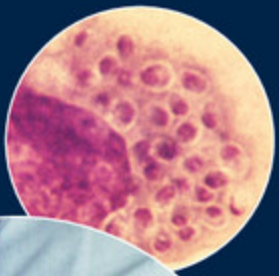
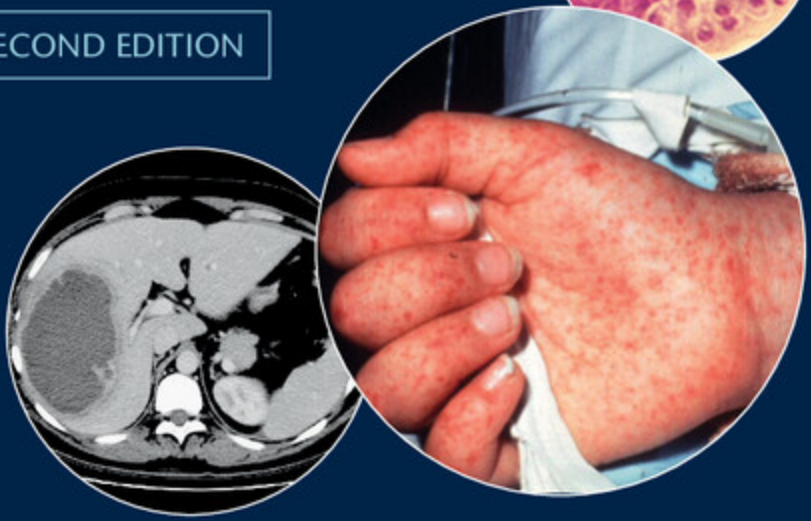
Clinical Infectious Disease

Edited by

DAVID SCHLOSSBERG

SECOND EDITION





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Edited by

David Schlossberg, MD, FACP

Professor of Medicine, Temple University School of Medicine,
Adjunct Professor of Medicine, University of Pennsylvania
School of Medicine, and Director, Tuberculosis Control Program,
Philadelphia Department of Public Health, Philadelphia, PA

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This book is dedicated to Dr. Jonas A. Shulman, respected mentor and valued friend.
In the Sayings of the Fathers, we are advised:

עשה לך רב, וקנה לך חבר
Provide yourself a teacher; take for yourself a friend.

I was very lucky to find both in the same person.

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† Deceased

Contributors

Fredrick M. Abrahamian, DO, FACEP, FIDSA
Clinical Professor of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California
Director of Education, Department of Emergency Medicine, Olive View-UCLA Medical Center, Sylmar, California

David W. K. Acheson, MD
Founder and CEO, The Acheson Group

Elisabeth E. Adderson, MD
Associate Member of St. Jude Faculty, Director of Pediatric Infectious Diseases Fellowship Program, Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee
Department of Pediatrics, University of Tennessee Health Science Center, Memphis, Tennessee

Adaora A. Adimora, MD, MPH
Professor of Medicine
University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

N. Franklin Adkinson, Jr., MD
Professor of Medicine and Program Director, Graduate Training Program in Clinical Investigation
Associate TP Director, Allergy-Immunology
Johns Hopkins Asthma & Allergy Center, Baltimore, Maryland

Payam Afshar, MS, MD
Gastroenterology Staff
Kaiser Permanente, San Diego/San Marcos, California

D'Jahna Akinyemi, MD
Instructor of Medicine, Division of Allergy and Clinical Immunology
Johns Hopkins Asthma and Allergy Center, Johns Hopkins University, Baltimore, Maryland

Timothy Aksamit, MD
Consultant, Pulmonary Disease and Critical Care Medicine
Mayo Clinic, Rochester, Minnesota

Daniel M. Albert, MD, MS, FACS
Founding Director of UW McPherson Eye Research Institute, F.A. Davis Professor in Department of Ophthalmology and Visual Sciences, Professor in Department of Pathology
University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

Zainab Alhamal
Postdoctoral Fellow
MD Anderson Cancer Center, Houston, Texas

Mir Akbar Ali, MD, MS
Infectious Diseases Fellow
Creighton University School of Medicine, Omaha, Nebraska

Donald Armstrong
Member and Chief of the Infectious Disease Service Emeritus
Memorial Sloan-Kettering Cancer Center, New York, New York

Andrew W. Artenstein, MD, FACP, FIDSA
Chair, Department of Medicine, Director, Center for Biodefense and Emerging Pathogens, Baystate Health, Springfield, Massachusetts
Tufts University School of Medicine Chair of Medicine at Baystate
Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts

Stephen Ash, MB, BS, FRCP
Consultant Physician
Ealing Hospital, London, UK

Aristides P. Assimacopoulos, MD, FIDSA
Physician
Metro Infectious Disease Consultants, LLC, Chicago, Illinois

Amir A. Azari, MD
Fellow in Opthalmic Pathology, Department of Ophthalmology and Visual Sciences
University of Wisconsin, Madison, Wisconsin

Alfred E. Bacon III, MD, FACP
Medical Director, Clinical Trials, Clinical Assistant Professor
Christiana Care Health System, Jefferson Medical College, Newark, Delaware

Rajinder P. S. Bajwa, MD
Infectious Disease Consultant
Niagara Falls Memorial Medical Center, Niagara Falls, New York

Johan S. Bakken, MD, PhD, FIDSA
Infectious Disease Associates, St. Luke's Hospital, Duluth, Minnesota

Robert S. Baltimore, MD
Professor of Pediatrics and Epidemiology
Yale School of Medicine, New Haven, Connecticut

David B. Banach, MD, MS, MPH
Assistant Professor of Medicine, Infectious Diseases
Yale University School of Medicine, New Haven, Connecticut

Amy S. Baranoski, MD, MSc
Assistant Professor, Department of Medicine, Division of Infectious Diseases and HIV Medicine
Drexel University College of Medicine, Philadelphia, Pennsylvania

Jodie A. Barkin, MD
Internal Medicine Resident
University of Miami, Miller School of Medicine/ Jackson Memorial Hospital, Miami Beach, Florida

Jamie S. Barkin, MD, MACG, MACP, AGAF, FASGE
Division of Gastroenterology
Mt. Sinai Medical Center, Miami Beach, Florida

John G. Bartlett, MD
Chief, Division of Infectious Diseases
Johns Hopkins School of Medicine, Baltimore, Maryland

Jules Baum, MD
Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts

Stephen G. Baum, MD
Professor, Department of Microbiology and Immunology
Albert Einstein College of Medicine, Bronx, New York

Daniel G. Bausch, MD, MPH&TM
Associate Professor, Department of Tropical Medicine
Tulane School of Public Health and Tropical Medicine, New Orleans, Louisiana

Gonzalo Bearman, MD, MPH, FACP
Associate Professor of Medicine, Epidemiology and Community Medicine, Associate Hospital Epidemiologist
Virginia Commonwealth University, Richmond, Virginia

Susan E. Beekmann, RN, MPH
Carver College of Medicine, University of Iowa, Iowa City, Iowa

Irmgard Behlau, MD
Instructor, Infectious Diseases
Mount Auburn Hospital, Harvard Medical School, Cambridge, Massacusetts

Nicholas J. Bennett, MA (Cantab), MBBChir, PhD
Assistant Professor of Pediatrics, Division of Pediatric Infectious Diseases and Immunology
Connecticut Children's Medical Center, Hartford, Connecticut

Joseph R. Berger, MD
Ruth L. Works Professor of Neurology
University of Kentucky Medical Center, Lexington, Kentucky

Karen Beydoun, MD
Infectious Disease Fellow
Virginia Commonwealth University, Richmond, Virginia

Kalyan Ram Bhamidimarri, MD, MPH
Assistant Professor of Medicine
University of Miami Miller School of Medicine, Miami, Florida

Lori A. Blauwet, MD, MA
Associate Professor of Medicine, Department of Medicine, Division of Cardiovascular Diseases and Internal Medicine
Mayo Clinic, Rochester, Minnesota

Ioannis A. Bliziotis, MD, MSc
Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece

Charles D. Bluestone, MD
Professor of Otolaryngology
University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Joseph A. Bocchini, Jr., MD
Professor and Chairman of Pediatrics, Pediatric Infectious Diseases Section, Department of Pediatrics
Director, Clinical Virology Laboratory, Louisiana State University, Shreveport, Louisiana

Andrea K. Boggild, MSc, MD, FRCPC
Assistant Professor, Department of Medicine, University of Toronto, Toronto, Canada
Clinical Director, Tropical Disease Unit, University Health Network, Toronto, Canada
Parasitology Lead, Public Health Ontario Laboratories, Public Health Ontario, Toronto, Canada

Charlotte E. Bolton, MD
Clinical Associate Professor in Respiratory Medicine, Honorary Consultant in Faculty of Medicine and Health Sciences
University of Nottingham, Nottingham, UK

Fouad Bouharb, MD
Infectious Disease Attending, New York Community Hospital, Brooklyn, New York; St. John's Episcopal Hospital, Far Rockaway, Queens, New York

Suzanne F. Bradley, MD
Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan
Division of Infectious Diseases, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan

Roy D. Brod, MD
Senior Partner, Lancaster Retina Specialists
Clinical Associate Professor of Ophthalmology, Pennsylvania State University School of Medicine, Hershey, Pennsylvania

Itzhak Brook, MD, MSc
Professor, Pediatrics
Georgetown University School of Medicine, Washington DC

Arthur E. Brown, MD, MACP, FIDSA, FSHEA
Chief and Medical Director, Employee Health & Wellness Services
Attending Physician, Infectious Disease Service, Memorial Sloan Kettering Cancer Center
Professor of Clinical Medicine, Weill Cornell Medical College, New York, New York

Steven C. Buckingham, MD
Associate Professor of Pediatrics
University of Tennessee Health Science Center, Memphis, Tennessee

Joseph Adrian L. Buensalido, MD
Division of Infectious Diseases
Wayne State University School of Medicine, Detroit, Michigan

Stefan Bughi, MD, FABD, MACM
Clinical Associate Professor of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California
Rancho Los Amigos National Rehabilitation Center, Downey, California

Michael Cappello, MD
Professor of Pediatrics, Microbial Pathogenesis and Public Health
Yale School of Medicine, New Haven, Connecticut

Jeanne Carey, MD
Chief of Infectious Diseases
Lutheran Medical Center, Brooklyn, New York

Christopher F. Carpenter, MD, FACP, FIDSA
Associate Professor of Medicine, Oakland University William Beaumont School of Medicine, Rochester, Michigan
Section Head, Infectious Diseases and International Medicine, Beaumont Hospital, Royal Oak, Michigan

Carlos Carrillo, MD, MSc
Instituto de Medicina Tropical Alexander von Humboldt Universidad Peruana Cayetano Heredia, Lima, Peru
Departamento de Enfermedades Transmisibles, Hospital Nacional Cayetano Heredia, Lima, Peru

Cheryll N. Cash, MD
Ochsner Health System, New Orleans, Louisiana

Eduardo Castro-Echeverry, MD
Scott & White Hospital, Temple, Texas

Gulfem E. Celik, MD
Professor of Medicine
Ankara University School of Medicine, Ankara, Turkey

Tania F. Cestari, MD, PhD
Department of Dermatology, School of Medicine
University of Rio Grande do Sul, Hospital de Clinicas de Porto Alegre, Brazil

Anne-Marie Chaftari, MD
Assistant Professor, Department of Infectious Diseases, Division of Internal Medicine
MD Anderson Cancer Center, Houston, Texas

Suttirak Chaiwongkarjohn, MD
Cedars-Sinai Multicampus Program, VA Greater Los Angeles Health Care System, UCLA-Olive View, Los Angeles, California

Joshua J. Chalkley, MD
Department of Neurology
University of Kentucky Medical Center, Lexington, Kentucky

Antoinette Chateau, MD
Dermatologist, Head of Department
Pietermaritzburg, South Africa

Tempe K. Chen, MD
Assistant Clinical Professor of Pediatrics, School of Medicine
University of California Irvine, California

Suyin Chi, MD
Infectious Disease, Internal Medicine
Franciscan Medical Specialists, Valparaiso, Indiana

Vivian Chidi, MD
Fellow, Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine
Vanderbilt University, Nashville, Tennessee

Lisa M. Chirch, MD
University of Connecticut Health Center, Farmington, Connecticut

Olivier Chosidow, MD, PhD
Professor of Dermatology, Chairman, Department of Dermatology
AP-HP, Hôpital Henri-Mondor, UPEC Université Paris-Est Créteil, Val de Marne, INSERM, Créteil, France

Iqra Choudary, MD
Internal Medicine Resident
Rochester General Hospital, Rochester, New York

Mashiul H. Chowdhury, MD
Chief of Infectious Diseases
Cancer Treatment Centers of America at Eastern Regional Medical Center, Philadelphia, Pennsylvania

Vivian H. Chu, MD
Duke University Medical Center, Durham, North Carolina

L. W. Preston Church, MD
Associate Professor, Division of Infectious Disease,
Medical University of South Carolina, Charleston, South Carolina
Chief of Hospital Epidemiology, Chief of Infectious Diseases, Ralph H. Johnson VA Medical Center, Charleston, South Carolina

Ross M. Clark, MD
Resident Physician, Department of Surgery
University of New Mexico HSC, Albuquerque, New Mexico

Clay J. Cockerell, MD
Clinical Professor, Department of Dermatology
University of Texas Southwestern Medical Center, Dallas, Texas

Carlo Contoreggi, MD
Diagnostic Radiology
Johns Hopkins Bayview Medical Center, Baltimore, Maryland

Roberto Baun Corales, DO, AAHIVS
Senior Director, HIV Medicine and Clinical Research
Trillium Health, Rochester, New York

Kent Crossley, MD
Professor of Medicine
University of Minnesota Medical School and the Minneapolis VA Healthcare System, Minneapolis, Minnesota

Burke A. Cunha, MD, MACP
Chief, Infectious Disease Division, Winthrop-University Hospital, Mineola, New York
Professor of Medicine, State University of New York School of Medicine, Stony Brook, New York

Cheston B. Cunha, MD
Assistant Professor of Medicine, Infectious Disease Division
Brown University Alpert School of Medicine, Rhode Island Hospital and Miriam Hospital, Providence, Rhode Island

John J. Cush, MD
Director of Clinical Rheumatology, Baylor Research Institute, Dallas, Texas
Professor of Medicine and Rheumatology, Baylor University Medical Center, Dallas, Texas

Sally J. Cutler, PhD
Reader in Medical Microbiology, School of Health, Sport and Bioscience
University of East London, London, UK

John S. Czachor, MD, FACP, FIDSA, FSHEA
Chief of Infectious Diseases, Professor and Vice Chair of Internal Medicine
Wright State University Boonshoft School of Medicine, Dayton, Ohio

Titus L. Daniels, MD, MPH, MMHC
Vice Chair for Clinical Affairs, Department of Medicine
Vanderbilt University School of Medicine, Nashville, Tennessee

Kathryn H. Dao, MD, FACP, FACR
Associate Director of Clinical Rheumatology
Baylor Research Institute, Dallas, Texas

Carly R. Davis, MD
Fellow, Division of Pediatric Infectious Diseases
University of Utah, Salt Lake City, Utah

Scott F. Davies, MD
Chief of Medicine
Hennepin County Medical Center, Minneapolis, Minnesota

E. Patchen Dellinger, MD
Professor of Surgery
University of Washington, Seattle, Washington

Louise M. Dembry, MD, MS, MBA
Professor of Medicine, Infectious Diseases and Epidemiology
Yale University School of Medicine, New Haven, Connecticut

Stan Deresinski, MD
Clinical Professor, Division of Infectious Diseases, Department of Medicine
Stanford School of Medicine, Stanford, California

Lisa L. Dever, MD
Professor of Medicine
Rutgers New Jersey Medical School, Newark, New Jersey

Gordon Dickinson, MD
Professor of Medicine, University of Miami Miller School of Medicine, Miami, Florida
Chair, Infectious Disease Section, Miami VA Medical Center, Miami, Florida

Kevin D. Dieckhaus
University of Connecticut Health Center, Farmington, Connecticut

Mark J. DiNubile, MD
Merck Research Laboratories, North Wales, Pennsylvania

Ncoza C. Dlova, MBChB, FcDerm (SA)
KwaZulu-Natal University, Durban, South Africa

J. Stephen Dumler, MD
Professor, Departments of Pathology and Microbiology & Immunology
University of Maryland School of Medicine, Baltimore, Maryland

Herbert L. DuPont, MD, MACP
Director, Center for Infectious Diseases, Houston School of Public Health, University of Texas, Houston, Texas
Chief, Internal Medicine Service, St Luke's Hospital, Houston, Texas
Vice Chairman, Department of Medicine, Baylor College of Medicine, Houston, Texas

Marlene L. Durand, MD
Associate Professor, Harvard Medical School
Director, Infectious Disease Service, Massachusetts Eye and Ear Infirmary
Physician, Massachusetts General Hospital, Boston, Massachusetts

Asim K. Dutt, MD
Chief, Medical Service (retired), Alvin C. York Veterans Administration Medical Center, Murfreesboro, Tennessee
Professor and Vice Chairman (retired),

Department of Medicine, Melharry Medical College, Nashville, Tennessee

Rima I. El-Herte, MD
Division of Infectious Diseases, Department of Internal Medicine
University of Iowa Carver College of Medicine, Iowa City, Iowa

N. Cary Engleberg, MD, DTM&H
Professor of Internal Medicine and Microbiology & Immunology
University of Michigan Medical School, Ann Arbor, Michigan

Lawrence J. Eron, MD, FACP, FIDSA
Associate Professor of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii
Consultant in Infectious Diseases, Kaiser Moanalua Medical Center, Honolulu, Hawaii

Janine Evans, MD
Associate Professor of Medicine, Section of Rheumatology, Department of Internal Medicine
Yale University School of Medicine, New Haven, Connecticut

Jessica K. Fairley, MD
Assistant Professor of Medicine
Emory University School of Medicine, Atlanta, Georgia

Matthew E. Falagas, MD, MSc, DSc
Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece
Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts

Sebastian Faro, MS, PhD, MD, FACOG
John T. Armstrong Professor and Vice Chairman, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Texas Health Science Center, Houston, Texas
Chief of Obstetrics and Gynecology, Lyndon Banes Johnson Hospital, Houston, Texas

Thomas Fekete, MD
Section Chief, Infectious Diseases
Professor, Department of Medicine
Associate Professor, Department of Microbiology and Immunology
Executive Vice Chair for Clinical Affairs, Department of Medicine
Temple University School of Medicine, Philadelphia, Pennsylvania

Thomas M. File Jr., MD, MSc
Chair, Infectious Disease Division, Summa Health System, Akron, Ohio
Professor of Internal Medicine, Infectious Disease Division, Northeast Ohio Medical University, Rootstown, Ohio

Sydney M. Finegold, MD
Staff Physician, Infectious Diseases Section, VA Medical Center, Los Angeles, California
Emeritus Professor, Department of Medicine
Emeritus Professor, Department of Microbiology, Immunology and Molecular Genetics
UCLA School of Medicine, Los Angeles, California

Mark Flasar, MD, MS
Assistant Professor of Medicine, Division of Gastroenterology and Hepatology
University of Maryland School of Medicine, Baltimore, Maryland

Thomas A. Fleisher, MD
Chief, Department of Laboratory Medicine
Chief, Immunology Service
National Institutes of Health, Bethesda, Maryland

Harry W. Flynn Jr., MD
Professor of Ophthalmology, The J. Donald M. Gass Distinguished Chair of Ophthalmology, University of Miami Miller School of Medicine, Miami, Florida
Bascom Palmer Eye Institute, Miami, Florida

Patricia M. Flynn, MD
Department of Infectious Diseases
St. Jude Children's Research Hospital, Memphis, Tennessee

Derek Forster, MD
Assistant Professor of Medicine, Division of Infectious Diseases
University of Kentucky, Lexington, Kentucky

Michelle E. Freshman, MPH, MSN, APRN, FNP-BC
Nurse Practitioner, Clinical Coordinator, Department of Medicine
Newton-Wellesley Hospital, Newton, Massachusetts

Gerald Friedland, MD
Professor of Medicine and Epidemiology
Yale School of Medicine, New Haven, Connecticut

Harvey M. Friedman, MD
Professor of Medicine and Infectious Diseases, Director of Botswana-UPenn Partnership
Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Lawrence S. Friedman, MD
Professor of Medicine, Harvard Medical School, Boston, Massachusetts
Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts
The Anton R. Fried, MD, Chair, Department of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts
Assistant Chief of Medicine, Massachusetts General Hospital, Boston, Massachusetts

Patrick G. Gallagher, MD
Professor of Pediatrics, Pathology and Genetics
Yale University School of Medicine, New Haven, Connecticut

Ritu Garg, MBBS, MD
Assistant Professor
Government Medical College and Hospital, Chandigarh, India

Gloria von Geldern, MD
Fellow in Neuroimmunology and Neurological Infections
NINDS, NIH, Bethesda, Maryland

Jomy George, PharmD
Clinical Pharmacist, Infectious Diseases
Cooper Medical School of Rowan University, Camden, New Jersey

Nicholas Gilpin, DO
Section Head, Infectious Disease
William Beaumont Hospital, Grosse Pointe, Michigan

Shelley A. Gilroy, MD, FACP
Associate Professor of Medicine, Specialist in Infectious Diseases and HIV Medicine
Albany Medical College, Albany, New York

Aaron E. Glatt, MD, FACP, FIDSA, FSHEA
Executive Vice President/Chief Administrative Officer
Professor of Clinical Medicine
Mercy Medical Center, Rockville Center, New York

Richard A. Gleckman, MD (deceased)
Formerly Clinical Professor of Medicine
Mount Sinai Hospital, New York, New York

Marshall J. Glesby, MD, PhD
Professor of Medicine and Public Health
Weill Cornell Medical College, New York, New York

Roderick Go, MD
Department of Internal Medicine
SUNY School of Medicine at Stony Brook, Stony Brook, New York

Matthew Bidwell Goetz, MD
Professor of Clinical Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California
Chief, Infectious Diseases, VA Greater Los Angeles Healthcare System, Los Angeles, California

Mitchell Goldman, MD
Professor of Medicine, Division of Infectious Diseases
Indiana University School of Medical School, Indianapolis, Indiana

Ellie J. C. Goldstein, MD, FIDSA
Clinical Professor of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California
Director, R M Alden Research Laboratory, Santa Monica, California

Eduardo Gotuzzo, MD
Director, Instituto de Medicina Tropical 'Alexander von Humboldt'
Universidad Peruana Cayetano Heredia

Christopher J. Graber, MD, MPH
Associate Clinical Professor of Medicine
VA Greater Los Angeles Healthcare System, David Geffen School of Medicine at UCLA, Los Angeles, California

Jeremy D. Gradon, MD
Associate Professor of Medicine
The Johns Hopkins University School of Medicine, Baltimore, Maryland

David Y. Graham, MD
Departments of Medicine, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas
Department of Bacteriology II, National Institute of Infectious Diseases, Tokyo, Japan

Jennifer Rubin Grandis, MD, FACS
Vice Chair for Research, Professor of Otolaryngology and Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
Program Leader, Head and Neck Cancer Program, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania

Jane M. Grant-Kels, MD
University of Connecticut Health Center, Farmington, Connecticut

Ruth M. Greenblatt, MD
Professor of Clinical Pharmacy, Medicine, Epidemiology and Biostatistics
University of California, San Francisco, California

Ronald A. Greenfield, MD (deceased)
Professor, Department of Medicine, Infectious Diseases
University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

David W. Gregory, MD
Associate Professor of Medicine, Emeritus, Division of Infectious Diseases
Vanderbilt University School of Medicine, Nashville, Tennessee

David E. Griffith, MD
Professor of Medicine
University of Texas Health Center, Tyler, Texas

Varsha Gupta, MBBS, MD, DNB
Professor
Government Medical College and Hospital, Chandigarh, India

Lisa Haglund, MD
Associate Professor of Medicine, Division of Infectious Disease
University of Cincinnati College of Medicine, Cincinnati, Ohio

Keith W. Hamilton, MD
Department of Infectious Diseases
Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

Margaret R. Hammerschlag, MD
Professor of Pediatrics and Medicine, Director of Division of Pediatric Infectious Diseases
SUNY Downstate Medical Center, Brooklyn, New York

W. Lee Hand, MD, FIDSA
Retired: Professor of Internal Medicine (With Tenure), Texas Tech University Health Sciences Center, El Paso, Texas
Infectious Diseases Consultant, Texas Department of Aging and Disability Services, El Paso, Texas

Shahbaz Hasan, MBBS
Staff Physician, Infectious Diseases
THR-Presbyterian Hospital, Dallas, Texas

Rodrigo Hasbun, MD, MPH
Associate Professor in Infectious Diseases, Department of Internal Medicine
University of Texas Medical School, Houston, Texas

Bridget Hathaway, MD
Assistant Professor, Department of Otolaryngology
University of Pittsburgh Medical Center, Monroeville, Pennsylvania

Arash Heidari, MD
Assistant Clinical Professor of Medicine, David Geffen School of Medicine at UCLA
Associate Program Director, Kern Medical Center, Los Angeles, California

David K. Henderson, MD
Deputy Director for Clinical Care, Associate Director for Hospital Epidemiology and Quality Improvement
National Institutes of Health, Bethesda, Maryland

Ramin Sedaghat Herati, MD
Division of Infectious Disease
University of Pennsylvania, Philadelphia, Pennsylvania

H. Franklin Herlong, MD
Professor, Department of Gastroenterology, Hepatology and Nutrition, Division of Internal Medicine
University of Texas MD Anderson Cancer Center, Houston, Texas

Scott K. Heysell, MD, MPH
Assistant Professor, Division of Infectious Diseases and International Health, Department of Medicine
University of Virginia Health System, Charlottesville, Virginia

Mark Hobbs, MBChB
Clinical Medical Education Fellow
University of Auckland, Auckland, New Zealand

Lisa S. Hodges, MD
Assistant Professor of Pediatrics and Medicine
Louisiana State University, Shreveport, Louisiana

Paul D. Holtom, MD
Professor of Medicine and Orthopaedics
Keck School of Medicine, University of Southern California, Los Angeles, California

Thomas R. Howdieshell, MD, FACS, FCCP
Professor of Surgery, Trauma/Surgical Critical Care, Department of Surgery
University of New Mexico HSC, Albuquerque, New Mexico

Robert Huang, MD, DTM&H
Division of Infectious Diseases
Southern California Permanente Medical Group, San Diego, California

Nguyen Thanh Hung, MD, PhD
Vice Director
Children's Hospital 1, Ho Chi Minh City, Vietnam

Christopher D. Huston, MD
Associate Professor, Departments of Medicine, Microbiology and Molecular Genetics
University of Vermont College of Medicine, Burlington, Vermont

Michelle J. Iandiorio, MD
Associate Professor, Department of Internal Medicine
University of New Mexico, Albuquerque, New Mexico

David N. Irani, MD
Associate Professor of Neurology
University of Michigan Medical School, Ann Arbor, Michigan

Raúl E. Istúriz, MD, FACP
Global Lead, Adult Medicines Development Group & Scientific Affairs, Pfizer, Inc.

Jeffrey M. Jacobson, MD
Professor of Medicine, Microbiology and Immunology
Chief, Division of Infectious Diseases and HIV Medicine
Drexel University College of Medicine, Philadelphia, Pennsylvania

William R. Jarvis, MD
President
Jason and Jarvis Associates, LLC, Hilton Head Island, South Carolina

Selma M. B. Jeronimo, MD, PhD
Professor of Biochemistry, Director of Institute of Tropical Medicine
Universidade Federal do Rio Grande do Norte, Natal, Brazil

Caroline C. Johnson, MD
Philadelphia Department of Public Health, Philadelphia, Pennsylvania

Jonas T. Johnson, MD
Professor and Chairman, Department of Otolaryngology
The Dr Eugene N. Meyers Professor and Chairman of Otolaryngology
Professor, Department of Oral and Maxillofacial Surgery, School of Dental Medicine
University of Pittsburgh, Pittsburgh, Pennsylvania

Richard T. Johnson, MD
Distinguished Service Professor of Neurology, Microbiology and Neuroscience
The Johns Hopkins University School of Medicine and Bloomberg School of Public Health, Baltimore, Maryland

Royce H. Johnson, MD, FACP
Professor of Medicine, David Geffen School of Medicine at UCLA
Chief, Infectious Disease, Kern Medical Center, Los Angeles, California

Ronald N. Jones, MD
Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts
President, JMI Laboratories, North Liberty, Iowa

Elaine C. Jong, MD, FIDSA
Department of Medicine
University of Washington School of Medicine, Seattle, Washington

Mary Jordan, MD, CCRP
MD Cancer Center Houston, Texas

Jonathan J. Juliano, MD
Clinical Assistant Professor of Medicine, School of Medicine
University of North Carolina, Chapel Hill, North Carolina

Thomas N. Kakuda, PharmD
Scientific Director, Clinical Pharmacology (Quantitative Sciences), Infectious Diseases and Vaccines
Janssen Pharmaceuticals, Titusville, New Jersey

Lili G. Kaplan, MD
Ophthalmologist and Retina Specialist
Retina Associates of Cleveland, Beachwood, Ohio

Ravi Karra, MD, MHS
Medical Instructor, Division of Cardiology
Duke University Medical Center, Durham, North Carolina

Keith S. Kaye, MD
Professor of Medicine
Wayne State University and Detroit Medical Center, Detroit, Michigan

Paul Kelly, MA, MD, FRCP
Professor of Tropical Gastroenterology
Barts and the London School of Medicine, Queen Mary University of London, Blizzard Institute, London, UK

Louis E. Kennedy, REHS, BS
Clinical Research Assistant
Ealing Hospital NHS Trust, Southall, UK

Jay S. Keystone, MD, MSc (CTM), FRCPC
Tropical Disease Unit, Division of Infectious Disease, Toronto General Hospital, UHN, Toronto, Canada
Professor of Medicine, University of Toronto, Toronto, Canada

Stephen A. Klotz, MD
Professor of Medicine, Division Chief, Infectious Diseases
University of Arizona, Tucson, Arizona

Lisa M. Kodadek, MD
Resident, Department of Surgery
Johns Hopkins University School of Medicine

Evelyn K. Koestenblatt, MS
Department of Ophthalmology
Montefiore Medical Center, Bronx, New York

James R. Korndorffer Jr, MD, MHPE, FACS
Professor, Department of Surgery
Tulane University School of Medicine, New Orleans, Louisiana

Peter J. Krause, MD
Senior Research Scientist
Yale School of Public Health, Yale School of Medicine

Ilona Kronig
Division of Infectious Diseases, Department of Specialties of Internal Medicine
Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Amol D. Kulkarni
University of Wisconsin Department of Ophthalmology and Visual Sciences, Madison, Wisconsin

David T. Kuhar
Adjunct Assistant Professor, Infectious Diseases
Emory University School of Medicine, Atlanta, Georgia

Sampath Kumar, MD
Infectious Diseases Attending
Metro Infectious Diseases, Chicago, Illinois
University of Illinois, Chicago, Illinois

Alvaro Lapitz, MD
Assistant Professor of Clinical Medicine, Division of Internal Medicine and Geriatrics
Indiana University School of Medical School, Indianapolis, Indiana

Chuen-Yen Lau, MD, MS, MPH
National Institutes of Health, Bethesda, Maryland

William J. Ledger, MD
The Given Foundation Professor Emeritus of Obstetrics and Gynecology
Weill Cornell Medical College, New York, New York

Thomas Lee

Matthew E. Levison, MD
Adjunct Professor of Medicine, Professor of Public Health
Drexel University, Bryn Mawr, Pennsylvania

Stuart M. Levitz, MD
Professor, Department of Medicine
University of Massachusetts Medical School, Worcester, Massachusetts

Daniel Lew, MD
Division of Infectious Diseases, Department of Specialties of Internal Medicine
Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Neil S. Lipman, VMD
Director, Center of Comparative Medicine and Pathology
Professor of Veterinary Medicine in Pathology and Laboratory Medicine
Memorial Sloan-Kettering Cancer Center and the Weill Medical College of Cornell University, New York, New York

Pamela A. Lipsett, MD, MHPE
Warfield M. Firor Endowed Professorship in Surgery, Professor of Surgery, Anesthesiology and Critical Care Medicine
Johns Hopkins University School of Medicine, Baltimore, Maryland

Ann-Marie Lobo, MD
Assistant Professor of Ophthalmology, Ocular Immunology and Uveitis Specialist
Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts

Sarah S. Long, MD
Professor of Pediatrics, Drexel University College of Medicine, Philadelphia, Pennsylvania
Chief, Section of Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Bennett Lorber, MD, MACP
Thomas M. Durant Professor of Medicine, Professor of Microbiology and Immunology
Temple University School of Medicine, Philadelphia, Pennsylvania

Alice Lorch, MD
Resident in Ophthalmology
Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts

Benjamin J. Luft, MD
Professor, Department of Internal Medicine
Stony Brook University Hospital, Stony Brook, New York

Larry I. Lutwick, MD, FACP
Professor, Medicine and Biomedical Sciences
Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, Michigan

John Maa, MD
Department of Surgery
University of California, San Francisco, California

Rodger D. MacArthur, MD
Director and Principal Investigator
Newland Immunology Center of Excellence, Southfield, Michigan

Karl Madaras-Kelly, PharmD, MPH
Professor, Department of Pharmacy Practice and Administrative Sciences
Idaho State University College of Pharmacy, Meridian, Idaho

Joanne T. Maffei, MD
Associate Professor
Louisiana State University Health Sciences Center, New Orleans, Louisiana

Rafael Gerardo Magaña, MD
NYC Plastic Surgery, New York, New York

James H. Maguire, MD, MPH
Professor of Medicine, Harvard Medical School, Boston, Massachusetts
Division of Infectious Disease, Brigham and Women's Hospital, Boston, Massachusetts

Francis S. Mah, MD
Ophthalmologist
Scripps Health, San Diego, California

Anita Mahadevan, MD
Associate Professor, Neuropathology
National Institute of Mental Health & Neurosciences, Bangalore, India

Mark A. Malangoni, MD
Associate Executive Director,
American Board of Surgery, Philadelphia, Pennsylvania

Choukri Ben Mamoun, PhD
Associate Professor of Medicine
Yale School of Medicine, New Haven, Connecticut

Suzaan Marais, MBChB, FC NeuroI(SA), PhD
Senior Research Officer, Clinical Infectious Diseases Research Initiative, Institute of Infectious Disease and Molecular Medicine (IIDMM), University of Cape Town, Cape Town, South Africa
Department of Medicine, University of Cape Town, Cape Town, South Africa

Peter Mariuz, MD
Professor of Medicine
University of Rochester, Strong Memorial Hospital, Rochester, New York

Thomas J. Marrie MD, FRCPC
Dean, Faculty of Medicine
Dalhousie University, Clinical Research Centre, Halifax, Canada

Paul Martin, MD, FRCP, FRCPI
Professor of Medicine
Chief, Division of Hepatology
University of Miami Miller School of Medicine, Miami, Florida

Richard A. Martinello, MD
Associate Professor of Internal Medicine and Pediatrics, Yale School of Medicine, New Haven, Connecticut
Office of Public Health, Department of Veterans Affairs, Washington DC

Amy J. Mathers, MD
Assistant Professor, Division of Infectious Diseases and International Health
University of Virginia Health System, Charlottesville, Virginia

J. Anthony Mebane, MD
Division of Infectious Diseases
VA Medical Center, Boise, Idaho

Jay B. Mehta, MD, FCCP
Professor of Medicine, Chief of Division of Preventive Medicine and Epidemiology
East Tennessee State University, James H. Quillen College of Medicine, Johnson City, Tennessee

Jeffery L. Meier, MD
Associate Professor, Internal Medicine
University of Iowa, Iowa City, Iowa

Graeme Meintjes, MBChB, FRCP(Glasg), FCP(SA), DipHIVMan(SA), PhD, MPH
Associate Professor, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa

Gregory J. Mertz, MD
Professor of Internal Medicine
University of New Mexico, Albuquerque, New Mexico

Burt R. Meyers, MD, FACP
Adjunct Professor of Medicine
New York Medical College, Valhalla, New York

Amanda M. Michael, DO
Fellow of Infectious Diseases and HIV Medicine
Drexel University College of Medicine, Philadelphia, Pennsylvania

Christopher T. Miller, MD
Infectious Diseases Fellow, Division of Infectious Diseases, Department of Internal Medicine
Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania

Laurence F. Mirels, MD
Physician, Division of Infectious Disease
Santa Clara Valley Medical Center, Santa Clara, California

Amirkaveh Mojtahed, MD
Resident Physician, Internal Medicine
Board Certified Anatomic Pathologist
Scripps Green Hospital, La Jolla, California

Gentiane Monsel, MD
Consultant, Department of Internal Medicine, Centre Hospitalier intercommunal de Crèteil, Crèteil, France
Department of Dermatology, AP-HP, Hôpital Henri-Mondor, Crèteil, France

Thomas A. Moore, MD, FACP
Clinical Professor, Department of Medicine
University of Kansas School of Medicine, Wichita, Kansas

Douglas R. Morgan, MD, MPH
Associate Professor of Medicine
Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt Ingram Cancer Center (VICC)
Vanderbilt Institute for Global Health (VIGH)
Vanderbilt University, Nashville, Tennessee

Anisa Mosam, MD
Dermatologist
University of KwaZulu-Natal, Durban, South Africa

Maurice A. Mufson, MD, MACP
Professor of Medicine Emeritus and Chairman Emeritus, Department of Medicine
Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia

Jorge Murillo, MD, FACP, FIDSA
Associate Professor of Medicine, Herbert Wertheim College of Medicine, Florida Intenational University, Miami, Florida
Consultant in Infectious Disease and Tropical Medicine, Baptist Health, Miami, Florida

Robert L. Murphy, MD
Director, Center for Global Health
Northwestern University Feinberg School of Medicine, Chicago, Illinois

Timothy F. Murphy, MD
Senior Associate Dean for Clinical and Translational Research
University at Buffalo School of Medicine and Biomedical Sciences, Buffalo, New York

Avindra Nath, MD
Chief, Section of Infections of the Nervous System
National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland

Kari A. Neemann, MD
Assistant Professor, Pediatric Infectious Disease
University of Nebraska Medical Center, Omaha, Nebraska

Ronald L. Nichols, MD, MS, FACS
William Henderson Professor of Surgery, Emeritus Professor of Microbiology and Immunology
Tulane University School of Medicine, New Orleans, Louisiana

Lindsay E. Nicolle, MD, FRCPC
Professor, Department of Internal Medicine and Medical Microbiology
University of Manitoba, Winnipeg, Canada

Nancy B. Norton, MD
Associate Professor, Department of Anatomy and Pathology
Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia

Judith A. O'Donnell, MD
Hospital Epidemiologist, Director of Department of Infectious Prevention and Control, Section Chief of Infectious Diseases Division, Associate Professor of Clinical Medicine
Penn Presbyterian Medical Center, Philadelphia, Pennsylvania

John C. Oeltjen, MD, PhD
Associate Professor of Surgery
University of Miami, Miami, Florida

Anthony Ogedegbe, MD
Division of Hospital Medicine
Weill Cornell Medical College, New York, New York

Todd D. Otteson, MD, MPH
Division Chief, Pediatric Otolaryngology, University Hospitals Case Medical Center, Cleveland, Ohio
Associate Professor, Otolaryngology and Pediatrics, Case Western Reserve University School of Medicine, Cleveland, Ohio

Michael N. Oxman, MD
Professor of Medicine and Pathology, University of California, San Diego, California
Staff Physician, Infectious Diseases, VA San Diego Healthcare System, San Diego, California

Robert L. Owen, MD
Department of Veteran Affairs Medical Center, San Francisco, California

George A. Pankey, MD
Director, Infectious Disease Research
Ochsner Clinic Foundation, New Orleans, Louisiana

George Pappas, MD
Institute for Continuing Medical Education of Ioannina, Greece

Peter G. Pappas, MD, FACP
Professor of Medicine, Department of Medicine and Division of Infectious Diseases, Director of Mycoses Study Group
University of Alabama at Birmingham, Birmingham, Alabama

Richard H. Parker, MD, FIDSA
Infectious Diseases and Internal Medicine, Supervisor of Primary Care and HIV Medicine
Andromeda Transcultural Health Center, Washington DC

Thomas F. Patterson, MD
Professor and Chief, Infectious Diseases
University of Texas Health Science Center at San Antonio and South Texas Veterans Health Care System, San Antonio, Texas

Andrew T. Pavia, MD
George and Esther Gross Presidential Professor
Chief, Division of Pediatric Infectious Diseases
University of Utah, Salt Lake City, Utah

Zbigniew S. Pawlowski, MD, DTMH Dr honoris causa Warsaw
Professor Emeritus, Clinic of Tropical and Parasitic Diseases
University of Medicine, Poznan, Poland

Richard D. Pearson, MD
Harrison Distinguished Professor of Medicine and Pathology, Departments of Medicine and Pathology, Division of Infectious Diseases and International Health
University of Virginia School of Medicine, Charlottesville, Virginia

Stephen I. Pelton, MD
Professor of Pediatrics and Epidemiology
Boston University Schools of Medicine and Public Health, Boston, Massachusetts

Rosalie Pepe, MD
Assistant Professor of Medicine
Cooper Medical School of Rowan University, Camden, New Jersey

Jeffrey M. Percak, MD
Assistant Professor of Clinical Medicine, Adult Infectious Diseases
Tulane University, New Orleans, Louisiana

Simone Pessato, MD
Department of Dermatology, School of Medicine
University of Rio Grande do Sul, Hospital de Clinicas de Porto Alegre, Brazil

K. Shad Pharaon, MD
Department of Surgery
PeaceHealth Southwest Medical Center, Vancouver, Washington

Phillippa Poole, BSc, MBChB, MD, FRACP
Professor, Department of Medicine
The University of Auckland, Auckland, New Zealand

William G. Powderly, MD
J. William Campbell Professor of Medicine
Director, Institute for Public Health
Co-Director, Division of Infectious Diseases
Washington University, St. Louis, Missouri

Laurel C. Preheim, MD
Professor of Medicine, Medical Microbiology, and Immunology, Division of Adult Infectious Diseases
Creighton University School of Medicine, Omaha, Nebraska

Anastácio de Queiroz Sousa, MD, PhD
Adjunct Professor of Medicine and Pathology
Director, São José Hospital for Infectious Diseases
Federal University of Ceará, Fortaleza, Ceará, Brazil

Thomas C. Quinn, MD
Professor of Medicine, Director of Johns Hopkins Center for Global Health
The Johns Hopkins University School of Medicine, Baltimore, Maryland

Issam Raad, MD, FACP, FIDSA, FSHEA
Chair, Department of Infectious Diseases, Infection Control and Employee Health, Division of Internal Medicine
University of Texas MD Anderson Cancer Center, Houston, Texas

Sanjay Ram, MD
Associate Professor, Department of Medicine
University of Massachusetts Medical School, Worcester, Massachusetts

Carlos R. Ramírez-Ramírez, MD
Department of Medicine
University of Puerto Rico School of Medicine, San Juan, Puerto Rico

Carlos H. Ramírez-Ronda, MD, MACP
Professor of Medicine
University of Puerto Rico School of Medicine, San Juan, Puerto Rico

Jean-Pierre Raufman, MD
Professor of Medicine and Head, Division of Gastroenterology and Hepatology
University of Maryland School of Medicine, Baltimore, Maryland

Raymund R. Razonable, MD
Professor of Medicine; Chair, Transplantation Virology and Infectious Diseases, Division of Infectious Diseases
Mayo Clinic, Rochester, Minnesota

Paulina A. Rebolledo, MD, MSc
Infectious Diseases Fellow, Division of Infectious Diseases, Department of Medicine
Emory University School of Medicine, Atlanta, Georgia

Sharon L. Reed, MD, MSCTM, D(ABMM)
Professor of Pathology and Medicine
University of California School of Medicine, San Diego, California

Robert V. Rege, MD
Laparoscopic Surgeon
University of Texas Southwestern Medical Center, Dallas, Texas

Michael F. Rein, MD
Professer Emeritus, Division of Infectious Diseases and International Health
University of Virginia Health System, Charlottesville, Virginia

Dalilah Restrepo, MD
St. Luke's – Roosevelt Hospital, New York, New York

Bruce S. Ribner, MD, MPH
Professor of Medicine, Emory University School of Medicine, Atlanta, Georgia
Epidemiologist, Emory University Hospital and The Emory Clinic, Atlanta, Georgia

Emiko Rimbara, PhD
Department of Bacteriology II
National Institute of Infectious Diseases, Tokyo, Japan

Allan Ronald, OC, MD, FRCPC, MACP
Distinguished Professor Emeritus
University of Manitoba, Winnipeg, Canada

Virginia R. Roth, MD, FRCPC
Associate Professor of Medicine, University of Ottawa
Director, Infectious Prevention and Control Program, The Ottawa Hospital, Ottawa, Canada

Nadine G. Rouphael, MD
Assistant Professor of Medicine, Division of Infectious Diseases
Emory University School of Medicine, Atlanta, Georgia

Thomas A. Russo, MD
Professor and Chief, Infectious Disease, Department of Medicine
University at Buffalo School of Medicine and Biomedical Sciences, Buffalo, New York
Staff Physician, Veterans Administration, Western New York Healthcare System

William A. Rutala, MS, MPH, PhD
Professor of Medicine, Director of Statewide Program for Infection Control and Epidemiology, Director of Hospital Epidemiology, Occupational Health and Safety Program
University of North Carolina School of Medicine, Chapel Hill, North Carolina

Eric Sachinwalla, MD
Clinical Instructor, Infectious Diseases
Temple University Hospital, Philadelphia, Pennsylvania

Amar Safdar, MD
Associate Professor of Medicine, Director Transplant Infectious Diseases
NYU Langone Medical Center, NYU School of Medicine, New York, New York

Wilmara Salgado-Pabón, MS, PhD
Post-Doctoral Fellow
University of Iowa, Carver College of Medicine, Iowa City, Iowa

Rafik Samuel, MD
Professor of Medicine
Temple University Hospital, Philadelphia, Pennsylvania

Nuria Sanchez Clemente, MBChB, MSc, DTMH, MRCPCH
Paediatric Infectious Diseases
St. Mary's Hospital, London, UK

Sarbjit S. Sandhu, MD
Infectious Disease Fellow
Robert Wood Johnson University Hospital, New Brunswick, New Jersey

Patrick M. Schlievert, PhD
Professor and Chair
University of Iowa, Iowa City, Iowa

Steven K. Schmitt, MD, FIDSA, FACP
Head, Section of Bone and Joint Infections
Associate Professor of Medicine, Department of Infectious Disease
Vice Chair for Professional Staff Affairs, Medicine Institute
Cleveland Clinic, Cleveland, Ohio

William A. Schwartzman, MD
Associate Clinical Professor of Medicine, UCLA School of Medicine, Los Angeles, California
Chief, Infectious Diseases, Sepulveda VA OPC, Sepulveda, California
Chair, Infection Control Committee
Attending in Infectious Diseases, VA Greater Los Angeles Healthcare System, Los Angeles, California

Pritha Sen, MD
Department of Medicine, Division of Infectious Disease
Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts

Arlene C. Seña, MD, MPH
Associate Professor of Medicine, Division of Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
Medical and Laboratory Director, Durham County Department of Public Health, Durham, North Carolina

John W. Sensakovic, MD, PhD
Infectious Disease
St. Michael's Medical Center, Newark, New Jersey

Susan K. Seo MD
Director, Antibiotic Management Program, Associate Clinical Member, Infectious Disease Service, Memorial Sloan-Kettering Cancer Center, New York, New York
Associate Professor of Clinical Medicine, Weill Medical College of Cornell University, New York, New York

Dennis J. Shale, MD
Clinical Professor, Institute of Molecular and Experimental Medicine
Cardiff University, Cardiff, UK

Susarla K. Shankar, MD
Emeritus Professor, Department of Neuropathology
National Institute of Mental Health and Neurosciences, Bangalore, India

Sylvia J. Shaw, MD
Assistant Professor of Clinical Medicine
Keck School of Medicine, University of Southern California, Los Angeles, California

Sheela Shenoi, MD, MPH
Assistant Professor of Medicine
Yale School of Medicine, New Haven, Connecticut

Kamaljit Singh MD, D(ABMM)
Associate Professor, Infectious Diseases
Rush University Medical Center, Chicago, Illinois

Upinder Singh, MD
Associate Professor of Medicine (Infectious Diseases and Geographic Medicine) and Microbiology and Immunology
Stanford School of Medicine, Stanford, California

Linda A. Slavoski, MD
Doctor of Infectious Disease Medicine and Internal Medicine
Wilkes Barre, Pennsylvania

James W. Smith, MD
Professor of Internal Medicine and Infectious Diseases
University of Texas Southwestern Medical School, Dallas, Texas

Leon G. Smith, MD
Chairman, Department of Medicine, St. Michael's Medical Center, Newark, New Jersey
Chairman, Department of Medicine, Seton Hall University School of Graduate Medical Education
Professor of Preventative Medicine, New Jersey Medical School, New Brunswick, New Jersey

Jessica N. Snowden, MD
Assistant Professor
University of Nebraska Medical Center, Omaha, Nebraska

Jack D. Sobel, MD
Division of Infectious Diseases
Wayne State University School of Medicine, Detroit, Michigan

Elizabeth Soda, MD
Infectious Diseases
Belmont, California

M. Rizwan Sohail, MD
Assistant Professor of Medicine, Divisions of Infectious Diseases and Cardiovascular Diseases, Department of Medicine
Mayo Clinic College of Medicine, Rochester, Minnesota

Joseph S. Solomkin, MD
Professor Emeritus, Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio
Director, Surgical Antimicrobial Stewardship Program, University of Cincinnati Hospital, Cincinnati, Ohio

Kathleen E. Squires, MD
Professor of Medicine, Division of Infectious Diseases, Department of Internal Medicine
Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania

Barbara W. Stechenberg, MD
Professor of Pediatrics, Tufts University School of Medicine, Springfield, Massachusetts
Associate Program Director, Pediatrics Residency Program, Baystate Medical Center, Springfield, Massachusetts

James M. Steckelberg, MD
Professor of Medicine, Division of Infectious Diseases, Department of Medicine
Mayo Clinic College of Medicine, Rochester, Minnesota

Roy T. Steigbigel, MD
Distinguished Service Professor, Medicine, Pathology, Pharmacology and Microbiology
Stony Brook University, Stony Brook, New York

James P. Steinberg, MD
Professor of Medicine, Division of Infectious Diseases
Emory University School of Medicine, Atlanta, Georgia

David S. Stephens, MD
Stephen W. Schwarzmann Distinguished Professor of Medicine, Director, Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia
Medical Research Service, Department of Veterans Affairs Medical Center (Atlanta), Decatur, Georgia

Dennis L. Stevens, MD, PhD
Professor of Medicine
University of Washington School of Medicine, Seattle, Washington
Chief, Infectious Disease, VAMC, Boise, Idaho

Kathryn N. Suh, MD, FRCPC
Associate Professor of Medicine, Division of Infectious Diseases
University of Ottawa, Ottawa, Canada

Domizio Suvà
Division of Orthopaedic and Trauma Surgery, Department of Surgery
Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Babafemi O. Taiwo, MBBS
Associate Professor of Medicine, Division of Infectious Diseases
Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Naasha J. Talati, MD
Division of Infectious Diseases, Department of Medicine
Emory University School of Medicine, Atlanta, Georgia

Giorgio Tarchini, MD
Associate Staff, Infectious Disease
Cleveland Clinic, Weston, Florida

Frank L. Tomaka, MD
Clinical Leader, STI Vaccines; Senior Director, Clinical Development
Janssen Pharmaceuticals, Titusville, New Jersey

Kenneth J. Tomecki, MD
Department of Dermatology
Cleveland Clinic, Cleveland, Ohio

Donato Torre, MD
Consultant in Infectious Diseases, Section of Infectious Diseases
General Hospital, Cittiglio (Varese), Italy

Marc Traeger, MD
Indian Health Service, White River, Arizona
Clinical Assistant Professor, University of Arizona College of Medicine, Tucson, Arizona

Edmund C. Tramont, MD, FACP
Director, Division of AIDS
National Institutes of Health, Bethesda, Maryland

Donald D. Trunkey, MD
Department of Surgery
Oregon Health & Science University, Portland, Oregon

Elmer Y. Tu, MD
Associate Professor of Clinical Ophthalmology, Department of Ophthalmology and Visual Science
University of Illinois Eye and Ear Infirmary, Chicago, Illinois

Allan R. Tunkel, MD, PhD, MACP
Professor of Medicine, Associate Dean for Medical Education
Warren Alpert Medical School of Brown University, Providence, Rhode Island

Ilker Uçkay, MD
Division of Infectious Diseases, Department of Specialties of Internal Medicine
Division of Orthopaedic and Trauma Surgery, Department of Surgery
Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Travis Vandergriff, MD
Assistant Professor, Department of Dermatology
University of Texas Southwestern Medical Center, Dallas, Texas

Pierre Vaudaux, PhD
Division of Infectious Diseases, Department of Specialties of Internal Medicine
Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Karen J. Vigil, MD
Assistant Professor, Division of Infectious Diseases
The University of Texas Health Science Center at Houston - Medical School, Houston, Texas

Alok Vij, MD
Chief Resident, Department of Dermatology
Cleveland Clinic Foundation, Cleveland, Ohio

Gian L. Vinelli, BA
Medical Student
New York Medical College, New York, New York

Duc J. Vugia, MD, MPH, FACP, FIDSA
Chief, Infectious Diseases Branch
California Department of Public Health, Richmond, California

Jatin M. Vyas, MD, PhD
Assistant Professor in Medicine, Department of Medicine, Division of Infectious Disease
Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts

Keyur S. Vyas, MD
Associate Professor of Medicine
University of Arkansas for Medical Sciences, Little Rock, Arkansas

Ken B. Waites, MD, FAAM
Professor of Pathology and Microbiology, Director of Diagnostic Mycoplasma Laboratory, University of Alabama at Birmingham, Birmingham, Alabama
Staff Pathologist and Microbiology Consultant, Birmingham Veterans Affairs Medical Center, Birmingham, Alabama

Richard R. Watkins, MD, MS, FACP
Associate Professor, Internal Medicine
Northeast Ohio Medical University, Rootstown, Ohio
Division of Infectious Diseases, Akron General Medical Center, Akron, Ohio

David J. Weber, MD, MPH
Professor of Medicine and Pediatrics, University of North Carolina School of Medicine, Chapel Hill, North Carolina
Professor of Epidemiology, Gillings School of Global Public Health, Chapel Hill, North Carolina

Jeffrey M. Weinberg, MD
Department of Dermatology
Columbia University College of Physicians and Surgeons, New York, New York

Debra L. Weiner, MD, PhD
Attending Physician, Emergency Medicine, Boston Children's Hospital, Boston, Massachusetts
Assistant Professor, Pediatrics, Harvard Medical School, Boston, Massachusetts

Richard J. Whitley, MD
Departments of Pediatrics, Medicine, Microbiology and Surgery
University of Alabama at Birmingham School of Medicine, Birmingham, Alabama

Nathan P. Wiederhold, PharmD
Associate Professor, Departments of Pathology and Medicine/Infectious Diseases; Director, Fungus Testing Laboratory
University of Texas Health Science Center, San Antonio, Texas

Mary Elizabeth Wilson, MD, FACP, FIDSA, FASTMH
Adjunct Professor, Global Health and Population
Harvard School of Public Health, Boston, Massachusetts
Visiting Professor of Epidemiology and Biostatistics, University of California, San Francisco, California

Brian Wispelwey, MD
Professor of Medicine, Infectious Diseases and International Health
University of Virginia School of Medicine, Charlottesville, Virginia

Patricia Wong, MD, MSCE
Lankenau Hospital/Main Line Gastroenterology Associates, Philadelphia, Pennsylvania
Adjunct Assistant Professor of Medicine, Johns Hopkins University, Baltimore, Maryland

Bian Wu, MD
Resident
UCSF School of Medicine, San Francisco, California

Henry M. Wu, MD, DTM&H
Assistant Professor of Medicine
Emory University School of Medicine, Atlanta, Georgia

Neal S. Young, MD
Chief of Hematology Branch, Director of Trans-NIH Center for Human Immunology, Autoimmunity and Inflammation
National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland

Roger W. Yurt, MD
Chief of Burns, Critical Care and Trauma
New York Presbyterian Hospital, New York, New York

John A. Zaia, MD
Chair and Professor of Virology, Professor of Pediatrics, Aaron D. Miller and Edith Miller Chair in Gene Therapy
City of Hope, Duarte, California

Tirdad T. Zangeneh, DO, MA
Assistant Professor of Clinical Medicine
University of Arizona, Tucson, Arizona

Jonathan M. Zenilman, MD
Johns Hopkins Bayview Medical Center, Baltimore, Maryland

Alimuddin Zumla MD, PhD, FRCP, FRCPath, FSBiol
Professor of Infectious Diseases and International Health, Department of Infection, Division of Infection and Immunity
University College London and University College London Hospitals NHS Foundation Trust, London, UK

Preface

The gratifying response to *Clinical Infectious Disease* has prompted this second edition. As with the first edition, our goal remains a complete and user-friendly guide to the diagnosis and treatment of infectious diseases.

The book is divided into 10 sections. First, Clinical syndromes, both general and by organ system, provides a traditional anatomic orientation, although within this section additional chapters are devoted to particularly challenging entities that are often difficult to research, such as infectious thyroiditis, deep neck infection, periocular infection, lymphadenopathy, mediastinitis, pacemaker infection, sexually transmitted enteric infection, bursitis, polyarthritis, psoas abscess, splenic abscess, spinal epidural abscess, cerebrospinal shunt infection, myelitis and peripheral neuropathy, and prion disease.

The second section, The susceptible host, includes individual chapters on infection in various immunocompromised states, including diabetes, transplantation, neutropenia, dialysis, pregnancy, and asplenia. Subsequent entire sections are devoted to HIV, nosocomial infection, surgery and trauma, prophylaxis, travel and recreation, and bioterrorism.

Organism-specific chapters follow, with individual chapters for specific bacteria, viruses, fungi, parasites, and other pathogens. Finally, a major section on antimicrobial therapy includes chapters on principles of antibiotic therapy, antifungal therapy, antiviral therapy, and hypersensitivity to antibiotics. A final chapter lists antimicrobial agents in tabular form, providing a convenient reference for dosage, side effects, cost, pregnancy class, effect of food, and dose adjustment for renal dysfunction. All chapters include suggested readings.

For this new edition every chapter has been updated, and four new chapters have been added: Tungiasis and bedbugs (in Skin and lymph nodes), Biologics (in Compromised host), Antibacterial agents (in Antimicrobial therapy), and Probiotics (in Antimicrobial therapy).

We hope this text continues to provide a practical, clinically oriented, and convenient resource for the diagnosis and treatment of infectious disease.

I am enormously grateful for the vision, talent, and dedication of the staff at Cambridge University Press, particularly Richard Marley, Jane Seakins, Rob Sykes, Ross Higman, Sarah Payne, Anne Kenton, and Ed Robinson.

PART I

Clinical syndromes: general

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1. Fever of unknown origin (FUO)

Cheston B. Cunha and Burke A. Cunha

OVERVIEW

Fever of unknown origin (FUO) describes prolonged fevers >101°F lasting for 3 or more weeks that remain undiagnosed after a focused FUO outpatient/inpatient workup. The causes of FUO include infectious and noninfectious disorders. A variety of infectious, malignant, rheumatic/inflammatory disorders may be associated with prolonged fevers, but relatively few persist undiagnosed for sufficient duration to be classified as FUOs.

CAUSES OF FUO

The distribution of disorders causing FUOs is dependent on age, demographics, family history, zoonotic exposures, and previous/current conditions, e.g., malignancies, rheumatic/inflammatory disorders, cirrhosis. Each category of FUO may also be approached by subgroups, e.g., elderly, immunosuppressed, transplants, febrile neutropenia, zoonoses, HIV, nosocomial, returning travelers. The differential diagnosis in each subgroup reflects the relative distribution of disorders within the subgroup, and the geographic distribution of endemic diseases. The relative distribution of causes of FUO has changed over time but, with few exceptions, the disorders responsible for FUOs have remained relatively constant over time (Table 1.1).

DIAGNOSTIC APPROACH TO FUOs

In patients presenting with prolonged fevers, the clinician should first determine if the patient indeed has an FUO. Because there are many causes of FUO, there is no "cookbook or algorithmic approach" for diagnosing FUOs. In medicine, the history provides important initial diagnostic clues and a general sense of the likely FUO category, e.g., weight loss with early anorexia suggests malignancy, arthralgias/myalgias suggest a rheumatic/inflammatory disorder, and fever with chills suggests an infectious etiology.

After an FUO category is suggested by historical clues, the physical examination should focus on history relevant findings in the differential diagnosis. The physical examination should not be comprehensive but more importantly should be carefully focused on demonstrating the presence or absence of key findings in the differential diagnosis, e.g., a complete neurologic exam is unhelpful in an FUO patient with probable adult Still's disease. On physical examination particular attention should be given to eye findings, liver, spleen, lymph nodes, joint findings, and skin lesions (Table 1.2). At this point, based upon the presence or absence of history and physical examination clues, the initial FUO diagnostic workup, e.g., nonspecific laboratory tests, should also be focused on ruling in or ruling out the most likely diagnostic possibilities. Since the patient has already been seen by one or more physicians prior to presentation, routine laboratory tests have already been done, e.g., CBC, liver function test (LFTs), urinalysis (UA), but these tests should be carefully re-reviewed for diagnostic clues, e.g., relative lymphopenia.

The "shot gun" approach to laboratory testing for FUOs should be avoided. Since the number of FUO causes are legion, it is not clinically or cost-effective to test for every cause of FUO. When asked why he robbed banks, Willy Sutton replied, "Because that's where the money is!" Similarly, a focused FUO workup should be directed at the most likely, not all, diagnostic possibilities, as suggested by the history, physical, and nonspecific laboratory tests. Nondirected testing often provides misleading information. It makes no sense to obtain thyroid function tests (TFTs) in FUOs with joint symptoms; neither should TFTs be obtained in FUOs likely due to adult Still's disease, giant cell arteritis/temporal arteritis (GCA/TA), or periarteritis nodosa (PAN).

Blood cultures should not be obtained in all cases of FUO. If the FUO differential diagnosis

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Table 1.1 Classic causes of fever of unknown origin (FUO)

Type of disorder	Common	Uncommon	Rare
Malignancy/neoplastic disorders	Lymphoma[a] Hypernephromas/renal cell carcinoma (RCC)	Pre-leukemias (AML)[a] Myeloproliferative disorders (MPDs)	Atrial myxomas Multiple myeloma Colon carcinoma Pancreatic carcinoma CNS metastases Hepatomas Liver metastases
Infectious diseases	Miliary TB SBE Brucellosis[a] Q fever[a]	Intra-abdominal/pelvic abscess Intra/perinephric abscess Typhoid fever/enteric fevers[a] Toxoplasmosis Cat scratch disease (CSD)[a] EBV CMV HIV Extrapulmonary TB (renal TB, CNS TB)	Periapical dental abscess Chronic sinusitis/mastoiditis Subacute vertebral osteomyelitis Aortoenteric fistula Relapsing fever[a] Rat-bite fever[a] Leptospirosis[a] Histoplasmosis Coccidiomycosis Visceral leishmaniasis (kala-azar) LGV Whipple's disease[a] Castleman's disease[a] (MCD) Malaria Babesiosis Ehrlichiosis
Rheumatologic/inflammatory disorders	Adult Still's disease[a] Giant cell arteritis (GCA)/temporal arteritis (TA)[a]	PAN/MPA[a] Late-onset rheumatoid arthritis (LORA)[a] SLE[a]	Takayasu's arteritis[a] Kikuchi's disease[a] Sarcoidosis (CNS) Felty's syndrome Gaucher's disease Polyarticular gout[a] Pseudogout[a] Schnitzler's syndrome[a] Behçet's disease[a] FAPA syndrome[a] (Marshall's syndrome)
Miscellaneous disorders	Drug fever[a] Alcoholic cirrhosis[a]	Subacute thyroiditis[a] Regional enteritis (Crohn's disease)[a]	Pulmonary emboli (small/multiple) Pseudolymphomas Kikuchi's disease[a] Rosai–Dorman disease[a] Erdheim–Chester disease (ECD)[a] Cyclic neutropenia[a] Familial periodic fever syndromes[a] • FMF • Hyper IgD syndrome[a] • TNF receptor-1-associated periodic syndrome (TRAPS) • Muckle–Wells syndrome Systemic mastocytosis Hypothalamic dysfunction Hypertriglyceridemia Factitious fever[a]

[a] Also cause of recurrent FUOs.

Disorders with FUO potential include any not easily diagnosed disorder with prolonged fevers, travel-related infections with prolonged fevers presenting in nonendemic areas, any relapsing/recurrent disorder with prolonged fevers, or any disorder with prolonged fevers with unusual clinical findings.

Abbreviations: CNS = central nervous system; TB = tuberculosis; SBE = subacute bacterial endocarditis; CMV = cytomegalovirus; HIV = human immunodeficiency virus; EBV = Epstein–Barr virus; LGV = lymphogranuloma venereum; PAN = periarteritis nodosa; MPA = microscopic polyangiitis; SLE = systemic lupus erythematosus; FMF = familial Mediterranean fever; MCD = multicentric Castleman's disease; FAPA = fever, aphthous ulcers, pharyngitis, adenitis; TNF = tumor necrosis factor; AML = acute myelogenous leukemia.

Adapted from: Cunha BA. Fever of unknown origin (FUO). In: Gorbach SL, Bartlett JB, Blacklow NR (Eds.) *Infectious Diseases in Medicine and Surgery*. (3rd edn.) Philadelphia: WB Saunders, 2004; pp. 1568–1577 and Cunha BA. Overview. In: Cunha BA (Ed.) *Fever of Unknown Origin*. New York: Informa Healthcare; 2007; pp. 1–16.

Table 1.2 History and physical examination clues to fever of unknown origin (FUO) categories

	Historical features		Clues from the history	Physical examination findings		Clues from the physical examination
Malignant/ neoplastic disorders	• PMH/FMH malignancy	→	Possibility of same disease likely	• Fever pattern:		
	• HA/mental confusion	→	CNS metastases, lymphomas, multiple myeloma, atrial myxoma (CNS emboli)	Relative bradycardia	→	CNS, malignancies, lymphomas
				Hectic/septic fevers (Pel-Ebstein)	→	Lymphomas
	• Weight loss (with early decreased appetite)	→	Any malignant/neoplastic disorder	• Cranial nerve palsies	→	CNS lymphomas, CNS neoplasms
	• Early satiety	→	Lymphomas, any malignant/neoplastic disorder causing splenomegaly	• Fundi: Roth spots	→	Lymphomas, atrial myxoma
				• Fundi: cytoid bodies (cotton wool spots)	→	Atrial myxoma
	• Pruritus (post hot shower/bath)	→	Lymphoma, MPDs	• Fundi: retinal hemorrhages	→	Pre-leukemia (AML)
	• Night sweats	→	Any malignant/neoplastic disorder	• Adenopathy	→	Lymphoma, Kikuchi's disease, Rosai–Dorfman disease
	• Abdominal discomfort/pain	→	Hypernephroma, hepatoma, liver metastases, colon carcinoma, pancreatic carcinoma	• Sternal tenderness	→	Pre-leukemia (AML), MPDs
				• Heart murmur	→	Marantic endocarditis, atrial myxoma
	• Testicular pain	→	Lymphoma	• Hepatomegaly	→	Hepatoma, hypernephroma, liver metastases
	• Bone pain	→	Multiple myeloma, any malignant/ neoplastic disorder with bone involvement	• Splenomegaly	→	Lymphomas, MPDs
				• Splinter hemorrhages	→	Atrial myxoma
				• Epididymitis	→	Lymphomas
Infectious diseases	• PMH/FMH of infections	→	Possibility of same disease high	• Fever pattern:		
	• HA/mental confusion	→	Brucellosis, CSD, ehrlichiosis, Q fever, malaria, leptospirosis, Whipple's disease, typhoid fever/enteric fevers, rat-bite fever, relapsing fever, CNS TB, HIV, LGV	Relative bradycardia	→	Typhoid fever/enteric fevers, leptospirosis, Q fever, malaria, babesiosis, ehrlichiosis
				Double quotidian fever	→	Visceral leishmaniasis (kala-azar)
				Camelback fever curve	→	Ehrlichiosis, leptospirosis, brucellosis, rat-bite fever (*S. minus*)
	• Recent/similar illness exposure	→	Possibility of same disease high		→	Miliary TB, typhoid fever/enteric fevers
	• Surgical/invasive procedures	→	Abscess, SBE	Morning temperature spikes		
	• Aortic aneurysm/ repair	→	Q fever, enteric fever	Relapsing fevers	→	Brucellosis, malaria, rat-bite fever (*S. moniliformis*)
	• STD history	→	LGV	• Abducens (CN VI) palsy	→	CNS TB
	• Recent travel	→	Typhoid/enteric fevers, leptospirosis, malaria, visceral leishmaniasis (kala-azar), brucellosis, Q fever	• Conjunctival suffusion	→	Trichinosis, relapsing fever, leptospirosis
				• Conjunctival hemorrhages	→	SBE
	• Insect exposure	→	Malaria, ehrlichiosis, babesiosis, visceral leishmaniasis (kala-azar), relapsing fever	• Chorioretinitis	→	Toxoplasmosis, TB, histoplasmosis
				• Choroid tubercles	→	Miliary TB
	• Pet/animal contact	→	Q fever, CSD, toxoplasmosis, rat-bite fever, relapsing fever, leptospirosis, brucellosis	• Roth spots	→	SBE
				• Palatal petechiae	→	EBV, CMV, toxoplasmosis
	• Unpasteurized milk/ cheese consumption	→	Q fever, brucellosis	• Tongue ulcer	→	Histoplasmosis
				• Adenopathy	→	CSD, EBV, CMV

	Historical features		Clues from the history	Physical examination findings		Clues from the physical examination
	• Undercooked meat consumption	→	Toxoplasmosis, trichinosis	• Heart murmur	→	SBE
				• Spinal tenderness	→	Subacute vertebral osteomyelitis, typhoid fever/enteric fever, skeletal TB, brucellosis
	• Blood transfusions	→	Malaria, babesiosis, ehrlichiosis, CMV, HIV	• Hepatomegaly	→	Q fever, typhoid fever/enteric fevers, brucellosis, visceral leishmaniasis (kala-azar), rat-bite fever, relapsing fever
	• Poor dentition	→	SBE, apical root abscess			
	• Sleep disturbances	→	Brucellosis, relapsing fever, leptospirosis	• Splenomegaly	→	Miliary TB, EBV, CMV, typhoid fever/enteric fevers, brucellosis, histoplasmosis, ehrlichiosis, malaria, Q fever, SBE, CSD Rat-bite fever, relapsing fever
	• Early satiety	→	EBV, CMV, Q fever, brucellosis, SBE, miliary TB			
	• Arthralgias	→	Rat-bite fever, LGV, Whipple's disease, brucellosis	• Splinter hemorrhages	→	SBE
				• Ostler's nodes/ Janeway lesions	→	SBE
	• Myalgias	→	Q fever, leptospirosis, relapsing fever, trichinosis	• Skin hyperpigmentation	→	Visceral leishmaniasis (kala-azar), Whipple's disease
	• Sinusitis	→	Chronic sinusitis			
	• Night sweats	→	Miliary TB, histoplasmosis	• Epididymitis	→	EBV, renal TB, brucellosis
	• Weight loss	→	Miliary TB, histoplasmosis			
	• Tongue pain	→	Histoplasmosis, relapsing fever			
	• Neck pain	→	Subacute vertebral osteomyelitis, chronic mastoiditis			
	• Tender finger tips	→	SBE			
	• Abdominal pain	→	Relapsing fever, leptospirosisv, typhoid fever/enteric fevers, trichinosis			
	• Back pain	→	Subacute vertebral osteomyelitis, brucellosis, SBE			
	• Testicular pain	→	EBV			
Rheumatic/ inflammatory disorders	• PMH/FMH of rheumatic disorders	→	Possibility of the same disease likely	• Fever pattern:		
	• HA/mental confusion	→	GCA/TA, CNS sarcoidosis, adult Still's disease	Double quotidian fever	→	Adult Still's disease
				Morning temperature spikes	→	PAN
	• Transient facial edema	→	Takayasu's arteritis			
	• Hearing loss	→	PAN	• Lacrimal gland enlargement	→	LORA, sarcoidosis, SLE
	• Nasal stuffiness	→	Sarcoidosis	• Parotid gland enlargement	→	Sarcoidosis
	• Joint pain/swelling	→	SLE, LORA, sarcoidosis, adult Still's disease	• Rash	→	Sarcoidosis, SLE, adult Still's disease
				• Unequal pulses	→	Takayasu's arteritis
	• Eye symptoms	→	PAN, sarcoidosis	• Conjunctival nodules	→	Sarcoidosis
	• Transient blindness	→	PAN, SLE, GCA/TA, Takayasu's arteritis	• Dry eyes	→	Sarcoidosis
	• Neck/jaw pain	→	GCA/TA, Takayasu's arteritis	• Watery eyes	→	PAN
	• Sore throat	→	SLE, adult Still's disease	• Argyll-Robertson or Adies' pupils	→	Sarcoidosis
	• Tongue tenderness	→	GCA/TA	• Band keratopathy	→	Adult Still's disease, sarcoidosis
	• Mouth ulcers	→	SLE	• Episcleritis	→	GCA/TA, LORA, PAN
	• Night sweats	→	Takayasu's arteritis	• Scleritis	→	SLE
	• Rash	→	Adult Still's disease, SLE, sarcoidosis	• Iritis	→	Adult Still's disease, SLE, sarcoidosis