Sujata Sawhney
Amita Aggarwal
Editors

Pediatric Rheumatology

A Clinical Viewpoint

Springer

Pediatric Rheumatology

Sujata Sawhney • Amita Aggarwal
Editors

Pediatric Rheumatology

A Clinical Viewpoint

Springer

Editors
Sujata Sawhney
Pediatric Rheumatology Division
Institute of Child Health
Sir Ganga Ram Hospital
New Delhi
India

Amita Aggarwal
Department of Clinical Immunology
Sanjay Gandhi Postgraduate Institute
of Medical Sciences
Lucknow
India

ISBN 978-981-10-1749-0 ISBN 978-981-10-1750-6 (eBook)
DOI 10.1007/978-981-10-1750-6

Library of Congress Control Number: 2016959763

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer Science+Business Media Singapore Pte Ltd.
The registered company address is 152 Beach Road, #22-06/08 Gateway East, Singapore 189721, Singapore

Foreword

I am honoured to be asked to provide a foreword for this book by its editors. It represents a significant educational and reference landmark. The editors have collated the latest knowledge in pediatric rheumatology written by an international faculty, many with regional authors and co-authors. This book is in an easy to understand format for the clinician, and in the context of the demographics of Southeast Asia. It is well known that although there are many similarities between the diseases described in mainly Caucasian populations, there are also epidemiological, genetic and phenotypic differences which influence what the pediatrician will see in the clinic in this region.

What is enduring and fascinating about medicine is that there are always patients that fail to conform to textbooks and guidelines. So the clinician will still need to use their powers of observation and analysis, and not stop thinking once a diagnosis is made. Childhood rheumatic diseases have a habit of changing with time. This book serves as a manual to clinicians, with basic discussions of the pathologies that are known so far, and provides clinical examples of such pathologies. When faced with a clinical problem, the patient's history and pattern recognition are still the essential basic tools, but knowledge of pathology will add to the final analysis and inform the clinician on the most appropriate treatment. Thus in this book there are chapters also on basic immunology and genetics. In each chapter on a disease, appropriate balance is given to clinical signs and diagnosis. The issue of pain perception

and control is also gaining importance and recognition. Perhaps one of the most important principles to keep in mind is that if the patient's problem does not fit the description, there are other as yet unknown diseases/problems out there to be found!

Patricia Woo MBBS MRCP FRCP FRCPCH FMedSci
Emeritus Professor of Pediatric
Rheumatology at University College London
Honorary Consultant at Great Ormond Street
Children's Hospital Foundation Trust, London, UK

About the Editors

Dr. Sujata Sawhney (MD, MRCP (UK), CCST (UK)) is a graduate of the Armed Forces Medical College, Pune, India, and did her MD in pediatrics from Delhi University. She specialized in pediatric rheumatology at the Great Ormond Street Hospital in London where she completed her MRCP and on completion of training was awarded the Completion Certificate of Specialist Training (CCST). She is currently based at Sir Ganga Ram Hospital, New Delhi, India, where she heads the Pediatric Rheumatology Division at the Institute of Child Health. She is the coeditor of the book *Rheumatic Diseases in Women and Children: Current Perspectives* (2014) and has over 30 publications in peer-reviewed journals and as textbook chapters. She runs a postdoctoral fellowship program at her center and has been the past president of the Pediatric Rheumatology Society of India.

Dr. Amita Aggarwal (MD, DM, FNASc, FASc, FAMS) graduated from the All India Institute of Medical Sciences (AIIMS), New Delhi. She is a professor of clinical Immunology at the Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India. She has more than 250 peer-reviewed publications to her credit. She has been involved in research on rheumatic diseases especially juvenile idiopathic arthritis for the last two decades. She has been awarded the DBT-Bioscience award for career development and multiple awards from the Indian Council of Medical Research. She is currently the president of the Indian Rheumatology Association.

Preface

We are proud to present our book *Pediatric Rheumatology: A Clinical Viewpoint*. This has been a challenging journey with many twists and turns, but we hope our readers find this book worth the while!

Our journeys in the world of pediatric rheumatology have been long: punctuated with routine, difficult, and heart-breaking times. We both work in one of the most populous countries in the world where resources are oftentimes a challenge and a major constraint for many of our patients. We have had the privilege of being trained, in India and abroad, at some of the world's best institutions, but nowhere did we learn how to treat a child where the family had no money to pay. Treating these children has taught us an important lesson: care with compassion and offer the best to the child in the circumstance that he or she is in.

Why did we embark upon the idea of this book when there are other well-respected textbooks in this field? It is for one reason: this book is a "go-to" for clinicians who are embarking upon a journey in this specialty. This book has five sections on basic principles, arthritides, connective tissue diseases, vasculitides, and a miscellaneous section on immunodeficiencies, bone health, genetic disorders, etc. Each chapter has a case vignette, learning points, and key "take-home" messages. Each section has a concluding chapter with case vignettes as well. Thus, this book is like a virtual clinic and has background information on approaching a child with suspected arthritis, connective tissue disease, and vasculitis.

We are privileged to have Professor Patricia Woo write the foreword for our book and are indebted to her for this. We are deeply grateful to our excellent contributors from across the world for their time, effort, and dedication to this project. The paintings that accompany each section have been drawn by Reeya Renee Rajpal, a 9-year-old child who fought and conquered childhood lupus and is a child protégé. We would also like to thank Springer for publishing this book.

We hope to receive a feedback from our readers to better this book in the next edition.

Lastly, we would like to thank our families for their support and love through all this time.

Happy reading!

New Delhi, India — Sujata Sawhney
Lucknow, India — Amita Aggarwal

Contents

Contributors

Bonnie Abujam Allergy & Immunology Division, Department of Pediatrics, Advanced Pediatrics Centre, PGIMER, Chandigarh, India

Khalid M. Abulaban Division of Pediatric Rheumatology, Helen DeVos Children's Hospital (Spectrum Health), Michigan State University, Grand Rapids, MI, USA

Manjari Agarwal Division of Pediatric and Adolescent Rheumatology, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India

Amita Aggarwal Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Balu H. Athreya AI duPont Hospital for Children, Wilmington, DE, USA

Tadej Avčin Department of Allergology, Rheumatology and Clinical Immunology, Children's Hospital, University Medical Center, Ljubljana, Slovenia

Mojca Zajc Avramovič Department of Allergology, Rheumatology and Clinical Immunology, Children's Hospital, University Medical Center, Ljubljana, Slovenia

Suma Balan Amrita Institute of Medical Science, Ponekkara, Kochi, India

Joanne M. Bargman University Health Network, Toronto General Hospital, Toronto, ON, Canada

Karyl Barron National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

Ezgi Deniz Batu Department of Pediatric Rheumatology, Hacettepe University Faculty of Medicine, Sihhiye, Ankara, Turkey

Susanne M. Benseler Rheumatology, Alberta Children's Hospital for Sick Children, Faculty of Medicine, University of Calgary, Calgary, AB, Canada

Aruna Bhat Majumdar Shaw Multispeciality Hospital, Narayana Health City, Bangalore, India

Sagar Bhattad Pediatric Allergy and Immunology Unit, Advanced Pediatrics Centre, PGIMER, Chandigarh, India

Roberto Ezequiel Borgia Pediatric Rheumatology Division, The Hospital for Sick Children, Toronto, Toronto, ON, Canada

Paul A. Brogan UCL Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust, London, UK

Hermine I. Brunner Division of Pediatric Rheumatology, Cincinnati Children Hospital Medical Center, Cincinnati, OH, USA

Ruben Burgos-Vargas Department of Rheumatology, Faculty of Medicine, Hospital General de México, Universidad Nacional Autónoma de México, México, DF, Mexico

T.B.S. Buxi Department of Radiology, Sir Ganga Ram Hospital, New Delhi, India

David A. Cabral Division of Rheumatology, Department of Pediatrics, British Columbia Children's Hospital and University of British Columbia, Vancouver, BC, Canada

Rolando Cimaz Unit of Pediatric Rheumatology, Meyer Children's Hospital, University of Florence, Florence, Italy

Alessandro Consolaro Istituto Giannina Gaslini, University of Genova and Second Division of Pediatrics, Genova, Italy

Randy Q. Cron University of Alabama at Birmingham, Birmingham, AL, USA

Roberta Culpo Pediatric Rheumatology Unit, Department for the Woman and Child Health, University of Padua, Padua, Italy

Sergio Davì Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genoa, Italy

Ivan Foeldvari Hamburg Centre for Pediatric and Adolescent Rheumatology, Centre for Treatment of Scleroderma and Uveitis in Childhood and Adolescence, Teaching Unit of the Asklepios Campus of the Semmelweis Medical School, Budapest, An der SchönKlinik Hamburg Eilbek, Hamburg, Germany

Helen Foster Department of Pediatric Rheumatology, Newcastle University Medical School, Institute Cellular Medicine, Newcastle upon Tyne, UK

S. Ghuman Department of Radiology, Sir Ganga Ram Hospital, New Delhi, India

Sanjeev Gulati Fortis Institute of Renal Sciences and Transplantation, Fortis & Escorts Hospitals, New Delhi, India

Anju Gupta Division of Allergy-Immunology, Department of Pediatrics, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Ranjan Gupta Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Mahesh Janarthanan Majumdar Shaw Multispeciality Hospital, Narayana Health City, Bangalore, India

Sharmila Jandial Great North Children's Hospital, Royal Victoria Infirmary, New Castle, UK

Mehul Jariwala Division of Rheumatology, Sir Ganga Ram Hospital, New Delhi, India

Nutan Kamath Kasturba Medical College, Manipal University, Mangalore, India

Chetna Khemani Jaslok Hospital and Research Center, Breach Candy Hospital, Mumbai, India

Raju Khubchandani Jaslok Hospital and Research Center, Breach Candy Hospital, Mumbai, India

Sathish Kumar Department of Pediatrics, Christian Medical College & Hospital, Vellore, India

Sharath Kumar Columbia Asia Hospitals Bengaluru, Bengaluru, Karnataka, India

Pamela Lee Department of Pediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong

Yu-Lung Lau Department of Pediatric and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong

Thomas J.A. Lehman Chief Division of Pediatric Rheumatology, Hospital for Special Surgery, New York, NY, USA,

Weill Medical College of Cornell University, New York, NY, USA

Maria Cristina Maggio Universitary Department Pro.Sa.M.I. "G. D'Alessandro", University of Palermo, Palermo, Italy

Susan Maillard Pediatric Rheumatology and Musculoskeletal Pain Service, Great Ormond Street Hospital, London, UK

Clara Malattia Department of Pediatrics, University of Genova, Genova, Italy

Pediatria II- Reumatologia, Istituto Giannina Gaslini, Genova, Italy

Prudence J. Manners School of Pediatrics and Child Health, Faculty of Medicine, Dentistry and Health Sciences, University of Western Australia, Crawley, WA, Australia

Alberto Martini Department of Pediatrics, University of Genova, Genova, Italy

Pediatria II- Reumatologia, Istituto Giannina Gaslini, Genova, Italy

Francesca Minoia Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genoa, Italy

Sumidha Mittal Division of Pediatric Rheumatology, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India

Kimberly Morishita Division of Rheumatology, Department of Pediatrics, British Columbia Children's Hospital and University of British Columbia, Vancouver, BC, Canada

Kevin J. Murray Rheumatology Department, Princess Margaret Hospital for Children, Perth, WA, Australia

Kaveri K. Nalianda Centre for Arthritis & Rheumatism Excellence (CARE), Kochi, India

Seza Özen, Department of Pediatric Rheumatology, Hacettepe University Faculty of Medicine, Sihhiye, Ankara, Turkey

Ross Petty Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

Shubha Phadke Department of Medical Genetics, Sanjay Gandhi, Postgraduate Institute of Medical Sciences, Lucknow, India

Clarissa Pilkington Pediatric Rheumatology Service, Great Ormond Street Hospital, London, UK

Sampath Prahalad Departments of Pediatrics, and Human Genetics, Emory University School of Medicine, Atlanta, GA, USA

Children's Healthcare of Atlanta, Atlanta, GA, USA

A.V. Ramanan Pediatric Rheumatology, Bristol Royal Hospital for Children, Bristol, UK

Anand Prahalad Rao Manipal Hospital and Indira Gandhi Institute of Child Health, Bangalore, India

D. Rastogi Department of Radiology, Sir Ganga Ram Hospital, New Delhi, India

Angelo Ravelli Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genoa, Italy

Università degli studi di Genova, Genoa, Italy

S. Reddy Department of Radiology, Sir Ganga Ram Hospital, New Delhi, India

Nicola Ruperto Istituto Giannina Gaslini, Pediatric Rheumatology International Trials Organization and Second Division of Pediatrics, Genova, Italy

Sanjay Sarup, Pediatric Orthopedic & Spine Surgery, Artemis Health Sciences, Gurgaon, Haryana, India

Sujata Sawhney Division of Pediatric Rheumatology, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India

Christiaan Scott Department of Pediatric Rheumatology, University of Cape Town, Red Cross War Memorial Children's Hospital, Cape Town, South Africa

Ethan S. Sen Pediatric Rheumatology, Bristol Royal Hospital for Children, Bristol, UK

Avinash Sharma Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Padmanabha Shenoy Centre for Arthritis & Rheumatism Excellence (CARE), Kochi, India

Abhay Shivpuri Division of Pediatric Rheumatology, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India

Earl D. Silverman Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada

Surjit Singh Pediatric Allergy Immunology Unit, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

S. Sud Department of Radiology, Sir Ganga Ram Hospital, New Delhi, India

Deepti Suri Pediatric Allergy and Immunology Unit, Advanced Pediatrics Centre, PGIMER, Chandigarh, India

Marinka Twilt Division of Rheumatology, Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark

P. Vignesh Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Vijay Viswanathan Jupiter Hospital, Thane, India

Patricia Woo Pediatric Rheumatology, Institute of Child Health, University College London, London, UK

Francesco Zulian Pediatric Rheumatology Unit, Department for the Woman and Child Health, University of Padua, Padua, Italy

Part I

Introduction to Pediatric Rheumatology

The paintings used in the book have been made by Indian child prodigy ***Reeya Rene Rajpal***, born 2004. Most of these paintings were made by her at a tender age of 6–7 years and have been exhibited at the prestigious Lalit Kala Akademy, New Delhi, India after being vetted by great Indian masters of art. Her passion for painting continues…

History of Pediatric Rheumatology

1

Balu H. Athreya

Pediatric rheumatology is one of the youngest medical specialties. Although, several authors including Still, Diamant-Berger and Cornil had published articles and monographs on various aspects of rheumatic diseases in children during the nineteenth and early twentieth century, the formal inauguration of the specialty took place in 1976. That is when the American College of Rheumatology (which was known at that time as American Rheumatism Association) sponsored a conference on pediatric rheumatic diseases at Park City, USA. The pioneers who attended that conference collected all the available information on the subject and compiled them into a monograph [1]. This became the core knowledge and foundation for the establishment of pediatric rheumatology.

The concept of rheumatic diseases evolved over several centuries. The word rheumatism comes from the Greek word *rheumatismo*s, a term coined by Galen in the second century CE. Early in history, this term rheumatism was applied to illnesses in general, particularly those with muscular aches and pains. Both arthritis and gout were included in the category, and the word gout also referred to arthritis in general. Baillou is credited with applying the term rheumatism to include joint diseases also [2, 3]. The etiology was considered to be bad "humor" (*rheuma* meaning *that which flows*) and there was no understanding of differences between infectious, inflammatory, and noninflammatory arthritides.

The monumental work of Morgagni, correlating organ pathology with symptoms and signs published in 1761, established the basis of scientific clinical medicine. He had also described lesions of heart valves in patients who died of rheumatic fever. Virchow's work with microscopic pathology extended the science of pathological anatomy and led to the rapid understanding of diseases of various organ systems of the human body. The focus was on single organs. It took another 200 years to realize that connective tissues and blood vessels are common to all the organs and therefore, diseases of connective tissue and blood vessels will affect multiple organs. An article by Klemperer [4] established this link in 1942.

After the multisystem nature of rheumatic diseases was understood and the relationship to autoantibodies were recognized, several other terms were used interchangeably with the term rheumatic diseases such as connective tissue diseases, collagen vascular diseases, and autoimmune diseases. Now, autoinflammatory diseases and

B.H. Athreya, MD
AI duPont Hospital for Children,
Wilmington, DE, USA
e-mail: balathreya@comcast.net

S. Sawhney, A. Aggarwal (eds.), *Pediatric Rheumatology*, DOI 10.1007/978-981-10-1750-6_1

several immune disorders are also included in textbooks of rheumatology.

Basically, rheumatic diseases are due to inflammation of connective tissues of the body, particularly those of muscles and joints. Connective tissues of the blood vessels may also be involved. Most of them are chronic diseases, and clinical features of these diseases tend to overlap. Many of them evolve over time and move from one pattern to another. Immune abnormalities and variations in the genetic makeup have been documented in most of these conditions. The role of infections, although suspected as a trigger, has been established in only a few of them.

Diagnosis of rheumatic diseases is still mostly based on the clinical patterns. Since rheumatic diseases tend to involve multiple systems and since aches, pains, fever, and rash are the presenting symptoms, pediatric rheumatologists are most often called upon to consult on some of the most puzzling and difficult-to-manage patients in pediatric practice and hospitals.

Ayurvedic literature refers to bone and joint conditions under the category of *vata*. It appears that *amavata* is probably what we now call rheumatoid arthritis, *vata* is probably osteoarthritis and *vatarakta* is most likely gout. Although Jivaka, the earliest documented pediatrician in history is from India, there is no clear description of childhood arthritis in the Indian literature [5, 6].

There are no descriptions of arthritis in children in the English literature before 1800. However, Thomas Phaer (Phayer) wrote two pages in his book on The *Boke of Chyldren* published in 1545 about "the stifnes or starckenes of limmes" which reads like chronic arthritis. However, art historians point out that a young person in the painting by Botticelli in 1483 shows changes in his hands suggestive of chronic arthritis [7].

Rheumatic fever was known for a long time probably because it was very common in childhood. However, Baillou, who introduced the term rheumatism to modern medical literature in 1642, is considered to have used the term specifically to acute rheumatism. In his description of acute rheumatism, Baillou was aware of chronic forms of rheumatism also. Later, Thomas Sydenham, who suffered from gout himself, separated gout from rheumatic fever and from other chronic arthritic conditions. Later still Sir Archibald Garrod coined the term rheumatoid arthritis for one subset in 1858 [3, 8].

The first detailed description of juvenile forms of arthritis in the English literature was by George Federick Still in 1897 [9]. There were several clinical descriptions earlier including a report from France on 38 children with chronic arthritis by Diamant-Berger [10]. The latter publication has diagrams of various forms of deformities of the hand and of the neck. However, it was Still's name which became associated with juvenile form of arthritis, particularly the systemic type.

Still described 22 patients and described the features of 19 patients he had seen himself at the Great Ormond Street Hospital or in the children at London [9]. He included three types: (a) with systemic features such as fever, splenomegaly, and lymphadenopathy (12 patients), (b) with feature similar to those of adults (6 patients), and (c) Jaccoud arthropathy (1 patient). After this publication, the term Still's disease came into common use to describe not just the systemic (febrile) type but all forms of chronic arthritis in children. Therefore, in order to separate the systemic type from the others, the term juvenile rheumatoid arthritis (JRA) was introduced in the USA in 1946 by Cass and Boots [11]. A few authors had suggested diagnostic criteria for JRA. However, the preferred term in England and Europe was juvenile chronic polyarthritis with a different set of criteria. In his Heberden Oration, Prof. Bywaters [12] pointed out "Chronic Juvenile polyarthritis is a wide term. Still's disease is a historic term and JRA is an exact but misleading term". Clearly some order and uniformity were needed to classify the subtypes.

A subcommittee for the classification of JRA (earlier nomenclature) was established in 1964 by the ARA, and the first set of criteria for classification was published in 1972 [13]. Three types of onset were recognized, namely, oligo (pauci)-articular, polyarticular, and systemic. These criteria were validated and revised. In the absence of clear understanding of its etiology and pathogenesis, the term JRA included various syndromes with phenotypic variations and genetic heterogeneity. Therefore, the Pediatric Standing

Committee of International League Against Rheumatism (ILAR) developed a classification of the idiopathic arthritides of childhood (juvenile idiopathic arthritis or JIA), and its latest version was published in 2004 [14]. The universal adaptation of this classification should help standardize nomenclature and collect data from a comparable set of patients from different parts of the world.

Since JIA makes up for a vast majority of patients seen by pediatric rheumatologists, the focus was on this entity in the beginning. Similar efforts had to be undertaken to classify other rheumatic diseases in children before reliable clinical and therapeutic studies could be done. This came about subsequently. Criteria for classification of systemic lupus erythematosus (SLE), dermato- and polymyosists, and scleorderma had already been developed for use in adults, and they were applicable to children also for the most part. The ACR criteria of 1982 for classification of SLE have been evaluated in children [15, 16]. Criteria for the diagnosis of dermatomyositis are still those established in 1975 by Bohan and Peter [17], although efforts are being made to modify them. Criteria for the diagnosis of juvenile scleroderma and various forms of vasculitis have recently been established [18, 19, 19A].

In 1947, the Canadian government presented a war-time hospital to Great Britain, and this became a major center for care of children with rheumatic diseases. This hospital was later known as "Taplow" where Prof. Eric Bywaters and Prof. Barbara Ansell laid the foundations for pediatric rheumatology as a scientific discipline and trained several physicians from all over the world. In the USA, there were similar specialized hospitals for the care of children with acute rheumatic fever (La Rabida in Chicago and Irvington House in New York). The incidence of acute rheumatic fever started declining during the middle of the century at least in the west, for a combination of reasons and an interest in other rheumatic diseases of childhood started to increase. All of the hospitals caring for children with acute rheumatic fever started to focus on JRA (JIA). In Europe, Prof. Elizabeth Stoeber was responsible for converting a TB sanatorium into a center for rheumatic diseases at Garmisch-Partenkirchen in Germany.

At present, the USA and Italy are leading the scientific advancements in pediatric rheumatology although the foundations were laid at Taplow, England. In the USA, the American College of Rheumatology (previously known as American Rheumatism Association or ARA), the American Academy of Pediatrics, the Arthritis Foundation, the American Board of Pediatrics, Office of Maternal and Child Health, and the March of Dimes Foundation were all involved in developing this field.

The earliest specialized centers for rheumatic diseases in modern times were established in U.S.A. with the help of the March of Dimes Foundation when it shifted its focus from poliomyelitis. Later, several innovations in delivery of care such as parent support groups, family-centered care, multidisciplinary care, and outreach programs were developed at centers supported by the Office of Maternal and Child Health.

The ARA (now known as ACR, the name changed in 1985) decided to establish a council on pediatric rheumatology in order to address the needs of children with rheumatic diseases. This effort resulted in the first Park City conference at Park City, Utah in 1976. The proceedings of this conference was published as a supplement [1] to the journal Arthritis and Rheumatism (the name of this journal has been changed recently to Arthritis and Rheumatology). Since then, several books and monographs on pediatric rheumatology have been published.

The American Academy of Pediatrics established a section of rheumatology in 1980, and its focus has been on the education of physicians and advocacy for the care of children with chronic diseases. The American Board of Pediatrics recognized the need for training of physicians in this important specialty and established a sub-board in pediatric rheumatology in 1990. In 2012, there were 30 academic centers in the USA with accredited training programs. There are several training programs in Canada, England, Italy, and other European countries. Standards for training in pediatric rheumatology and a process for certification of specialized training in this field are existent in several countries including India.

In the USA, the Arthritis Foundation (AF) has also played a major part in developing this field with

its support for training, research and delivery of care. The American Juvenile Arthritis Organization (AJAO) gets its greatest support from the AF. Similar organizations exist in other countries also. For example, *Il Volo* is a parent support group in Italy (www.ilvolo.org). There is a parent support group in India for children with Kawasaki Disease.

At the beginning of my career in pediatric rheumatology, there were very few options for the treatment of rheumatic diseases in children. To be more specific, they were aspirin, gold, and corticosteroids. In intractable situations, indomethacin, cyclophosphamide, and even chlorambucil were used, making the treatment more dangerous than the disease. Most of the drugs available in the market had not been tested for efficacy or safety in children and therefore were not formally approved for use in pediatric practice. In the late 1960s and early 1970s, newer NSAIDs with less adverse effects compared to aspirin were being introduced. To make sure the promising new drugs were properly tested and approved for use in children, the Pediatric Rheumatology Collaborative Study Group (PRCSG) was formed in 1973 and headed by Earl Brewer of Houston, Texas. The group conducted the first clinical study comparing aspirin with tolmetin sodium and placebo and published the results in 1977 [20]. Since then this group has been responsible for most of the clinical studies on the safety and efficacy of DMARDS and biological agents in children and has 79 published articles to its credit [21].

In 1996, pediatric rheumatologists from 14 European countries formed an organization similar to the PRCSG. This group (PRINTO) has worked collaboratively with PRCSG on various methodological papers and has also worked with regulatory agencies in the European Union. Recently, PRINTO has started collaborating with academic centers and professional organizations in Asian and South Asian countries in education and research.

The PRCSG has performed and published many studies on methodological issues [22], some of them in collaboration with PRINTO. This includes measurement of clinical response [23] and remission in JIA [24]. In its study on the use of the first biological agent etanercept (TNF blocker) in JIA, the PRCSG used its newly developed definition of clinical response and also introduced an innovative design which has since been adapted by several other groups [25].

The PRCSG and PRINTO designed Childhood Myositis Assessment Scale and core sets of outcome measures and definitions of improvement for children with Juvenile Idiopathic Inflammatory Myopathies [26–28].

Whereas PRCSG and PRINTO focused mostly on clinical trials and development of criteria, a new organization called CARRA was formed in 2002 and its Mission is to *improve the health*, *well-being, and outcomes of children and adolescents with rheumatic disease through fostering and facilitating collaborative research in prevention*, *treatment and cure*. At present, this group is focused on the development of consensus treatment protocols (CTPs) in each of the major disease areas – juvenile idiopathic arthritis, systemic lupus erythematosus, juvenile dermatomyositis, vasculitis, and scleroderma (http://carragroup.org).

In India, Brig. Menon and Prof. Chandrasekaran were the earliest physicians to focus on pediatric rheumatology, although both of them were internists. Some of the earliest rheumatology clinics for children were started in the 1980's in New Delhi, Lucknow, Chandigarh, and Chennai. Currently, there are about 25 trained pediatric rheumatologists in India and 12 centers offering specialty clinic for children with rheumatic diseases [29]. Although the Indian Rheumatism Association initiated the early efforts to address the problems of children with rheumatic diseases, the Indian Academy of Pediatrics has taken over the lead with the organization of CME programs including a 2-day annual course for practicing pediatricians. More recently, PGI at Chandigarh has started a 3-year training program in pediatric immunology and rheumatology. As mentioned earlier, pediatric rheumatologists from India are participating in several international studies in collaboration with PRINTO.

In his inaugural address at the first Park City conference, Prof. Bywaters said: "Pediatric rheumatology is one of the latest arrivals and one of

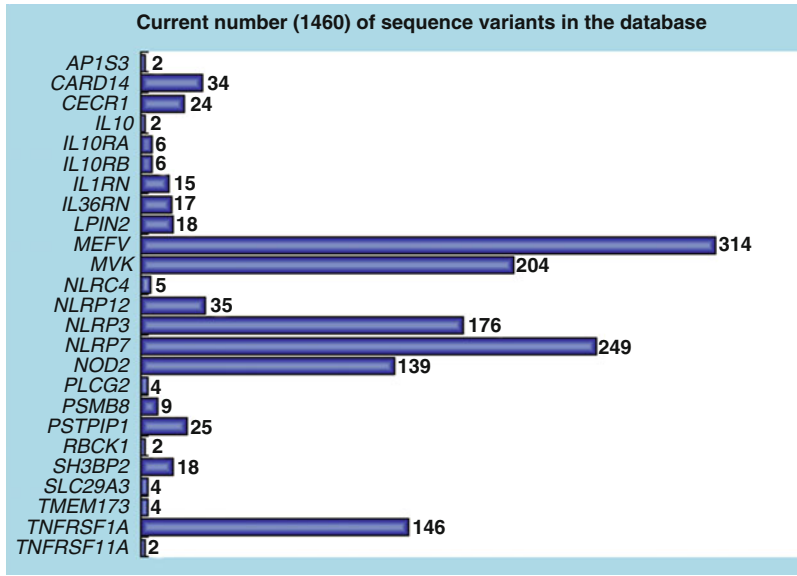

Fig. 1.1 An example of recent advances in pediatric rheumatology (From Infevers: an online database for autoinflammatory mutations. Copyright. Available at http://fmf.igh.cnrs.fr/ISSAID/infevers/. Accessed April 13, 2016)

the smallest, although I would say not premature. I think I can say I saw it arrive, although I cannot specify its birthday or place" [12]. This was in the year 1976. At that time we had very few therapeutic options. Children with rheumatic diseases grew up into adulthood with their chronic condition and associated disabilities (including joint replacements) or died of complications of the disease or the treatment. Fortunately, the field was growing into its adolescence at the same time as the explosive increase in knowledge in the fields of immunology, molecular biology, and genomics.

The most significant and exciting developments in the past two decades are the introduction of biological agents for the treatment of rheumatic diseases, a better understanding of syndromic and familial arthropathies, and a better understanding of systemic inflammatory disorders such as Familial Mediterranean Fever. These are areas in which history is being written at present.

The introduction of biologicals in the treatment of rheumatic and autoimmune diseases has resulted in better control of many of these diseases, and it is even possible to think of remission [30]. Gone are the days when children with JIA face blindness and several kinds of orthopedic procedures and even joint replacement at a very young age.

Advances in molecular biology, genetics, and genomics have made it possible to study several familial syndromes in which genetics play a part. These in turn have improved our understanding of the basic biology of rheumatic diseases, inflammation, and joint biology. For example, genetic studies of children with CPAP syndrome led to the identification of lubricin as a major lubricating agent in joint fluids, even more important than hyaluronic acid [31].

Pediatric rheumatologists are often consulted on patients with undiagnosed periodic fevers such as FMF. Once again, development in genetics and its associated technologies resulted in the identification of genes responsible for these diseases [32, 33]. They are aptly grouped under the name of autoinflammatory diseases. At present approximately 25 monogenic autoinflammatory diseases are listed at the website *infevers* (fmf.igh.cnrs.fr/ISSAID/infevers/accessed on April 13, 2016) with 1,460 known variants (Fig. 1.1). Studies on these patients have opened up new understanding of the basic mechanisms inflammation and also description of several new syndromes. These developments arrived at a time

when research into the use of biologicals and signal transduction molecules were also advancing, so that it is possible to treat some of these diseases effectively [34].

That indeed is progress.

References

1. Schaller JG, Hanson V, editors. Proceedings of the first ARA conference on the rheumatic diseases of childhood, Park City, 23–25 Mar 1976. Arthritis Rheum. 1976;20(Suppl 1):145–638.
2. Benedek TG, Rodnan G. A brief history of rheumatic diseases. Bull Rheum Dis. 1982;2:59–68.
3. Lagier R. Nosology versus pathology, two approaches to rheumatic diseases illustrated by Alfred Baring Garrod and Jean-Martin Charcot. Rheumatology. 2001;40:467–71.
4. Klemperer P, Pollack AD, Baehr G. Diffuse collagen disease. JAMA. 1942;119:331–2.
5. Ulrich-Merzenich G, Kraft K, Singh LM. Rheumatic diseases in Ayurveda: a historic perspective. Letters to the editor. Arthritis Rheum. 1999;42:1553–5.
6. Athavale VB. Bala Veda. Special issue for XV International Congress of Pediatrics. Pediatr Clin India. 1977.
7. Alarcon-Segovia D, Alaffron A, Alcoar Varela AJ. Probable depiction of JA by Sandro Botticelli. Arthritis Rheum. 1983;26:1266–8.
8. Garrod AB. The great practicality of separating rheumatoid arthritis from gout. Lancet. 1892;2:1033–7.
9. Still GF. On a form of chronic joint diseases in children. Med Chir Trans. 1897;80:47–59.
10. du Diamantberger MS. Rheumatisme noueux (polyarthrite déformante) chez les enfants. Paris: Lecrosnier et Barre; 1891.
11. Coss Jr JA, Boots RH. Juvenile Rheumatoid arthritis – a study of 56 cases with a note on skeletal changes. J Pediatr. 1946;29:143–56.
12. Bywaters EGL. The history of pediatric rheumatology. Arthritis Rheum. 1977;20 Suppl 2:145–52.
13. Brewer EJ, Bass JC, Cassidy JT, et al. Criteria for the classification of juvenile rheumatoid arthritis. Bull Rheum Dis. 1972;23:712–9.
14. Petty RE, Southwood TR, Manners P, et al. International League of Association for Rheumatology classification of juvenile idiopathic arthritis. Second revision, Edmonton, 2001. J Rheumatol. 2004;31:390–2.
15. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25:1271–7.
16. Ferraz MB, Goldenberg J, Hilario MO, et al. Evaluation of the 1982 ARA lupus criteria data set in pediatric patients. Clin Exp Rheumatol. 1994;1994:83–7.
17. Bohan A, Peters JB. Polymyositis and dermatomyositis. N Engl J Med. 1975;292:344–403.
18. Zulian F, Woo P, Athreya BH, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. Arthritis Rheum. 2007;57(2):203–12.
19. Ruperto N, Ozen S, Pistorio A, et al.; Paediatric Rheumatology International Trials Organisation (PRINTO). EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part I: overall methodology and clinical characterisation. Ann Rheum Dis. 2010;69:790–7.

19.A Ozen S, Pistorio A, Iusan SM, et al.; Paediatric Rheumatology International Trials Organisation (PRINTO). EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa,childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis. 2010;69:798–806.

20. Levinson JE, Baum J, Brewer EJ, et al. Comparison of tolmetin sodium and aspirin in the treatment of juvenile rheumatoid arthritis. J Pediatr. 1997;91:799–804.
21. Pediatric Rheumatology Collaborative Study Group Website: http://prcsg.org.
22. Giannini EH, Lovell DJ, Hepburn B. FDA draft guidelines for the clinical evaluation of anti-inflammatory and anti-rheumatic drugs in children. Executive summary. Arthritis Rheum. 1995;38:715–8.
23. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum. 1997;40(7):1202–9.
24. Wallace CA, Ruperto N, Giannini EH. Preliminary criteria for clinical remission for selected categories of juvenile idiopathic arthritis. J Rheumatol. 2004;31:2290–4.
25. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Whitmore J, Finck BK. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000;342(11):763–9.
26. Ruperto N, Ravelli A, Pistorio A, Ferriani V, Calvo I, Ganser G, Brunner J, Dannecker G, Silva CA, Stanevicha V, Cate RT, van Suijlekom-Smit LW, Voygioyka O, Fischbach M, Foeldvari I, Hilario O, Modesto C, Saurenmann RK, Sauvain MJ, Scheibel I, Sommelet D, Tambic-Bukovac L, Barcellona R, Brik R, Ehl S, Jovanovic M, Rovensky J, Bagnasco F, Lovell DJ, Martini A. The provisional Paediatric Rheumatology International Trials Organisation/American College of Rheumatology/European League Against Rheumatism Disease activity core set for the evaluation of response to therapy in juvenile dermatomyositis: a prospective validation study. Arthritis Rheum. 2008;59:4–13.

27. Rider LG, Giannini EH, Brunner HI, Ruperto N, James-Newton L, Reed AM, Lachenbruch PA, Miller FW. International consensus on preliminary definitions of improvement in adult and juvenile myositis. Arthritis Rheum. 2004;50:2281–90.
28. Lovell DJ, Lindsley CB, Rennebohm RM, Ballinger SH, Bowyer SL, Giannini EH, Hicks JE, Levinson JE, Mier R, Pachman LM, Passo MH, Perez MD, Reed AM, Schikler KN, Smith M, Zemel LS, Rider LG. Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies. II. The Childhood Myositis Assessment Scale (CMAS): a quantitative tool for the evaluation of muscle function. The Juvenile Dermatomyositis Disease Activity Collaborative Study Group. Arthritis Rheum. 1999;42:2213–9.
29. Khubchandani R. PReS13-SPK-1127: pediatric rheumatology in India. Pediatr Rheumatol. 2013;11 Suppl 2:I34.
30. Gilbert M, Punaro M. Blood gene expression profiling in pediatric systemic lupus erythematosus and systemic juvenile idiopathic arthritis: from bench to bedside. Pediatr Rheumatol. 2014;12:16. http://www.ped-rheum.com/content/12/1/16.
31. Rhee DK, Marcelino J, Baker M, Gong Y, Smits P, LeFebvre V, et al. The secreted glycoprotein lubricin protects cartilage surfaces and inhibits synovial cell overgrowth. J Clin Invest. 2005;115:622–31.
32. International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell. 1997;90:797–807.
33. McDermott MF, Aksentijevich I, Galon J, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell. 1999;97:133–44.
34. Goldbach-Mansky R. Immunology in clinic review series; focus on autoinflammatory diseases: update on monogenic autoinflammatory diseases: the role of interleukin (IL)-1 and an emerging role for cytokines beyond IL-1.9. Clin Exp Immunol. 2011;167:391–404.

Further Reading

Brewer EJ. A peripatetic pediatrician's journey into pediatric rheumatology. Pediatr Rheumatol. 2007;5:11. doi:10.1186/1546-0096-5-11.
Cassidy JT. Pediatric rheumatology – a personal history. In: Pisetsky D, editor. The ACR at 75. A Diamond Jubilee. Hoboken: Wiley-Blackwell; 2009. p. 31–6.
Garrod AB. The great practicality of separating rheumatoid arthritis from gout. Lancet. 1892;2:1033–7.
Schaller JG. The history of pediatric rheumatology. Pediatr Res. 2005;58:997–1007.
Schlesinger B. The relationship of throat infection to acute rheumatism in childhood. Arch Dis Child. 1930;5:411–30.

Basic Immunology for the Pediatrician

2

Amita Aggarwal and Bonnie Abujam

Learning Objectives

1. To learn about the innate immune system: recognition and generation of immune response
2. To know about cells of the adaptive immune system including various T-cell subsets
3. To know the cytokines involved in inflammation
4. To know how different drugs act on immune system

Introduction

One must be wondering why a chapter on players of the immune response is needed in a book on pediatric rheumatology. Pathology in most serious rheumatic diseases is driven by the immune system either by auto-inflammation or autoimmunity. Further, children with a deficient immune system, due to genetic defects, also present to pediatric rheumatologists with varying rheumatic manifestations. In the last decade all the advances in the management of juvenile idiopathic arthritis are due to the use of therapies, targeted at various immune mediators or cells. Thus, to have a good understanding of these aspects of pediatric rheumatology, one needs to be aware of the various cells and soluble mediators of the immune system. In addition knowledge of how a coordinated immune response is generated in response to infection and how it goes awry in autoimmune diseases as well as in auto-inflammatory syndromesis useful in understanding the clinical manifestations of the disease [1, 2].

The three basic aspects of the immune system are recognition of foreign threats, such as microbes, generation of an appropriate immune response for elimination of the microbe, and finally to have memory of this encounter so that the next time the body is able to respond faster and better.

The immune system, like the army, has two lines of defense: the immediate one also called called innate immune response and then a more coordinated and specific adaptive immune response. These two differ in the cells participating and the time course of the required response (Table 2.1).

A. Aggarwal (✉)
Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical sciences, Lucknow, India
e-mail: aa.amita@gmail.com

B. Abujam
Allergy & Immunology Division, Department of Pediatrics, Advanced Pediatrics Centre, PGIMER, Chandigarh, India
e-mail: bo.abuja@gmail.com

S. Sawhney, A. Aggarwal (eds.), *Pediatric Rheumatology*, DOI 10.1007/978-981-10-1750-6_2

Table 2.1 Innate vs Adaptive immunity

	Innate immunity	Adaptive immunity
Physical barriers	Skin, mucous membrane	Mucosal immune system
Cellular component	Neutrophils Macrophages and dendritic cells Natural killer cells	T and B lymphocytes
Soluble molecules (circulating in the blood)	Complement C-reactive protein Mannose-binding lectin Cytokines (IL-1,TNF,IFN-α)	Antibodies (immunoglobulins) Cytokines like IL-4, IL-17, and IFN-γ
Time to response	Minutes to hours	Days
Memory generation	No	Yes

Innate Immune Response

As the innate immune response is an immediate and a broad based response, the sensing of the pathogen is done by recognizing particular molecular patterns present on microbial surfaces called pathogen-associated molecular patterns (PAMPs). These PAMPs are recognized by pattern recognition receptors like Toll-like receptors (TLRs), inflammosome, or NOD2.

TLRs [3] are a family of multiple receptors. Of these TLRs 1 to 9 have been well characterized. Different TLRs differ in their ligand recognition, adapter molecules involved in activation, and expression on different cells (Table 2.2).

In addition, two other families of receptors sense PAMPs in the cytoplasm: NOD-like receptors (NLRs), inflammasomes, and RIG-like helicases (RLHs). Inflammasomes are multicomponent complexes that contain a NLR-containing protein that recognizes the microbe, adaptor proteins that bring together different molecules, and caspase 1 which activates pro-IL-1 and pro-IL-18 to active IL-1 and IL-18 [4]. These 2 cytokines cause a severe pro-inflammatory response. This is dealt in more detail in the chapter on auto-inflammatory syndromes.

Effector Cells and Molecules

Neutrophils They are the major players in acute inflammation, and their main function is phagocytosis of microbe and subsequent killing of the microbe by an oxidative "burst" leading to release of reactive oxygen species as well as release of neutrophil granule content containing acidic and alkaline phosphatases, defensins, and peroxidase.

Macrophages/Monocytes Macrophages are another group of phagocytic cells which are larger than neutrophils and are predominantly involved in chronic inflammation. In addition to their phagocytic and microbicidal activity, they also bridge the innate immune response to the adaptive immune response by presenting the antigen to T lymphocytes.

Dendritic Cells (DC) Like macrophages, dendritic cells also present the antigen to the T-helper cell. They are also called professional antigen-presenting cells (APCs). Naïve or immature DCs can take up the antigen but are poor APCs [5]. On activation by TLR signaling they become mature DCs and acquire co-stimulatory molecules, and thus become efficient at processing the antigen and presenting it to CD4 cells. In addition they secrete chemokine (C-C motif) ligand 18 (CCL18) that attracts naive T cells toward the dendritic cell in the lymph nodes thus increasing the interaction between DCs and T cells.

Natural Killer (NK) Cell They comprise about 5–10% of circulating lymphocytes and as the name suggests, they have an inherent property to kill the target cell. The usual targets are virus-infected cells or tumor cells. NK cells have killer activation receptors and killer inhibition receptors on their cell surface in addition to receptor for immunoglobulin type G [6]. The inhibiting receptors interact with MHC class I molecules on cells and thus prevent killing of normal cells. A cell such as a tumor or virus-infected cell that lacks MHC class I will be recognized by NK

Table 2.2 Human Toll-like receptors

Receptor	Cell types	Ligand	Adaptor molecule used	Location
TLR1	Monocytes/macrophages Dendritic cells B lymphocytes	Multiple triacyl lipopeptides	MyD88/MAL	Surface
TLR2	Monocytes/macrophages Neutrophils Myeloid dendritic cells	Lipoteichoic acid HSP70 Zymosan (beta-glucan)	MyD88/MAL	Surface
TLR3	Dendritic cells B lymphocytes Monocytes/macrophages Neutrophils	Double-stranded RNA poly I:C	TRIF	Intracellular
TLR4	Monocytes/macrophages Neutrophils Dendritic cells B lymphocytes Intestinal epithelium	Lipopolysaccharide Heat shock proteins Fibrinogen Heparan sulfate	MyD88/MAL/ TRIF/ TRAM	Surface
TLR5	Monocyte/macrophages Dendritic cells Intestinal epithelium	Flagellin	MyD88	Surface
TLR6		Multiple diacyl lipopeptides	MyD88/MAL	Surface
TLR7	Monocytes/macrophages Dendritic cells B lymphocytes	Single-stranded RNA	MyD88	Intracellular
TLR8	Monocytes/macrophages Dendritic cells	Single-stranded RNA	MyD88	Surface
TLR9	Monocytes/macrophages Dendritic cells B lymphocytes	Unmethylated CpG Oligodeoxynucleotide DNA	MyD88	Intra cellular

cells and be killed by induction of apoptosis or by release of perforins and granzyme from its granules. NK cells also secrete IFN-γ and thus augment the CD8 T-cell response against virally infected cells. In addition, NK cells can also kill cells coated by antibodies by binding to them via IgG receptors by a mechanism termed antibody-dependent cellular cytotoxicity (ADCC).

Complement Products The complement system primarily helps to fight bacterial infections by generating multiple complement products during its activation. Complement system can be activated by immune complexes, bacterial products, or mannose binding lectins [7]. Early complement products like C4b and C2a act as opsonins and help in the phagocytosis of bacteria by neutrophils and macrophages. C3a and C5a act as chemo-attractants and help in recruiting neutrophils to the site of inflammation and as anaphylatoxins help in release of histamine from basophils and mast cells. The complex formed at the end by late complement components causes lysis of the bacterial cell.

Adaptive Immune Response

Though for understanding we often separate the innate and adaptive immune response, in reality they are interlinked [1, 2]. The adaptive immune system mainly consists of multiple types of lymphocytes, the major subset being T and B lymphocytes. The bone marrow is the major site of hematopoiesis and gives rise to different blood cells. Most of the hematopoietic cells mature in the bone marrow except for the T cells that migrate to the thymus for their complete maturation.

T Lymphocytes T cells can be broadly divided into CD4 or T-helper (Th) and CD8 or T cytotoxic cells (Tc). CD4 Th cells are divided into many different subsets based on the cytokine produced,

transcription factor needed for their development, and chemokine receptors expressed by them (Fig. 2.1) [8]. Depending on the kind of pathogen or inciting stimuli, different subsets of Th cells are generated.

The T cells recognize the antigen in context with the MHC on the antigen-presenting cell (APC). MHC is located on chromosome 6 and codes for class I and Class II HLA antigens. HLA A, B, and C comprise HLA Class I antigens, whereas HLA-DR, DP, and DQ comprise HLA Class II antigens. HLA class I molecule consists of alpha chain associated with invariant beta 2 microglobulin, whereas HLA class II molecule consists of two chains: alpha and beta. The APCs have to process the antigen into a small peptide and then express it on the cell surface in context with MHC for a T cell to recognize it. CD4 T cells recognize antigens in context with MHC class II, whereas CD8 cells recognize antigen in context with MHC class I. The CD8 cells are mainly cytotoxic and thus kill the target cell bearing the antigen, whereas CD4 cells mainly produce cytokines on activation as well as provide help to B cells to produce antibodies.

B Lymphocytes B lymphocytes are the major players in the generation of the humoral response, i.e., antibody production. B lymphocytes interact with antigens through their B-cell receptor and undergo proliferation and affinity maturation in the germinal centers of lymph nodes with the help of T follicular helper cells to give rise to antibody-producing plasma cells as well as memory B cells [9]. The B cells also changes the type of antibody produced from IgM to IgG/IgA/IgE, which is the so-called isotype switch. All this leads to better quality of antibodies for removal of the microbe.

Antibodies Antibodies are immunoglobulins produced by plasma cells. There are five different types of antibodies in the human immune system – namely, IgM, IgG, IgA, IgE, and IgD. In addition, there are four sub classes of IgG (IgG1-4). The basic antibody unit consists of a glycosylated protein consisting of two heavy and two light polypeptide chains. The region which binds to the antigen is known as the Fab region, while the constant region, Fc, not only determines the isotype but is the region responsible for evoking effector systems. The major effector functions of antibody are complement activation and ADCC by NK cells as well as neutralization and opsonization of the microbe.

Cytokines Cytokines are small peptides that help in cross talk between the cells. They can be considered similar to hormones in the endocrine system. Cytokines include chemokines, interferons,

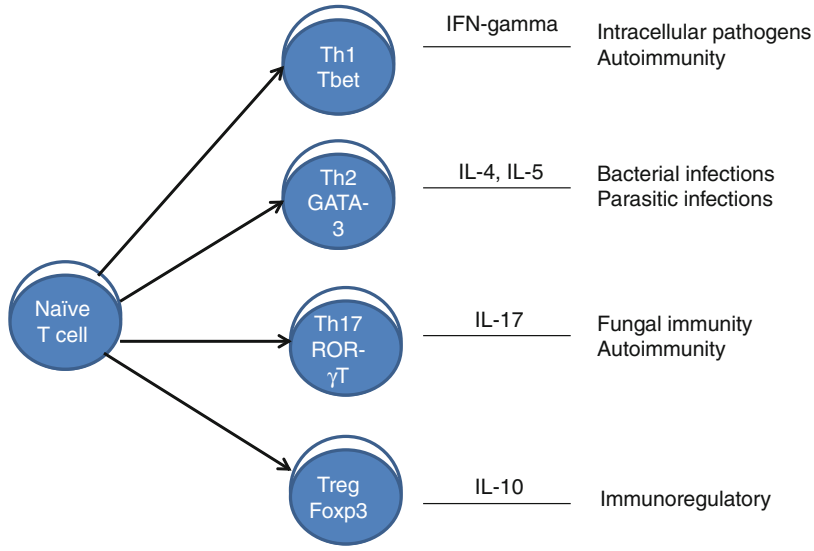

Fig. 2.1 Different T-helper (Th) cell subsets along with their signature transcription factors and the cytokines produced by them