Pediatric Autoimmunity and Transplantation

A Case-Based Collection with MCQs, Volume 3

Farzaneh Rahmani
Nima Rezaei
Editors

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Preface

Immunology has found its way well into the practice of pediatrics. Years after publication of the first pediatric textbooks, footprints 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 phenotypic 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 III of this series is the final frame and a diverse constellation of case discussions, from autoimmunity and pediatric rheumatologic disorders to immunohematology and transplantation, to autoimmune skin disorders, and finally to

secondary conditions causing immunodeficiency. Chapters 1–19 and 82–83 showcase case discussions with childhood-onset rheumatologic disorders, adult rheumatic disorders with pediatric onset, and disorders of potential autoimmune origin such as idiopathic thrombocytopenia. Cutaneous immune-related conditions and cutaneous manifestations of systemic disorders are a must know for every pediatric practitioner and are hence addressed in Chaps. 57–81. Secondary conditions that mimic presentations of primary immunodeficiency disorders comprise heterogeneous entities that are the main focus of the few cases presented in Chaps. 20–34. Finally, the fine art of recipient, i.e., donor matching in hematopoietic stem cell and solid organ transplantation, is skillfully discussed in Chaps. 35–56 of this volume.

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 also like to extend my gratitude to the Springer publication for providing me the opportunity to publish the book.

We are hopeful that this book provides an exemplary touch to the fast-growing intersection of pediatrics and immunology, and a useful guide for pediatric practitioners worldwide.

Tehran, Iran Farzaneh Rahmani
Tehran, Iran Nima Rezaei

Abbreviations

3TC	Lamivudine
4CmenB	4-Component meningococcal serogroup B vaccine
AA	Alopecia areata
ABC	Abacavir
ACE	Angiotensin-converting enzyme
ACLE	Acute cutaneous lupus erythematosus
ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
AD	Autosomal dominant
ADCC	Antibody-dependent cellular cytotoxicity
AECA	Anti-endothelial cells
AGEP	Acute generalized exanthematous pustulosis
aGVHD	Acute GVHD
AIDS	Acquired immunodeficiency syndrome
AIHA	Autoimmune hemolytic anemia
ALDY	Annular lichenoid dermatitis of youth
ALL	Acute lymphoblastic leukemia
ALPS	Autoimmune lymphoproliferative syndrome
AML	Acute myeloid leukemia
AMR	Antibody-mediated rejection
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
ANCA	Anti-neutrophil cytoplasmic antibodies
Anti-CCP	Anti-cyclic citrullinated peptide
Anti-dsDNA	Anti-double-stranded DNA
Anti-EMA	Anti-endomysial antibodies
Anti-ENA	Anti-extractable nuclear antigens
Anti-eTG	Anti-epidermal transglutaminase
Anti-MDA5	Anti-melanoma differentiation-associated gene 5 antibodies
Anti-TG	Anti-thyroglobulin

Anti-TPO	Antithyroid peroxidase
Anti-tTG	Tissue transglutaminase antibody
APC	Antigen-presenting cells
APECED	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
APGAR	Appearance, pulse, grimace, activity, and respiration
APS-1	Autoimmune polyendocrine syndrome type 1
AR	Autosomal recessive
ARF	Acute rheumatic fever
ART	Anti-retroviral therapy
A-T	Ataxia-telangiectasia
AT1R	Anti-angiotensin II type 1 receptor
ATG	Anti-thymocyte globulin
ATN	Acute tubular necrosis
ATR	Ataxia-telangiectasia and Rad3 related
AZT	Zidovudine
BB-UVB	Broadband ultraviolet B
BCG	Bacillus Calmette-Guérin
BD	Behçet's disease
BMT	Bone marrow transplantation
BMZ	Basement membrane zone
BNP	Brain natriuretic peptide
BP	Blood pressure
BPAg2	Bullous pemphigoid antigen
bpm	Beats per minute
BSA	Body surface area
BSLE	Bullous SLE
CAJDM	Clinically amyopathic juvenile dermatomyositis
c-ANCA	Cytosolic anti-neutrophil cytoplasmic antibodies
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CAT	Cutaneous assessment tool
CBC	Complete blood count
CBDC	Chronic bullous disease of childhood
CBT	Cord blood transplantation
CCLE	Chronic cutaneous lupus erythematosus
CD	Cluster of differentiation
CDC	Complement-dependent cytotoxicity
CGD	Chronic granulomatous disease
CHAQ	Childhood Health Assessment Questionnaire
CHB	Congenital heart block
CHS	Chediak-Higashi syndrome
CID	Combined immunodeficiency
CLAD	Childhood linear IgA disease
CM	Cutaneous mastocytosis
CMAS	Childhood Myositis Assessment Scale

CMC	Chronic mucocutaneous candidiasis
CMG2	Capillary morphogenesis gene 2
CML	Chronic myeloid leukemia
CMP	Cartilage matrix protein
cMPO	Myeloperoxidase deficiency
CMV	Cytomegalovirus
CNIs	Calcineurin inhibitors
CRP	C-reactive protein
CsA	Cyclosporine A
CSF	Cerebrospinal fluid
CT	Computed tomography
CTL	Cytotoxic T-lymphocytes
CVID	Common variable immune deficiency
CWD	Common and well-documented alleles
CXCR4	CXC chemokine receptor 4
CXR	Chest X-ray
DAT	Direct antiglobulin test
DCM	Diffuse cutaneous mastocytosis
DFA	Direct fluorescent antibody
DGP	Gliadin-derived peptides
DH	Dermatitis herpetiformis
DIF	Direct immunofluorescence
DIHS	Drug-induced hypersensitivity syndrome
DIRA	Deficiency of interleukin-1 receptor antagonist
DLE	Discoid lupus erythematosus
DLI	Donor lymphocyte infusion
DMARDs	Disease-modifying antirheumatic drugs
DNA	Deoxyribonucleic acid
DOCK8	Dedicator of cytokinesis 8
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSA	Donor-specific antibodies
dsDNA	Double-stranded DNA antibodies
Dsg	Desmoglein
DT	Diphtheria 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 diphtheria-tetanus-acellular pertussis-inactivated polio-hepatitis B vaccine
E	Ethambutol
EB	Epidermolysis bullosa

EBV	Epstein-Barr virus
ECDS	En coup de sabre
ECP	Extracorporeal photopheresis
EFE	Endocardial fibroelastosis
ELE	Erysipelas-like erythema
ELISA	Enzyme-linked immunosorbent assay
EM	Erythema multiforme
EmA	Anti-endomysium
EMG	Electromyography
EMM	Erythema multiforme major
ERK	Extracellular signal-regulated kinases
ES	Evans syndrome
ESID	European Society for Immunodeficiencies
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
ETaR	Anti-endothelin-1 type A receptor
EULAR	European League Against Rheumatism
FACS	Fluorescence-activated cell sorting
Fas	First apoptosis signal
FCXM	Flow cytometric crossmatch
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
FHLH/FHL	Familial hemophagocytic lymphohistiocytosis
FIA	Flow injection analysis
FiO2	Fraction of inspired oxygen
FISH	Fluorescence in-situ hybridization
FLAMSA	Fludarabine, cytarabine, amsacrine
Flt3L	FMS-like tyrosine kinase 3 ligand
FOXP3	Forkhead box protein 3
FS-MPGN	Focal segmental membranoproliferative glomerulonephritis
FTT	Failure to thrive
FUMHD	Febrile ulceronecrotic Mucha-Habermann disease
G6PD	Glucose-6-phosphatase deficiency
GATA2	GATA-binding factor 2
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GPCR	G protein-coupled receptor
GU	Genitourinary
GVHD	Graft versus host disease
GvL	Graft-versus-leukemia
H	Isoniazid
HAART	Highly active anti-retroviral therapy
HAV	Hepatitis A vaccine

Hb	Hemoglobin
HBV	Hepatitis B virus
HCT	Hematopoietic cell transplantation
HCV	Hepatitis C virus
HFS	Hyaline fibromatosis syndrome
Hib	Haemophilus influenza type b vaccine
HiDAC	High-dose cytarabine
HIGM	Hyper-IgM syndrome
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigens
HLA-B27	Human leukocyte antigen-B27
HLH	Hemophagocytic lymphohistiocytosis
HNIG	Human normal immunoglobulin
HPA	Hereditary papulotranslucent acrokeratoderma
HPLC	High-performance liquid chromatography
HPS	Hermansky-Pudlak syndrome
HPS2	Hermansky-Pudlak type 2
HPV	Human papilloma virus
HRCT	High-resolution computed tomography
HSC	Hematopoietic stem cells
HSCT	Hematopoietic stem cell transplantation
HSE	Herpes simplex encephalitis
HSP	Henoch-Schönlein purpura
HSV	Herpes simplex virus
HUS	Hemolytic uremic syndrome
HUV	Hypocomplementemic urticarial vasculitis
HUVS	Hypocomplementemic urticarial vasculitis syndrome
IA	Idiopathic anaphylaxis
IBD	Inflammatory bowel disease
ICU	Intensive care unit
IFN	Interferon
IFN-γ	Interferon-γ
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IIF	Indirect immunofluorescence
IIV	Inactivated influenza vaccine
IL	Interleukin
IL-12	Interleukin-12
ILAR	International League Against Rheumatism
ILD	Interstitial lung disease
IM	Intramuscular
IMA	Inherited maternal antigens/haplotype

IMGT	International ImMunoGeneTics information
Inf	Influenza vaccine
INH	Isoniazid
IPA	Inherited paternal antigens/haplotype
IPSS	International Prognostic Scoring System
IPV	Inactivated polio vaccine
ITK	IL-2 inducible tyrosine/T-cell kinase
ITP	Idiopathic thrombocytopenic purpura
IV	Intravenous
IVIG	Intravenous immunoglobulin
JDM	Juvenile dermatomyositis
JIA	Juvenile idiopathic arthritis
JPsA	Juvenile psoriatic arthritis
kD	Kilodalton
KD	Kawasaki disease
kg	Kilogram
KS	Kaposi sarcoma
LABD	Linear IgA bullous disease
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
LP	Lumbar puncture
LPV	Lopinavir
LQTS	Long QT syndrome
LRD	Living-related donor
LSc	Localized scleroderma
LSS	Lymphocyte steroid sensitivity
LTs	Leukotrienes
LTT	Lymphocyte transformation test
LYST	Lysosomal trafficking regulator protein
MAC	Membrane attack complex
MAPK	Mitogen-activated protein kinases
MAS	Macrophage activation syndrome
MBEH	Monobenzyl ether of hydroquinone
MCV	Mean corpuscular volume
MDR-AML	Myelodysplasia-related-AML
MDS	Myelodysplastic syndrome
MDS/AML	Myelodysplastic syndrome/acute myeloid leukemia
Men	Meningococcal vaccine
MenCV4	4-Valent (A,C,W-135,Y) conjugate meningococcal vaccine

MF	Mycosis fungoides
MFI	Mean fluorescence intensity
MIS	Mastocytosis in the skin
MIV	Marginal inflammatory vitiligo
MMF	Mycophenolate mofetil
mmHg	Millimeter of mercury
MMR	Measles-mumps-rubella
MODS	Multi-organ dysfunction syndrome
MOTT	Mycobacteria other than tuberculosis
MPO	Myeloperoxidase
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSA	Myositis-specific autoantibodies
Msc/MSCs	Mesenchymal stem cells
MSH6	mutS homolog 6
MSMD	Mendelian susceptibility to mycobacterial disease
mTOR	Mechanistic target of rapamycin
MUD	Matched unrelated donors
WHIM syndrome	Warts, hypogammaglobulinemia, infections, and myelokathexis
NASH	Nonalcoholic steatohepatitis
NAT	Nucleic acid testing
NBT	Nitroblue tetrazolium
NB-UVB	Narrowband ultraviolet B
NEC	Necrotizing enterocolitis
NEMO	NF-kB essential modulator
NIH	National Institutes of Health
NIMA	Non-inherited maternal HLA antigen/haplotype
NIPA	Non-inherited paternal HLA antigen/haplotype
NK cell	Natural killer cell
NKT cells	Natural killer T cells
NLE	Neonatal lupus erythematosus
NLRs	NOD-like receptor
NMDP	National Marrow Donor Program
NOTA	National Organ Transplantation Act
NPV	Nevirapine
NRTI	Nucleoside reverse transcriptase inhibitors
NSAIDs	Nonsteroidal anti-inflammatory drugs
NTM	Non-tuberculous mycobacteria
NT-proBNP	N-terminal proBNP
NUV	Normocomplementemic urticarial vasculitis
OCA	Oculocutaneous albinism
OLT	Orthotopic liver transplantation
OPO	Originating organ procurement organization
OPV	Oral polio vaccine

OS	Omenn's syndrome
PAF	Platelet-activating factor
PAN	Polyarteritis nodosa
p-ANCA	Perinuclear anti-neutrophil cytoplasmic antibodies
PAP	Pulmonary alveolar proteinosis
PAPA	Pyogenic sterile arthritis, pyoderma gangrenosum, and acne
PBSCT	Peripheral blood stem cell transplantation
PCP	*Pneumocystis jirovecii* pneumonia
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
PF	Pemphigus foliaceus
PG	Pyoderma gangrenosum
PKCδ	Protein kinase C-delta
PL	Pityriasis lichenoides
PLC	Pityriasis lichenoides chronica
PLE	Protein-losing enteropathy
PLEVA	Pityriasis lichenoides et varioliformis acuta
PMA	Phorbol 12-myristate 13-acetate
PO	Per os/oral
PPSV	Pneumococcal polysaccharide vaccine
PRCSG	Pediatric Rheumatology Collaborative Study Group
PRI	Potential repigmentation index
PRINTO	Paediatric Rheumatology International Trials Organisation
PRP	Pityriasis rubra pilaris
PRS	Parry-Romberg syndrome
PUVA	Psoralen and ultraviolet A
PV	Pemphigus vulgaris
R	Rifampicin
RA	Rheumatoid arthritis
RAST	Radioallergosorbent test
RBC	Red blood cell
RF	Rheumatoid factor
RIC	Reduced-intensity conditioning
ROS	Reactive oxygen species
RV	Rotavirus vaccine
SAA	Serum amyloid A
SAB	Single-antigen antibody
SAM	Severe acute malnutrition
SBEG	Suction blister epidermal grafts
SBS	Short bowel syndrome
SCID	Severe combined immunodeficiency
Scl-70	Anti-toposiomerase I
SCLE	Subacute cutaneous lupus erythematosus
sIL-2R or sCD25	Soluble interleukin-2 receptor

sIL-2Rα	Soluble IL-2 receptor alpha
SIRS	Systemic inflammatory response syndrome
SJIA	Systemic juvenile idiopathic arthritis
SJS	Stevens-Johnson syndrome
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
SM	Systemic mastocytosis
SMA II	Spinal muscular atrophy type 2
SoJIA	Systemic-onset juvenile idiopathic arthritis
SPD	Subcorneal pustular dermatosis
SPINK5	Serine protease inhibitor, Kazal type 5
SPT	Skin prick test
SSc	Systemic sclerosis
SSLR	Serum sickness-like reaction
SSSS	Staphylococcal scalded skin syndrome
STEC	Shiga toxin-producing strains of *Escherichia coli*
STR	Short tandem repeat
T	Tetanus toxoid
TACO	Transfusion associated volume overload
TA-TMA	Transplant-associated thrombotic microangiopathy
TBI	Total body irradiation
TCE	T-cell epitopes
TCR	T-cell receptor
TCRαβ	Alpha/beta T-cell receptor
TCRγδ	Gamma/delta T-cell receptor
Tdpa	Tetanus-diphtheria-acellular pertussis with reduced content of diphtheria an pertussis antigens
TEN	Toxic epidermal necrolysis
TG	Triglyceride
Th1	T helper 1
Th17	T helper 17
Th2	T helper 2
TIA	Transient ischemic attack
TIV	Trivalent influenza vaccine
TKI	Tyrosine kinase inhibitor
TMA	Thrombotic microangiopathy
TORCH	Toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes
TPMT	Thiopurine *S*-methyltransferase
TPN	Total parenteral nutrition
TPO	Thyroid peroxidase
TRALI	Transfusion-associated lung injury
TREC	T-cell receptor excision circles
UA	Urinary analysis
UC	Ulcerative colitis

UCB	Umbilical cord blood
UNOS	United Network for Organ Sharing
UP	Urticaria pigmentosa
URI	Upper respiratory tract infection
UV	Ultraviolet
UVA-1	Ultraviolet-A1
V(D)J	Variable, diversity, joining
Var	Varicella vaccine
VASI	Vitiligo Area Severity Index
VETF	Vitiligo European Task Force
VIDA	Vitiligo Disease Activity Score
VOD	Veno-occlusive disease
VZIG	Varicella-zoster immune globulin
VZV	Varicella zoster virus
WAS	Wiskott-Aldrich syndrome
WBC	White blood cell
WES	Whole-exome sequencing
XLP	X-linked lymphoproliferative disease
XLP1	X-linked proliferative disorder type I
Z	Pyrazinamide

Contents

1 Introduction to Autoimmunity, Secondary Immunodeficiency, and Transplantation 1
Terry Harville, Soumya Pandey, Piyush Kumar, Marco Antonio Yamazaki-Nakashimada, Larry Ngek Tangie, Farzaneh Rahmani, and Nima Rezaei

2 Fever and Cervical Lymphadenopathy 17
Berenise Gamez-Gonzalez and Marco Antonio Yamazaki-Nakashimada

3 Prolonged Refractory High Fever 25
Ross Petty and Farhad Salehzadeh

4 Pain in Both Knees 31
Ross Petty and Farhad Salehzadeh

5 Challenging Pain in Knee and Ankle 35
Peter Jandus

6 Fever and Urticarial Rash 43
Mojgan Kianiamin

7 Knee Swelling and Rash 47
Ross Petty and Farhad Salehzadeh

8 Malaise, Weight Loss and Intermittent Fever 53
Ross Petty, Farhad Salehzadeh, and Marco Antonio Yamazaki-Nakashimada

9 Anemia, Microhematuria and Proteinuria 57
Živanović S. Snežana, Ivana Djuric-Filipovic, and Zorica Živković

10 Fever, Anasarca and Arthralgia 61
Erika Sifuentes-Rodriguez, Francisco Rivas-Larrauri, and Marco Antonio Yamazaki-Nakashimada

11 Bradycardia in a Neonate 65
Ross Petty and Farhad Salehzadeh

12 Annular Rash in a Neonate 71
Yan Ling Kong and Emily Yiping Gan

13 Itchy Facial Rash 77
Yan Ling Kong and Emily Yiping Gan

14 Muscle Weakness and Fever 85
Piyush Kumar and Anupam Das

15 Pruritic Erythematous Rashes on Face and Eyelids 91
Selcen Kundak and Malik Ergin

16 Edema of Hands and Hypopigmented Lesions on Her Neck and Cheeks 97
Ana Luisa Rodríguez-Lozano and Marco Yamazaki-Nakashimada

17 Asymptomatic Atrophic Plaque on the Face 103
Yan Ling Kong and Emily Yiping Gan

18 Morbiliform Rash and Fever 109
Luciana Paula Samorano, João Avancini, and Marcella Soares Pincelli

19 Recurrent Interstitial Keratitis and Audiovestibular Dysfunction 115
Kristina A. Dzhuma, Oleg B. Iaremenko, and Maksym I. Situkho

20 Breathlessness and Weight Loss 121
Sowmya Shashidhara, H. Koushik, and Sangita Trivedi

21 Neck Swelling and Fever 127
Sowmya Shashidhara, H. Koushik, and Sangita Trivedi

22 Puffy Face and Abdominal Distension 133
Sowmya Shashidhara, H. Koushik, and Sangita Trivedi

23 Hematuria and Abdominal Mass 139
Sowmya Shashidhara, H. Koushik, and Sangita Trivedi

24 Pitting Edema and Desquamation 143
Sowmya Shashidhara, H. Koushik, and Sangita Trivedi

25 Fever and Cutaneous Nodules 149
Sowmya Shashidhara, H. Koushik, and Sangita Trivedi

26 Neck Stiffness and Fever 153
Tangie Ngek Larry and Derrick Tembi Efie

27 Rash and Generalized Body Pains 157
Tangie Ngek Larry and Derrick Tembi Efie

28 Positive HIV and Violet Macular Rash 161
Tangie Ngek Larry and Derrick Tembi Efie

29 Weight Loss and Tuberculin Skin Test Anergy 165
Léila Dangou, Medeton Grâce Hounkpe, Josephiel Fortunato, and Crescent Darius Cossou-Gbeto

30 Edema on Lower Limbs 169
Medeton Grâce Hounkpe, Léila Dangou, Josephiel Fortunato, and Crescent Darius Cossou-Gbeto

31 Asthenia and Fatigue 173
Dominique M. A. Bullens and Isabelle Meyts

32 Infections, Whitish Skin Papules and Subcutaneous Nodules 179
Delara Babaei

33 Recurrent Pneumonia and History of Transplantation 185
Sonia de Arriba-Méndez, Eva Macías, and Ignacio Dávila

34 Painful Skin Nodules, Prolonged Fever and Cervical Lymphadenopathy 189
Michelle N. G. Ying, Emily Yiping Gan, and Jean Aan Mark Koh

35 Malaise, Laryngitis and Fever 197
Claus-Philipp Maier and Dominik Schneidawind

36 Acute Myeloid Leukemia Requiring Hematopoietic Stem Cell Transplantation 203
Soumya Pandey and Terry Harville

37 Discrepant Cytomegalovirus Serology Between Donor and Recipient in Hematopoietic Stem Cell Transplantation 207
Soumya Pandey and Terry Harville

38 Suspected Immunodeficiency 211
Soumya Pandey and Terry Harville

39 Linkage Disequilibrium Between HLA Alleles in Hematopoietic Stem Cell Transplantation 217
Soumya Pandey and Terry Harville

40 T-Lymphoblastic Lymphoma 223
Soumya Pandey and Terry Harville

41 No Lymphocytes in an Infant 229
Beatriz Morillo-Gutierrez and Mary Slatter

42 DOCK8 Deficiency and No Matched Donor 237
Beatriz Morillo-Gutierrez and Mary Slatter

43 Diarrhea Post-HSCT 241
Beatriz Morillo-Gutierrez and Mary Slatter

44 Follow-Up of a Severe Combined Immunodeficiency, Who Received Bone-Marrow Transplantation Four Decades Ago 247
Romina Dieli-Crimi and Teresa Español

45 Nonalcoholic Steatohepatitis Referred for Liver Transplantation . . . 251
Laura Cooling

46 Acute Respiratory Distress During Stem Cell Infusion 255
Laura Cooling

47 Acute Dyspnea After Platelet Transfusion 259
Laura Cooling

48 Requiring Immunization After Rescue Autologous HSCT 265
Darko Richter

49 Fever and Abdominal Pain 273
Esraa M. Eloseily and Randy Q. Cron

50 Prolonged Fever, Rash and Mucosal Bleeding 281
Beata Derfalvi

51 Recurrent Infections, Diarrhea and Hypereosinophilia 289
Haskologlu Sule, Islamoglu Candan, and Ikinciogullari Aydan

52 Liver Transplantation Who Developed Pancytopenia Post-transplantation 295
Soumya Pandey and Terry Harville

53 Kidney Transplant Candidate Showing Presence of Pre-formed Donor-Specific Antibodies Against a Prospective Living Donor 305
Soumya Pandey and Terry Harville

54 Heart Transplant Candidate Who Required Extra-Corporal Membrane Oxygenation (ECMO) 311
Soumya Pandey and Terry Harville

55 Acute Antibody-Mediated Rejection of Transplantation with Negative Prospective Crossmatch Results 319
Soumya Pandey and Terry Harville

56 Kidney Transplantation in a Patient with End Stage Renal Disease (ESRD) Secondary to Focal Segmental Glomerulosclerosis 325
Soumya Pandey and Terry Harville

57 Itchy Violaceous Plaques 329
Yan Ling Kong and Emily Yiping Gan

58 Photosensitivity and Bullous Lesions 337
Ashi and Piyush Kumar

59 Recurrent Bullous Lesions 345
Santoshdev P. Rathod and Piyush Kumar

60 Refractory Blisters and Erosions 349
Ziying Vanessa Lim and Emily Yiping Gan

61 Annular Blisters and Erosions 357
Soner Uzun and Aslı Bilgic-Temel

62 Vesicular Pruriginous Lesions 363
Dario Didona and Biagio Didona

63 Widespread Vesiculobullous Rash 369
Soner Uzun and Aslı Bilgic-Temel

64 Itchy Skin Rashes 375
Marzieh Tavakol

65 Blisters on Back and Upper Extremities 381
Gulsen Akoglu

66 Itchy Blisters 387
Yan Ling Kong and Emily Yiping Gan

67 Sudden Onset Grouped Blisters 393
Soner Uzun and Aslı Bilgic-Temel

68 Pruritic Blisters 399
Anupam Das and Piyush Kumar

69 Widespread Depigmented and Hypopigmented Patches 403
Piyush Kumar and Sunil K. Kothiwala

70 Whitish Patches 409
Gulsen Akoglu

71 Hyperpigmented Patches 415
Yan Ling Kong and Emily Yiping Gan

72 Outbreaks of Erythematous and Necrotic Papules with Hemorrhagic Crusts 421
Selcen Kundak and Malik Ergin

73 Persistent, Annular Urticarial Plaque 427
Selcen Kundak and Malik Ergin

74 Yellow, Reddish Brown Skin Lesions 433
Alireza Shafiei

75 Erythroderma 435
Wojciech Baran and Jacek Szepietowski

76 Erythematous Scaly Plaques 439
Sunil K. Kothiwala and Piyush Kumar

77 Multiple Circinate, Sterile, Flaccid, Relapsing Pustules 445
Selcen Kundak and Malik Ergin

78 Purpuric Macules and Oral Erosions 451
Dipak Kr. Agarwalla and Piyush Kumar

79 Diffuse Skin Rash and Mucosal Lesions 459
Marzieh Tavakol

80 Painful Facial Ulceration 465
Dario Didona and Biagio Didona

81 Patchy Hair Loss 469
Anupam Das and Piyush Kumar

82 Concerning Weight Loss Over Three Weeks 475
Farzaneh Rahmani and Nima Rezaei

83 Toddler with Bruising on Knees 479
Farzaneh Rahmani and Nima Rezaei

Index 483

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Chapter 1
Introduction to Autoimmunity, Secondary Immunodeficiency, and Transplantation

Terry Harville, Soumya Pandey, Piyush Kumar, Marco Antonio Yamazaki-Nakashimada, Larry Ngek Tangie, Farzaneh Rahmani, and Nima Rezaei

This book is a constellation of case discussions on pediatric autoimmune disorders, rheumatological diseases, secondary immunodeficiency disorders, and case discussions on hematopoietic stem cell and solid organ transplantations. The following is an overview and head start of the content related to each topic.

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Human immune system is trained to recognize self from non-self-tissue. Adaptive or pathologic changes in self-antigens, acquired functions in the immune system or lack of proper initial training to the immune system, can all result in **autoimmunity**. Clinical manifestations depend on the organ(s) affected, which in turn depends on nature and type of autoimmunity reaction, autoantibodies and autoreactive T cells.

Pediatric **rheumatologic disorders** are good examples of autoimmune disease in childhood that bear substantial health burden considering the high prevalence of systemic manifestations and the more severe course in this age group. The hallmark pathology of rheumatological disorders is "inflammatory response against self-antigens", the same as other autoimmune disorders. Unfortunately, chronicity might leave a full picture of the disease only to be revealed during adulthood and presents early diagnosis in pediatric patients.

Practice of adult rheumatologic disorders in the pediatric population puts forward a number of special health issues related to this age group. As an example, the higher prevalence of certain complications such as uveitis in children with juvenile idiopathic arthritis, mandates close follow-up with ophthalmologic consult, and growth problems associated with treatment side-effects might restrict the use of corticosteroids and biologic agents in children with rheumatologic disorders.

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease and a prototype of rheumatic disorders in pediatric patients [1]. Systemic-onset juvenile idiopathic arthritis is now classified as an autoinflammatory disorder and discussed in volume II of this series. Henoch-Schönlein purpura (HSP) and Kawasaki disease (KD) are two prototypic childhood vasculitides. Frequency of Kawasaki disease has been increasing worldwide over the years, raising serious concern knowing that up to 50% of untreated infants and toddlers face the threat of developing coronary artery aneurysms, a serious condition with lifelong morbidity and mortality. It is worth mentioning that 20% percent of patients with systemic lupus erythematosus (SLE) first manifest during childhood, often by cutaneous symptoms, making it crucial to make an early diagnosis. JIA, HSP, KD and SLE along with a number of other pediatric rheumatologic disorders are given special attention in the first chapters of this volume (Chapters 1–19, 82 and 83). Examples of autoimmune conditions that affect the skin as a single organ system such as vitiligo, alopecia areata, and pemphigus, or cutaneous manifestations of the more common multi-systemic autoimmune conditions such as SLE or dermatomyositis [2], are discussed the final chapters of the book (Chapters 57–81).

Right before getting through chapters describing patients with hematopoietic cell transplantation, we have gathered a series of case discussion of patients with **secondary immunodeficiency disorders** (Chapters 20–34). Immune defects observed in secondary immunodeficiency are usually heterogeneous in their clinical presentation, and their prognosis depends on the severity of the primary condition [3]. Secondary immunodeficiency conditions could be classified into three broad classes based on the etiologic factor:

1. Immunosuppression combined with non-immune disorders: malnutrition, cancer and infection are three major factors that cause secondary immunodeficiency in children. There are strong evidence that malnutrition can adversely impact

immune system. Childhood malignancies such as Hodgkin's disease often destroy cell mediated and humoral immunities, thereby reducing the capacity of the immune system to fight infections. All infective agents, from *Mycobacterium tuberculosis* to HIV virus can give rise to secondary immunodeficiency.
2. Iatrogenic factors: immunosuppressive agents are the most common cause of iatrogenic immunodeficiency. Two most common indication are treatment of autoimmune disorders or prevent transplant rejection.
3. Physiological factors: physiological factors such as immaturity of the immune system in preterm infants, could predispose to secondary immunodeficiency.

Worldwide, protein-calorie malnutrition is the leading cause of secondary immunodeficiencies, considering more than 200 million children being wasted or stunted in WHO reports in 2016 [4, 5]. Unfortunately, limited access to food sources in the main etiology of malnutrition, followed by chronic diseases that induce cachexia, chronic infections and neoplastic conditions.

HIV infection is a global challenge, and among leading causes of secondary immunodeficiency in children and adolescents. HIV infection follows the inevitable course eventually leading to acquired immunodeficiency syndrome (AIDS) state that is characterized by combined immunodeficiency, lymphopenia, increased susceptibility to infections with opportunistic pathogens. Something about 1,990,000 children under 15 years old need anti-retroviral therapy worldwide, less than 30% of which are currently under coverage [6].

Immune defects, aberrations in laboratory tests, and clinical presentation of secondary immunodeficiencies are heterogeneous in nature. Fortunately the immune impairment generally improves with the resolution of the primary condition. A series of case presentations regarding conditions associated with secondary immunodeficiency are presented and discussed in Chapters 20–34.

Hematopoietic Cell Transplantation (HCT) (originally known as Bone Marrow Transplantation or BMT, and also been known as **Hematopoietic Stem Cell Transplantation or HSCT**) began as a successful endeavor in 1968, by Dr. Robert A Good in an infant with severe combined immunodeficiency (SCID). Several things had to come to pass to allow for this. A better understanding of human leukocyte antigens (HLA), and in particular the ability to "type" patients and donors were the foremost essentials for appropriate donor selection [7]. Dr. Paul Terasaki developed a cellular-based typing system, in part based on the work of Dr. Bernard Amos, who had led the way for a better understanding of HLA in the 1950s and early 1960s [8–21]. In the following paragraphs of this writing readers are provided with a head start introduction on HLA and the complex donor selection process for HCT. The aim is to provide prerequisite knowledge for the reader to get ready for the real-life examples of donor-patients selection for HCT presented in Chapters 35–51 of this volume.

The HLA gene locus found on chromosome 6p21, can be divided into Class I (A, B, and C Loci) and Class II (DR, DQ, and DP Loci) (Figs. 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6). Class I HLA are responsible for presenting "endogenous" antigens to $CD8^+$ T lymphocytes and are found to be expressed on essentially all nucleated cells in

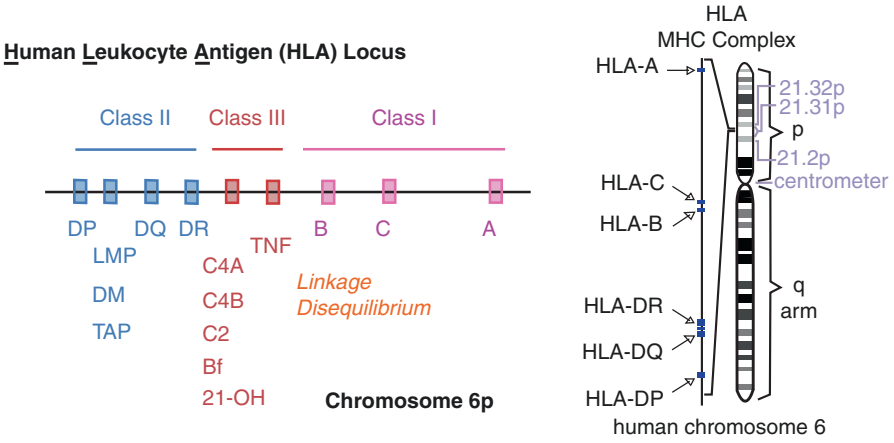

Fig. 1.1 HLA Gene Locus on Chromosome 6p21. Linkage disequilibrium is the concept that "the genes remain inherited together" more than expected form normal chromosome crossover events during meiosis and gametogenesis

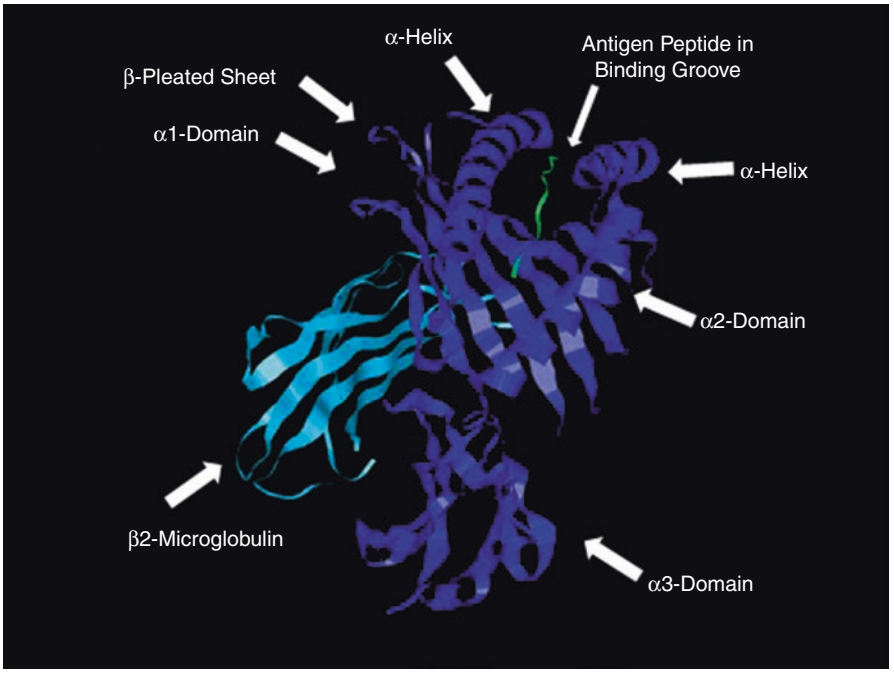

Fig. 1.2 The ultrastructure of HLA Class I molecule (Image constructed from data from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/protein) using RasWin. Components are labelled and discussed in the text. Most of the diversity resides in amino acid substitutions in the α-helices, with some in the β-pleated sheet. HLA class I is comprised of the polymorphic α-chain and the non-covalently attached non-polymorphic β2-microglobulin. The antigen-binding groove resides between the α-helices on top of the β-pleated sheet between the α1- and α2-domains)

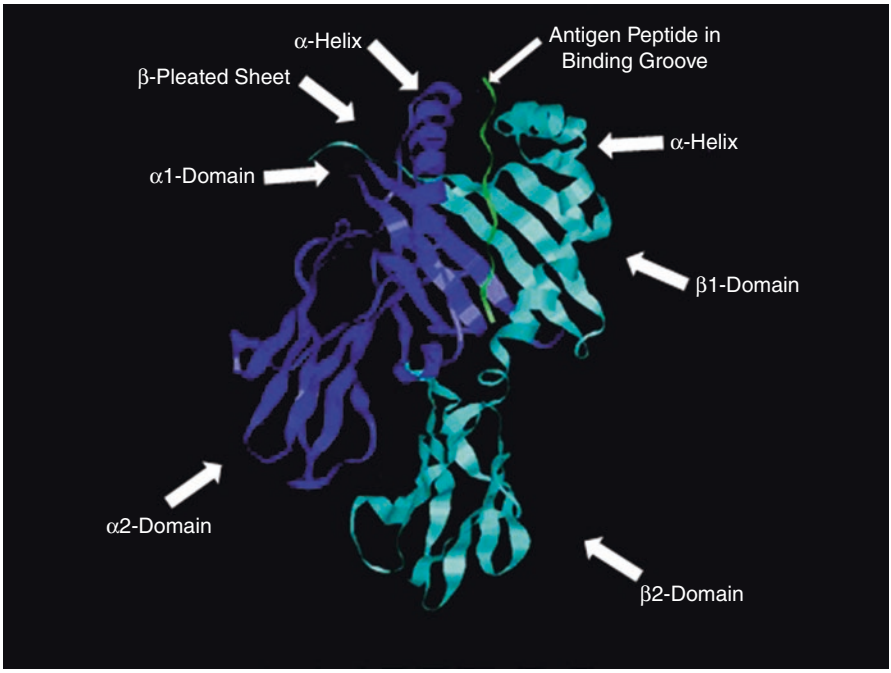

Fig. 1.3 The ultrastructure of HLA Class II molecule (Image constructed from data from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/protein) using RasWin. Components are labelled and discussed in the Text. Most of the diversity resides in amino acid substitutions in the α-helices and some in the β-pleated sheet. HLA class II is comprised of the polymorphic β-chain and the non-covalently attached relative non-polymorphic α-chain, for DR, and two polymorphic α- and β-chains each for DQ and DP. The antigen-binding groove resides between the α-helices on top of the β-pleated sheet between the α1- and β2-domains)

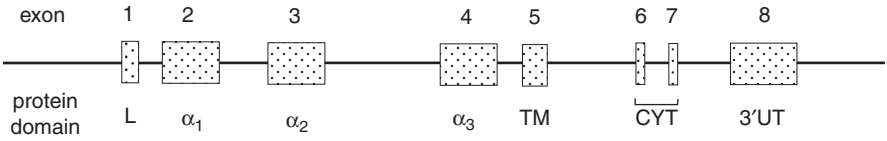

Fig. 1.4 HLA Class I Gene Structure Organization (Exons and introns are shown for class I HLA. The corresponding protein domains are depicted, indicating the exon location. The polymorphisms in exons 2 and 3 (α1 and α2 domains, respectively) generate the main diversity of HLA class I)

humans. To "complete" the molecule for cell-surface expression, β2-microglobulin is non-covalently complexed with HLA class I. Human RBCs do not express HLA, except for some "remnant" occasional expression. These are known as Bennett-Goodspeed (Bg) antigens (Bg^a, HLA-B7; Bg^b, HLA-B17; which includes B57 and B58 subtypes, and Bg^c, HLA-A28; which includes A68 and A69 subtypes). Importantly, platelets express class I HLA proteins. Class II are typically responsi-

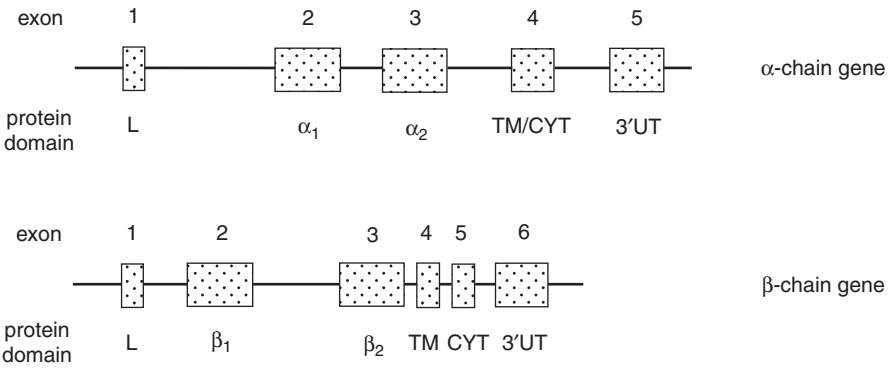

Fig. 1.5 HLA Class II Gene Structure Organization (Exons and introns are shown for class II HLA, A and B gene components, α and β subunit proteins, respectively. The corresponding protein domains are depicted, indicating the exon location. The polymorphisms in exons 2 of the α and β protein subunits (α1 and β1 domains, respectively) generate the main diversity of HLA class II, for DQ and DP, and the β1 domain for DR, since the α1 domain of DR is not very polymorphic)

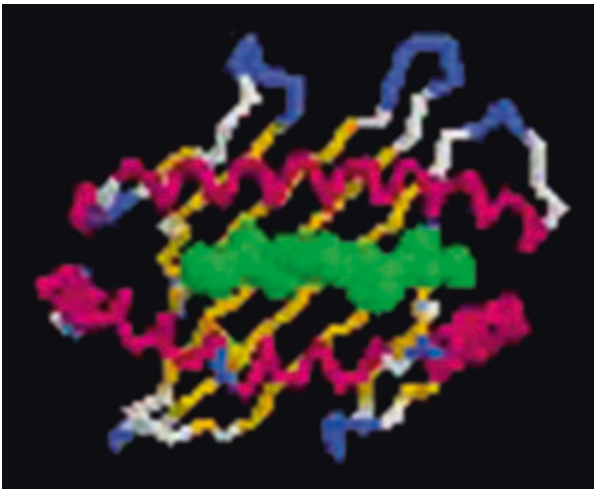

Fig. 1.6 Antigen-Binding Region of HLA: "Looking down" on the top of an HLA molecule, the view "seen" by the T cell receptor. The polymorphic regions include the α-helices and the β-turns of the β-pleated sheet. These are the areas "exposed", for which antibodies can be generated and can elicit T lymphocyte reactivity. These are the areas, which define the "name" of the specific HLA component present. These are the regions, which "must" be matched in order to have successful HCT

ble for presenting "exogenous" antigens to $CD4^+$ T lymphocytes, and are found on the cell surface of "professional" antigen presenting cells (APC). Major APCs include dendritic cells, macrophage/monocytes and B lymphocytes. Also included are Kupffer cells in the liver, microglial cells in the brain, and renal peritubular and glomerular capillary cells in the normal human kidney.

An additional consideration is that mesenchymal stem cells (Msc SC) express lower than normal levels of class I HLA and do not express detectable levels of class II HLA. Human hematopoietic stems cells (HSC) are thought to have variable amounts of HLA expression. Lower levels are thought to be present on undifferentiated HSC, with increasing levels as the cells become more differentiated. A progenitor cell may have as much as 80% of HLA expression as that of a fully-differentiated cells.

The diversity of HLA antigens is generated by polymorphisms primarily in the α-helices and β-pleated sheet of the α1 and α2 domains (exons 2 and 3) for class I HLA and the α1 and β1 domains (exons 2 of the A and B gene products) for class II HLA (Figs. 1.2, 1.3, 1.4, 1.5, and 1.6).

Originally, patients and donors were typed at serologic level determination of the HLA type, while now, molecular-level typing is being increasingly performed. The original typing was typically for a 6 of 6 HLA-A, HLA-B, and HLA-DR match which meant matching of both sets of alleles from the patient and the donor. This has expanded to 8 of 8 (HLA-A, -B, -C, and -DR), 10 of 10 (HLA-A, -B, -C, −DR, and -DQ), and finally 12 of 12 (HLA-A, -B, -C, −DR, −DQ, and -DP). As described below, some may consider 10 of 10 matching, with HLA-A, -B, -C, -DRB1, and -DPB1, since HLA-DQB1 mismatches are not believed to influence HCT outcomes, whereas HLA-DPB1 mismatching may influence the outcomes. The greater the extent of overall matching is thought the overall better are outcomes. Note that HLA-DRB3, -DRB4, and -DRB5 are not considered in the matching process.

Mendelian genetics predicts that 25% of sibling donors would be HLA-matched. Yet, in most programs, only 10–15% of patients have an HLA-identical sibling. To deal with issue, the National Marrow Donor Program (NMDP) was established to act as an entity to enroll potential non-related HLA-matched donors (matched-unrelated donors; MUD). More than seven million potential donors are in the registry. Additionally, there are registries in Europe and elsewhere in the world. Umbilical Cord Blood Registries (UCB) came into existence in the early 1990s, as an alternative source of HSC for MUD transplants.

The registries maintain information about the potential donors, including age, ethnicity, ABO status, CMV status, availability to donate, as well as, the HLA typing results. The donor typing results in the registry may be as little as HLA-A, -B, and -DR at the serologic designation, or may be a complete molecular type. When potential donors are selected from the registries, specimens are sent for typing and verification that the potential donor has the correct HLA type to be considered for the patient.

HLA Nomenclature

The original HLA typing by serologic techniques was developed by Amos and Terasaki in the 1950s and 1960s. However, as molecular biologic techniques were developed in the 1970s and 1980s, it became obvious that the serologic

determination was inadequate to fully define an individual HLA type. Newer, molecular based typing approaches began in the 1990s, but only came into widespread use after 2005.

Tables 1.1, 1.2, and 1.3 indicate the current numbers of alleles determined by gene sequencing for each of the HLA components. Since most amino acids have multiple triplet codons, "wobble", differences in the third base will produce different DNA sequences, but not changes in the protein structure. These genes will generate different names though, since the naming is based on the DNA sequence, although producing the same proteins. Therefore, a new nomenclature was developed to deal with these issues.

The original nomenclature was based on serologic determinations and names, for example, HLA-A2. The original "molecular" naming merely converted the values to a "four-digit" number, for example, HLA-A0201. Soon though, greater than 100 A2s were found, so that a new system was required.

The current nomenclature takes the same concept but uses digits in "fields" separated by colons (:), so that as many digits as needed could reside in a field between the colons. For example, A∗0101 would become A∗01:01 (Fig. 1.7), but A∗01:714 is also allowed (http://hla.alleles.org/).

Currently, for transplantation purposes, only the Field 1 and Field 2 components are used in donor-patient selection (e.g. A∗01:01). This is also known as "four-digit" in the old concept and "two-field" in the new concept.

The current nomenclature could produce a type such as HLA-A∗01:01:01:01. As noted in Fig. 1.7, the first two digits or first field are derived from the original serow-

Table 1.1 Class I allele frequencies

	A	B	C
Number of alleles	3997	4859	3605
Number of null alleles	186	147	131
Number of proteins	2792	3518	2497

http://www.ebi.ac.uk/ipd/imgt/hla/stats.html and http://www.allelefrequencies.net/

Table 1.2 Class II DR allele frequencies

	DRA	DRB1	DRB3	DRB4	DRB5
Number of alleles	7	2122	145	66	54
Number of null alleles	0	52	4	7	3
Number of proteins	2	1532	119	52	48

http://www.ebi.ac.uk/ipd/imgt/hla/stats.html and http://www.allelefrequencies.net/

Table 1.3 Class II DQ and DP allele frequencies

	DQA1	DQB1	DPA1	DPB1
Number of alleles	92	1152	56	942
Number of null alleles	3	31	0	22
Number of proteins	35	779	26	655

http://www.ebi.ac.uk/ipd/imgt/hla/stats.html and http://www.allelefrequencies.net/