Pediatric Immunology

A Case-Based Collection with MCQs, Volume 2

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Editor
Nima Rezaei
Department of Immunology, School of Medicine
Research Center for Immunodeficiencies (RCID)
Children's Medical Center
Tehran University of Medical Sciences (TUMS)
Tehran
Iran

Network of Immunity in Infection, Malignancy
and Autoimmunity (NIIMA)
Universal Scientific Education and Research
Network (USERN)
Tehran
Iran

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Preface

Immunology has found its way well into the practice of pediatrics. Years after publication of the first pediatric textbooks, foot prints of immunology can be found in diagnosis and practice of almost all pediatric disorders. Delivering a magnificent contribution is the advent of novel diagnostic methods in molecular genetics in pediatric practice. Genetic diagnosis is now an indispensable part of the routine practice of primary immunodeficiency disorders, inborn metabolic errors, and monogenic malformations, making way into diagnostic criteria of some as well. It won't go far wrong to state that the science of pediatrics has entered into an era of interdisciplinary practice with genetics and immunology. The rapid flow of discovery of biological drugs during the last decade, availability of next-genome and whole-exome sequencing methods, and the outstanding boost in the rate of success of hematopoietic and solid organ transplantation are all affirmative to this notion. Thanks to molecular genetic methods, an increasing number of the newly introduced "autoinflammatory disorders" are being characterized, donors and recipients are being cross-matched using intricate genotype:phenotype cross matching, and immunotherapy for allergy benefits from state-of-the-art characterization of culprit epitopes in peptide scales. This book tries to strike a balance between cutting-edge science of immunology and clinical practice of pediatrics, through a series of meticulously chosen case discussions, presented by pediatric practitioners and immunology experts.

Pediatric Immunology Series is a three-volume book series and a collection of well-presented case discussions in pediatric medicine. Volume I, *Pediatric Allergy*, is focused on diagnosis and practice of allergy, asthma, atopy, and relevant disorders. Volume II, *Pediatric Immunology*, thoroughly addresses cases on primary immunodeficiency disorders; and finally, Volume III, *Pediatric Autoimmunity and Transplantation*, is a constellation of cases in autoimmune and rheumatologic disorders of childhood, secondary immunodeficiency conditions, and real cases with hematopoietic and solid organ transplantation.

Volume II of this series is a comprehensive guide to the essentials of diagnosis and practice of primary immunodeficiency disorders (PID). Covering all groups of PIDs, the book starts with Chaps. 2–24, and 25 on humoral immunodeficiency,

Chaps. 25–49, and 50 on combined immunodeficiency, Chaps. 51–65, and 66 on phagocyte defects, and Chaps. 67–74, and 75 on innate immunity defects. By this far in the book the reader has already gained a head start on four of the five classic types of PID, continued by Chaps. 114–121, and 122 presenting patients with complement system defects. Immune dysregulation disorders and autoinflammatory disorders are on the other facet of the coin of PID disorders and are presented in Chaps. 76–112, and 113, respectively. Chapters 123–146, and 147 comprise the final frame of this volume, with case-based discussions on a new and fast-growing domain of PIDs: PIDs associated with syndromic features.

The Pediatric Immunology Series is the result of a multinational collaboration of more than 350 scientists from more than 100 well-known universities/institutes worldwide. I would like to hereby acknowledge the expertise of all contributors, for their generous devotion of time and effort in preparing each of the chapters. I would like to extend my gratitude to Springer publication for providing me the opportunity to publish the book.

Hopeful I remain, that this book provides an exemplary touch to the fast-growing intersection of pediatric medicine and basic immunology, and a useful guide for pediatric practitioners worldwide.

Tehran, Iran Nima Rezaei

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Nima Rezaei

Abbreviations

4CmenB	4-Component meningococcal serogroup B vaccine
ACE	Angiotensin-converting enzyme
AD	Autosomal dominant
ADA	Adenosine deaminase
ADHD	Attention-deficit hyperactivity disorder
AD-HIES	Autosomal dominant hyper-IgE syndrome
AFP	Alpha-fetoprotein
AID	Activation-induced deaminase
AIDS	Acquired immunodeficiency syndrome
AIFEC	Autoinflammation with infantile enterocolitis
AIHA	Autoimmune hemolytic anemia
AIN	Autoimmune neutropenia
AIRE	Autoimmune regulator
AKI	Acute kidney injury
ALL	Acute lymphoblastic leukemia
ALPS	Autoimmune lymphoproliferative syndrome
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
Anti-CCP	Anti-cyclic citrullinated peptide
Anti-dsDNA	Anti-double-stranded DNA
APC	Antigen-presenting cells
APDS1	Activated phosphoinositide 3-kinase δ syndrome type 1
APDS2	Activated phosphoinositide 3-kinase δ syndrome type 2
APECED	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy
APGAR	Appearance, pulse, grimace, activity, and respiration
APS-1	Autoimmune polyendocrine syndrome type 1
AR	Autosomal recessive
AR-HIES	Autosomal recessive hyper-IgE syndrome
array CGH, aCGH	Microarray-based comparative genomic hybridization
A-T	Ataxia-telangiectasia

AT1R	Anti-angiotensin II type 1 receptor
ATG	Anti-thymocyte globulin
ATR	Ataxia-telangiectasia and Rad3 related
BCG	Bacillus Calmette–Guérin (BCG)
BD	Behçet's disease
BLNK	B cell linker protein
BMT	Bone marrow transplantation
BP	Blood pressure
bpm	Beats per minute
BSA	Body surface area
BTK	Bruton's tyrosine kinase
C1-INH	C1 esterase inhibitor
C3c	C3 convertase
c-ANCA	Cytosolic anti-neutrophil cytoplasmic antibodies
CARD9	Caspase recruitment domain family member 9
CAT	Cutaneous assessment tool
CBC	Complete blood count
CD	Cluster of differentiation
CD40L	CD40 ligand
CDC	Complement-dependent cytotoxicity
CDCA7	Cell division cycle-associated protein 7
CECR1	Cat eye syndrome chromosome region 1
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CGD	Chronic granulomatous disease
CHS	Chediak-Higashi syndrome
CID	Combined immunodeficiency
CINCA	Chronic infantile neurological and cutaneous articular syndrome
CK	Creatine kinase
CK-MB	Creatine kinase-MB
CLD	Chronic lung disease
CLR	Clarithromycin
CMC	Chronic mucocutaneous candidiasis
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
CNO	Chronic non-bacterial osteomyelitis
Con-A	Concanavalin A
CRMO	Chronic recurrent multifocal osteomyelitis
CRP	C-reactive protein
CS	Cogan's syndrome
CsA	Cyclosporine A
CSF	Cerebrospinal fluid
CSR	Class-switch recombination
CT	Computed tomography

CTL	Cytotoxic T lymphocytes
CVID	Common variable immune deficiency
CXCR4	CXC chemokine receptor 4
CXR	Chest X-ray
DADA2	Deficiency of adenosine deaminase type-2
DAT	Direct antibody test
DCLRE1C	DNA cross-link repair protein 1C
DDS	Deafness-dystonia-optic neuropathy syndrome
DHR	Dihydrorhodamine test
DIC	Dsseminated intravascular coagulation
DIF	Direct immunofluorescence
DIRA	Deficiency of interleukin-1 receptor antagonist
DNA	Deoxyribonucleic acid
DNT	Double negative T cells
DOCK8	Dedicator of cytokinesis 8
DSB	Double-strand breaks
dsDNA	Double-stranded DNA autoantibodies
DT	Diphteria and tetanus toxoids full strength
dT	Diphtheria-tetanus toxoids with reduced content of diphtheria
DtaP	Diphtheria-tetanus acellular pertussis vaccine
DTaP3	Diphtheria-tetanus-3-component acellular pertussis vaccine
DTaP5-IPV-Hib	Diphtheria-tetanus-3-component acellular pertussis-inactivated polio-haemophilus influenzae type b"
DTaP-IPV-HBV+Hib	Hexavalent diphteria-tetanus-acellular pertussis-inactivated polio-hepatitis B vaccine
EBV	Epstein-Barr virus
EDA	Anhidrotic ectodermal dysplasia
EDA-ID	Anhidrotic ectodermal dysplasia and immunodeficiency
EGPA	Eosinophilic granulomatosis with polyangiitis
ELANE	Neutrophil elastase
ELE	Erysipelas-like erythema
ELISA	Enzyme-linked immunosorbent assay
EMG	Electromyography
ENA	Anti-extractable nuclear antigens panel
ERK	Extracellular signal regulated kinases
ES	Evans syndrome
ESBL	Extended spectrum beta lactamase positive *E. coli*
ESID	European Society for Immunodeficiencies
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FADD	Fas-associated death domain
Fas	First apoptosis signal
FCAS	Familial cold autoimmune syndrome

FCAS4	Familial cold autoinflammatory syndrome 4
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FFP	Fresh frozen plasma
FHLH	Familial HLH
FHLH/FHL	Familial hemophagocytic lymphohistiocytosis
FIA	Flow injection analysis
FIM	Fulminant infectious mononucleosis
FISH	Fluorescence in situ hybridization
Flt3L	Fms-like tyrosine kinase 3 ligand
FMF	Familial Mediterranean fever
FOXP3	Forkhead box protein 3
FPD	Familial platelet disorder
FPD/AML	FPD with predisposition to AML
FTT	Failure to thrive
G6PC3	Glucose-6-phosphatase catalytic subunit 3
G6PD	Glucose-6-phosphatase deficiency
GATA2	GATA-binding factor 2
G-CSF	Granulocyte colony stimulating factor
GI	Gastrointestinal
GLILD	Granulomatous-lymphocytic interstitial lung disease
GM-CSF	Granulocyte, monocyte colony stimulating factor
GOF	Gain-of-function
GPA	Granulomatosis with polyangiitis
GPCR	G protein-coupled receptor
GS	Griscelli syndrome
GS2	Griscelli type 2
GU	Genitourinary
GVHD	Graft versus host disease
HAE	Hereditary angioedema
HAX1	HS-1-associated protein X-1
Hb	Hemoglobin
HBV	Hepatitis B virus
HCT	Hematopoietic cell transplantation
HCV	Hepatitis C virus
HDM	House dust mite
HELLS	Helicase, lymphoid-specific
Hib	Haemophilus influenza type b vaccine
HIDS	Hyper-IgD syndrome
HIES	Hyper-IgE syndrome
HIGM	Hyper-IgM syndrome
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigens
HLA-B27	Human leukocyte antigen-B27
HLH	Hemophagocytic lymphohistiocytosis

HPS	Hermansky-Pudlak syndrome
HPS2	Hermansky-Pudlak type 2
HPV	Human papilloma virus
HRCT	High resolution computed tomography
HSC	Hematopoietic stems cells
HSCT	Hematopoietic stem cell transplantation
HSE	Herpes simplex encephalitis
HSP	Henoch-Schönlein purpura
HSV	Herpes simplex virus
HUS	Hemolytic uremic syndrome
IBD	Inflammatory bowel disease
ICF	Immunodeficiency with centromeric instability and facial anomalies
ICU	Intensive care unit
IDR score	Immunodeficiency-related score
IFI	Invasive fungal infection
IFN	Interferon
IFN-γ	Interferon-γ
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IGHM	mu variant of heavy chain of immunoglobulins
IgM	Immunoglobulin M
IGRA	Interferon-γ release assays
IIV	Inactivated influenza vaccine
IkB	Inhibitor of NF-κB
IL	Interleukin
IL-12	Interleukin-12
ILD	Interstitial lung disease
IM	Intramuscular
IMIg	Intramuscular injections of immunoglobulin
Inf	Influenza vaccine
INH	Isoniazide
INO80	DNA helicase INO80
IP	Incontinentia pigmenti
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome
IPV	Inactivated polio vaccine
IRF-3	Interferon regulatory factor 3
ITK	IL-2 inducible tyrosine/T-cell kinase
ITP	Idiopathic thrombocytopenic purpura
IV	Intravenous
IVIG	Intravenous immunoglobulin
JAK	Janus kinase
JIA	Juvenile idiopathic arthritis

JRA	Juvenile rheumatoid arthritis
KD	Kawasaki disease
kD	Kilodalton
Kg	Kilogram
KID	Keratitis-ichthyosis-deafness
KREC	Kappa-deleting element recombination circle
KS	Kaposi sarcoma
LAD	Leukocyte adhesion deficiency
LAIV	Live attenuated influenza vaccine
LDH	Lactate dehydrogenase
LE	Lupus erythematosus
LEKTI	Kazal-type related inhibitor
LFT	Liver function test
LOF	Loss-of-function
LRBA	LPS-responsive beige-like anchor protein
LRD	Living related donor
LTRAs	Leukotriene receptor antagonists
LTT	Lymphocyte transformation test
LYST	Lysosome trafficking regulator protein
MAC	Membrane attack complex
MAIT	Mucosal associated invariant T cell
MAPK	Mitogen activated protein kinases
MAS	Macrophage activation syndrome
MASP	Mannose-binding lectin–associated serine proteases
MBL	Mannose-binding lectin
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MDS/AML	Myelodysplastic syndrome/acute myeloid leukemia
Men	Meningococcal vaccine
MenCV4	4-Valent (A,C,W-135,Y) conjugate meningococcal vaccine
MFI	Mean fluorescence intensity
MHC	Major histocompatibility complex
MKD	Mevalonate kinase deficiency
MLPA	Multiplex ligation PCR amplification
MMA	Methyl malonic acid
MMF	Mycophenolate mofetil
mmHg	Millimetre of mercury
MMP8 and MMP9	Matrix metalloproteinase 8 and 9
MMR	Measles-mumps-rubella
MOTT	Mycobacteria other than tuberculosis
MPO	Myeloperoxidase
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSH6	mutS homolog 6

MSMD	Mendelian susceptibility to mycobacterial disease
mTOR	Mammalian target of rapamycin
MTS	Mohr-Tranebjaerg syndrome
MUD	Matched unrelated donors
MVA	Mevalonic aciduria
NADPH	Nicotinamide adenine dinucleotide phosphate
NAT	Nucleic acid testing
NBS	Nijmegen breakage syndrome
NBT	Nitroblue tetrazolium
NEC	Necrotizing enterocolitis
NEMO	NF-kB essential modulator
NF-kB	Nuclear factor kappa B
NGS	Next-generation sequencing
NIH	National Institute of Health
NK cell	Natural killer cell
NKT cells	Natural killer T cells
NLRs	NOD-like receptor
NOMID	Neonatal-onset multisystem inflammatory disease
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSDHL	NAD(P) dependent steroid dehydrogenase-like
NTM	Non-tuberculous mycobacteria
OCA	Oculocutaneous albinism
OL-EDA-ID	Osteopetrosis, lymphedema and hemangiomas
OPV	Oral polio vaccine
OS	Omenn's syndrome
PACNS	Primary angiitis of the central nervous system
PAMPs and DAMPs	Pathogen- and damage-associated molecular patterns
PAN	Polyarteritis nodosa
p-ANCA	Perinuclear anti-neutrophil cytoplasmic antibodies
PAP	Progressive pulmonary alveolar proteinosis
PASLI	p110δ-activating mutations causing senescent T cells, lymphadenopathy, and immunodeficiency
PBSCT	Peripheral blood stem cell transplantation
PCP	*Pneumocystis jirovecii* pneumonia
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
PEG-ADA	PEGylated ADA
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis
PFT	Pulmonary function test
PG	Pyoderma gangrenosum
PGD	Preimplantation genetic diagnosis
PHA	Phytohemagglutinin
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
PI3KCD	PI3K catalytic subunit delta isoform

PICU	Pediatric intensive care unit
PID	Primary immunodeficiency disorder
PMA	Phorbol 12-myristate 13-acetate
PMS2	Post-meiotic segregation increased 2
PO	Per os/oral
PPD	Para-phenylenediamine
PPSV	Pneumococcal polysaccharide vaccine
PRRs	Pattern recognition receptors
RA	Rheumatoid arthritis
RBC	Red blood cell
RF	Rheumatoid factor
RIF	Rifabutin
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus
RSV-A	Respiratory syncytial virus A
RTE	Recent thymic emigrants
RV	Rotavirus vaccine
SAA	Serum amyloid A
SAD	Specific antibody deficiency
SAP	SLAM-associated protein
SCID	Severe combined immunodeficiency
SCIG	Subcutaneous immunoglobulin
SDF1	Stromal cell-derived factor 1
SDP	Solvent detergent plasma
SERPING1	Serpin family G member 1
SI	Stimulation index
SIGAD	Selective IgA deficiency
sIL-2R/sCD25	Soluble interleukin-2 receptor
sIL-2Rα	Soluble IL-2 receptor alpha
SJIA	Systemic juvenile idiopathic arthritis
SLE	Systemic lupus erythematosus
SMA-II	Spinal muscular atrophy type 2
SPINK5	Serine protease inhibitor, Kazal type 5
SSSS	Staphylococcal scalded skin syndrome
STAT3	Signal transducer and activator of transcription 3
STR	Short tandem repeat
SURFS	Systemic undifferentiated recurring fever syndrome
T	Tetanus toxoid
TACI	Transmembrane activator and CAML interactor
TCE	T cell epitopes
TCR	T cell receptor
TCRV	T cell receptor variable chain
TCRαβ	Alpha/beta T cell receptor
TCRγδ	Gamma/delta T cell receptor
TCS	Topical corticosteroids
TG	Triglyceride

Th1	T helper 1
Th17	T helper 17
Th2	T helper 2
THI	Transient hypogammaglobulinemia of infancy
TIA	Transient ischemic attack
TIV	Trivalent influenza vaccine
TLRs	Toll-like receptors
TNFRSF13B	Tumor necrosis factor receptor superfamily member 13B
TnT	Troponin T
TORCH	Toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes
TPN	Total parenteral nutrition
TRAF3	TNF receptor-associated factor 3
TRAPS	TNF receptor-associated periodic syndrome
TREC	T cell receptor excision circles
TRIF	TIR domain-containing adaptor inducing IFN-β
TSH	Thyroid stimulating hormone
TYK2	Tyrosine kinase 2
UA	Urinary analysis
UC	Ulcerative colitis
UNC-SAID or uSAID	Unclassified systemic autoinflammatory disease
UNG	Uracil-DNA glycosylase
UP	Urticaria pigmentosa
URI	Upper respiratory tract infection
V(D)J	Variable, diversity, joining
Var	Varicella vaccine
VUS	Variants of unclear significance
VZIG	Varicella-zoster immune globulin
VZV	Varicella zoster virus
WAS	Wiskott-Aldrich syndrome
WASp	Wiskott-Aldrich syndrome protein
WBC	White blood cell
WES	Whole exome sequencing
WGS	Whole genome sequencing
WHIM	Warts, hypogammaglobulinemia, infections and myelokathexis
XLA	X-linked agammaglobulinemia
XL-MDS	X-linked myelodysplasia
XLN	X-linked neutropenia
XLP	X-linked lymphoproliferative disease
XLP1	X-linked proliferative disorder type I
XLT	X-linked thrombocytopenia
ZBTB24	Zinc-finger and BTB domain-containing 24 gene
αβDNT	Alpha/beta double negative T cells
γc	Common gamma chain
γδDNT	Gamma/delta double negative T cells

Contents