

11 Ocular Involvement in AIDS .................................................. 293
  Ophthalmic Manifestations ....................................................... 293
    Cytomegalovirus Retinitis ....................................................... 294
    Necrotizing Herpetic Retinitis ............................................... 295
    Toxoplasma Retinochoroiditis ............................................... 296
    Syphilitic Chorioretinitis ....................................................... 297
    Pneumocystis jirovecii Choroiditis ........................................ 298
    Cryptococcus neoformans Choroiditis .................................... 298
    Multifocal Choroiditis and Systemic Dissemination ............... 299
  External Eye Manifestations ..................................................... 299
    Ocular Adnexal Kaposi Sarcoma ............................................ 299
    Molluscum Contagiosum ....................................................... 300
    Herpes Zoster .................................................................... 300
    Other Infections .................................................................. 300
  HIV Infection in Resource-Limited Regions of the World ....... 301
  Precautions in the Health Care Setting .................................... 301
    Precautions in Ophthalmic Practice ...................................... 301

Appendix: Diagnostic Survey for Uveitis .................................. 303
Basic Texts .............................................................................. 307
Related Academy Materials ....................................................... 309
Requesting Continuing Medical Education Credit .................. 311
Study Questions ..................................................................... 313
Answer Sheet for Section 9 Study Questions ............................ 319
Answers ................................................................................... 321
Index ....................................................................................... 327
General Introduction

The Basic and Clinical Science Course (BCSC) is designed to meet the needs of residents and practitioners for a comprehensive yet concise curriculum of the field of ophthalmology. The BCSC has developed from its original brief outline format, which relied heavily on outside readings, to a more convenient and educationally useful self-contained text. The Academy updates and revises the course annually, with the goals of integrating the basic science and clinical practice of ophthalmology and of keeping ophthalmologists current with new developments in the various subspecialties.

The BCSC incorporates the effort and expertise of more than 90 ophthalmologists, organized into 13 Section faculties, working with Academy editorial staff. In addition, the course continues to benefit from many lasting contributions made by the faculties of previous editions. Members of the Academy Practicing Ophthalmologists Advisory Committee for Education, Committee on Aging, and Vision Rehabilitation Committee review every volume before major revisions. Members of the European Board of Ophthalmology, organized into Section faculties, also review each volume before major revisions, focusing primarily on differences between American and European ophthalmology practice.

Organization of the Course

The Basic and Clinical Science Course comprises 13 volumes, incorporating fundamental ophthalmic knowledge, subspecialty areas, and special topics:

1. Update on General Medicine
2. Fundamentals and Principles of Ophthalmology
3. Clinical Optics
4. Ophthalmic Pathology and Intraocular Tumors
5. Neuro-Ophthalmology
6. Pediatric Ophthalmology and Strabismus
7. Orbit, Eyelids, and Lacrimal System
8. External Disease and Cornea
9. Intraocular Inflammation and Uveitis
10. Glaucoma
11. Lens and Cataract
12. Retina and Vitreous
13. Refractive Surgery

In addition, a comprehensive Master Index allows the reader to easily locate subjects throughout the entire series.

References

Readers who wish to explore specific topics in greater detail may consult the references cited within each chapter and listed in the Basic Texts section at the back of the book.
These references are intended to be selective rather than exhaustive, chosen by the BCSC faculty as being important, current, and readily available to residents and practitioners.

**Videos**

This edition of Section 9, *Intraocular Inflammation and Uveitis*, includes videos related to topics covered in the book. The videos were selected by members of the BCSC faculty and are available to readers of the print and electronic versions of Section 9. Mobile-device users can scan the QR code below (a QR-code reader must already be installed on the device) to access the video content.

**Study Questions and CME Credit**

Each volume of the BCSC is designed as an independent study activity for ophthalmology residents and practitioners. The learning objectives for this volume are given on page 1. The text, illustrations, and references provide the information necessary to achieve the objectives; the study questions allow readers to test their understanding of the material and their mastery of the objectives. Physicians who wish to claim CME credit for this educational activity may do so by following the instructions given at the end of the book.

**Conclusion**

The Basic and Clinical Science Course has expanded greatly over the years, with the addition of much new text, numerous illustrations, and video content. Recent editions have sought to place greater emphasis on clinical applicability while maintaining a solid foundation in basic science. As with any educational program, it reflects the experience of its authors. As its faculties change and medicine progresses, new viewpoints emerge on controversial subjects and techniques. Not all alternate approaches can be included in this series; as with any educational endeavor, the learner should seek additional sources, including Academy Preferred Practice Pattern Guidelines.

The BCSC faculty and staff continually strive to improve the educational usefulness of the course; you, the reader, can contribute to this ongoing process. If you have any suggestions or questions about the series, please do not hesitate to contact the faculty or the editors.

The authors, editors, and reviewers hope that your study of the BCSC will be of lasting value and that each Section will serve as a practical resource for quality patient care.
Objectives

Upon completion of BCSC Section 9, *Intraocular Inflammation and Uveitis*, the reader should be able to

- describe the immunologic and infectious mechanisms involved in the development of and complications from uveitis and related inflammatory conditions, including acquired immunodeficiency syndrome
- identify general and specific pathophysiologic processes in acute and chronic intraocular inflammation that affect the structure and function of the uvea, lens, intraocular spaces, retina, and other tissues
- differentiate infectious from noninfectious uveitic entities
- formulate appropriate differential diagnoses for ocular inflammatory disorders
- based on the differential diagnosis, choose examination techniques and appropriate ancillary studies to differentiate infectious from noninfectious causes
- describe the principles of medical and surgical management of infectious and noninfectious uveitis and related intraocular inflammation, including indications for, adverse effects of, and monitoring of immunosuppressive drugs
- describe the structural complications of uveitis, their prevention, and their treatment
- describe the main principles for differentiating masquerade syndromes from true uveitis and increasing clinical suspicion for these syndromes