PART XII | IMMUNOLOGY

Pediatric Immunology

Chapters 164–181

52 one-best-answer study questions with original source tables

Nelson Textbook of Pediatrics, 22nd edition, Volume 1

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An infant has recurrent pneumonias due to encapsulated bacteria and Giardia infection. Which immune arm is most likely impaired?

A. Neutrophil oxidative burst
B. Type I interferon signaling
C. Cytotoxic lymphocyte granule release
D. Antibody production
E. Terminal complement assembly

ORIGINAL SOURCE TABLE | Table 164.1 | PDF p. 1265 | printed p. 1252

Table 164.1 Patterns of Infections and Other Conditions in Primary Immunodeficiency

DISORDER	ILLNESSES: TYPE OF INFECTION	ILLNESSES: OTHER CONDITIONS
Antibody defects	Sinopulmonary infections (*Streptococcus pneumoniae, Haemophilus influenzae,* or *Mycoplasma sp.*) Gastrointestinal (enteroviruses, *Salmonella, Campylobacter, Giardia,* norovirus)	Autoimmune disease (thrombocytopenia, hemolytic anemia, neutropenia) Inflammatory bowel disease Lymphadenopathy, splenomegaly Otitis, mastoiditis
Cell-mediated immunity defects	Pneumonia *(Pneumocystis jirovecii), Mycobacterium avium-intracellulare* Severe Epstein-Barr infection Gastrointestinal disease (viruses, cytomegalovirus) Fungi of the skin, nails, mucous membranes	Failure to thrive Splenomegaly, lymphadenopathy
Defects of phagocytosis	Skin, liver, lymph nodes, abscesses (*Staphylococcus,* gram-negative bacteria, fungi)	Inflammatory bowel disease Granulomatous infiltrations
Defects of complement	Sepsis and other blood-borne encapsulated bacteria; meningitis, *(Streptococcus, Pneumococcus, Neisseria)*	Autoimmune disease (systemic lupus erythematosus, ANA+, glomerulonephritis)

ANA, Antinuclear antibodies.
From Leung DYM, Akdis CA, Bacharier LB, et al., eds. *Pediatric Allergy Principles and Practice*. 4th ed. Philadelphia: Elsevier; 2021. Table 4.1, p. 32.

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A newborn has very low T cells, preserved B cells, and absent NK cells. Which category in the classification table fits?

A. Properdin deficiency
B. T–B+NK– severe combined immunodeficiency
C. Isolated selective IgA deficiency
D. Classical complement deficiency
E. Isolated neutropenia

ORIGINAL SOURCE TABLE | Table 164.2 | PDF p. 1266 | printed p. 1253

Table 164.2 Types of Primary Immune Defects

IMMUNODEFICIENCIES AFFECTING CELLULAR AND HUMORAL IMMUNITY	
$T^-B^+NK^-$ SCID	Common gamma chain (IL2RG, X-linked), JAK3
$T^-B^+NK^+$ SCID	IL7-α, T-cell receptor defects, CD45, PNP deficiency
T^-B^- SCID	RAG1, RAG2 defects, adenosine deaminase deficiency
COMBINED IMMUNODEFICIENCIES, GENERALLY LESS SEVERE	
MHC class I and II defects; T-cell receptor defects; DOCK8, IL21, and IL21R, and others	
COMBINED IMMUNODEFICIENCIES WITH SYNDROMIC OR OTHER FEATURES	
With thrombocytopenia	Wiskott-Aldrich syndrome
DNA repair defects	Ataxia telangiectasia, Nijmegen breakage syndrome; Bloom syndrom dyskeratosis congenital, LIG-4
Hyper-IgE syndromes	STAT3 loss of function, and others
Immuno-osseous dysplasias	Cartilage hair hypoplasia Schimke immuno-osseous dysplasia
Ectodermal dysplasia	IKBKG deficiency (NEMO)
THYMIC DEFECTS WITH ADDITIONAL CONGENITAL ANOMALIES	
DiGeorge, velocardiofacial syndrome CHARGE syndrome	
ANTIBODY DEFECTS	
Agammaglobulinemias	X-linked and autosomal forms of agammaglobulinemia
Hyper-IgM syndromes	X-linked and autosomal forms
IgG or IgA deficiency	IgG subclass and IgA deficiency
IgG, and IgA and or IgM deficiency	Common variable immunodeficiency
DISEASES OF IMMUNE DYSREGULATION	
Familial hemophagocytic lymphohistiocytosis	Perforin deficiency; UNC13D.
With hypopigmentation	Chédiak-Higashi, Griscelli, Hermansky-Pudlak syndromes
With autoimmunity	Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy, autoimmune lymphoproliferative syndrome
With defects of regulatory T cells	X-linked immune dysregulation, polyendocrinopathy enteropathy (IPEX), defects of CTLA4, STAT3
Leading to severe Epstein-Barr virus	X-linked autoimmune lymphoproliferative syndrome, XIAP deficiency, magnesium transporter 1 (MAGT1)
With colitis	IL-10 defects
CONGENITAL DEFECTS OF PHAGOCYTE NUMBER OR FUNCTION	
Neutropenia	Elastase deficiency, HAX1 deficiency, and others
Defects of motility	Leukocyte adhesion deficiency
Defects of respiratory burst	Chronic granulomatous disease
Other nonlymphoid defects	GATA2 deficiency
DEFECTS IN INTRINSIC AND INNATE IMMUNITY	
Mycobacterial disease	IL-12, IL-23, INF-γ, STAT1 defects, and others
Warts	Epidermodysplasia verruciformis (EVER), hypogammaglobulinemia, infections, myelokathexis syndrome (WHIM)
Viral infections	STAT1, STAT2, IRF7, and others
Herpes simplex encephalitis	TLR3, UNC93B1
Fungal diseases	CARD9, IL17 defects, STAT1
Bacterial susceptibility	IRAK4, MYD88, IRAK1, and others
COMPLEMENT DEFICIENCY	
Classical pathway	C1q-C9 defects
Alternative pathway	Factors B, D, I, H, properdin, and others
Regulatory and membrane controls	Co-factor proteins

CHARGE defect, Disorder with coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities; Ig, immunoglobulin; MHC, major histocompatibility complex; NK, natural killer; PNP, purine nucleoside phosphorylase; SCID, severe combined immunodeficiency.
From Leung DYM, Akdis CA, Bacharier LB, et al., eds. *Pediatric Allergy Principles and Practice*. 4th ed. Philadelphia: Elsevier; 2021. Table 4.2, p. 33-34.

A child has a second episode of herpes simplex encephalitis without recurrent mucocutaneous herpes. Which listed pathway should be investigated?

A. Terminal C5–C9 assembly
B. BTK-dependent B-cell maturation
C. Neutrophil CD18 adhesion
D. C1-inhibitor regulation
E. TLR3-related antiviral signaling

ORIGINAL SOURCE TABLE | Table 164.3 | PDF p. 1267 | printed p. 1254

Table 164.3 Sentinel Infections and Related Genes

INFECTIONS	RECOGNIZED GENE DEFECTS AND WELL-CHARACTERIZED SYNDROMES
VIRUSES	
Herpes simplex encephalitis	*TBK1, TLR3, TRAF3, TRIF, UNC93B*
Cutaneous herpes simplex	Severe T-cell defects, *DOCK8, GATA2, WAS*
EBV—chronic	*CD21, CD27, CORO1A, ITK, MAGT1, PRKCD, CXCR4*
EBV—HLH	*AP3B1, LYST1, PRF1, RAB27A, SH2D1A, STX11, UNC13D, XIAP*
CMV	Severe T-cell defects, Good syndrome, *DOCK8, GATA2, STIM1, WAS*
Papilloma virus	Idiopathic CD4 lymphopenia, *ATM, CD40L, EVER1, EVER2, DOCK8, GATA2, IKBKG, MST1, RORH, STK4, CXCR4*
FUNGI	
Candida	*AIRE, CARD9, IL17F, IL17RA, STAT1*
Aspergillus	Idiopathic CD4 lymphopenia, *CYBA, CYBB, DOCK8, GATA2, ITGB2, NCF1, NCF2, NCF4, STAT3*
BACTERIA	
Pseudomonas	Congenital neutropenia, *IRAK4, ITGB2, MYD88, BTK* (neutropenia), *CD40LG* (neutropenia)
Salmonella	*CYBB, IFNGR1, IFNGR2, IL12B, IL12RB1*
Serratia	*CYBA, CYBB, NCF1, NCF2, NCF4*
Neisseria	*C5, C6, C7, C8A, C8B, C8G, C9, CFD, CFH, CFI, CFP*
Streptococcus pneumoniae	*C1QA, C1QB, C1QC, C4A + C4B, C2, C3, IRAK4, MYD88*
MYCOBACTERIA	
Mycobacteria	*CYBA, CYBB, GATA2, IFNGR1, IFNGR2, IKBKG, IL12, IL12RB1, IRF8, NCF1, NCF2, NCF4, STAT1, TYK2*

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis.
From Sullivan KE, Stiehm ER, eds. *Stiehm's Immune Deficiencies*. 2nd ed. London: Elsevier; 2020. Table 1.2.

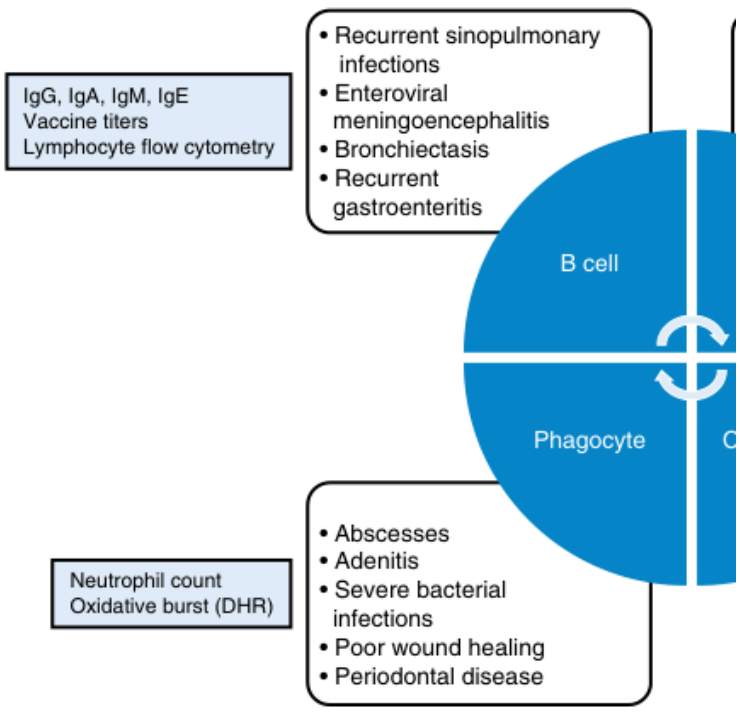

Fig. 164.1 When infections are the major manifestation of the inborn error c

A child has recurrent invasive pneumococcal sepsis despite previously normal health. Which anatomic condition is included in the differential table?

A. Isolated laryngomalacia
B. Congenital pyloric stenosis
C. Asplenia
D. Thymic hyperplasia
E. Splenomegaly alone

ORIGINAL SOURCE TABLE | Table 164.4 | PDF p. 1268 | printed p. 1255

Table 164.4 Recurrent Invasive Pneumococcal Infections

CONDITION	GENE/CONDITION SUBSET	INHERITANCE	OTHER FEATURES
Asplenia	*ATRX*	XL	Developmental delay, low-set ears, single palmar crease
Asplenia	*HMOX1*	AR	Hemolysis, nephritis
Asplenia	*NKX2-5*	AD	
Asplenia	*RPSA*	AD	
Asplenia	*ZEB2*	AD	Mowat-Wilson syndrome, microcephaly, Hirschsprung disease, defects in corpus callosum
Asplenia	Gene unknown/syndromic		Can occur in heterotaxy syndromes
Antibody deficiency	*BTK*	XL	
Antibody deficiency	Hypogammaglobulinemia	Various	
Antibody deficiency	Specific antibody deficiency	Various	
Antibody deficiency	IgG subclass deficiency	Various	
Antibody deficiency	CVID	Various	
Innate immune deficiency	*MYD88*	AR	Poor fever formation
Innate immune deficiency	*IRAK4*	AR	Poor fever formation
Innate immune deficiency	*IKBKG*	XL	Peg teeth, ectodermal dysplasia
Complement deficiency	C2	AR	Can have lupus
Complement deficiency	C1	AR	Can have lupus
Complement deficiency	C4	AR	Can have lupus
Complement deficiency	C3	AR	Glomerulonephritis

AD, Autosomal dominant; AR, autosomal recessive; CVID, common variable immunodeficiency; XL, X-linked.

A child develops EBV-associated hemophagocytic lymphohistiocytosis. Which clinical framing best reflects the table?

A. Investigate an underlying primary immune deficiency
B. Exclude inherited immune disease because EBV is present
C. Diagnose isolated antibody deficiency from EBV alone
D. Attribute it exclusively to complement consumption
E. Presume that no genetic evaluation can be informative

ORIGINAL SOURCE TABLE | Table 164.5 | PDF p. 1269 | printed p. 1256

Table 164.5 Primary Immune Deficiency Disease and Risk of Hemophagocytic Lymphohistiocytosis*

CONDITION	GENE/CONDITION SUBSET	INHERITANCE	RISK OF HLH	OTHER FEATURES
CD48 deficiency	*CD48*	AD	High	
Chédiak-Higashi syndrome	*LYST*	AR	High	Pigmentary dilution
NLRC4	*NLRC4*		High	IBD
Perforin deficiency (FHL2)	*PRF1*	AR	High	
Griscelli syndrome, type 2	*RAB27A*	AR	High	Pigmentary dilution
X-linked lymphoproliferative disease 1	*SH2D1A*	XL	High	
Syntaxin 11 deficiency (FHL4)	*STX11*	AR	High	
STXBP2/Munc18-2 deficiency (FHL5)	*STXBP2*	AR or AD	High	Hypogammaglobulinemia, IBD
UNC13D/Munc13-4 deficiency (FHL3)	*UNC13D*	AR	High	
X-linked lymphoproliferative disease 2	*XIAP*	XL	High	
CD27 deficiency	CD27	AR	Medium	Unable to control EBV
Chronic granulomatous disease	*All genetic types*	XL, AR	Low	Infections, granulomas
Hermansky-Pudlak syndrome, type 2	*AP3B1*	AR	Low	Pigmentary dilution
Hermansky-Pudlak syndrome, type 10	*AP3D1*	AR	Low	Pigmentary dilution
Lysinuric protein intolerance SLC7A7 deficiency	*SLC7A7*	AR	Low	Lung disease, feeding intolerance

*Other primary immune deficiency diseases, including most T-cell deficiencies have been associated with HLH in rare patients.
AD, Autosomal dominant; AR, autosomal recessive; HLH, Hemophagocytic lymphohistiocytosis; IBD, inflammatory bowel disease.

A 7-month-old has persistent oral candidiasis, chronic diarrhea, failure to thrive, and very low age-adjusted lymphocytes. Which immune defect is most strongly suggested?

A. Selective IgA deficiency alone
B. C1-inhibitor deficiency
C. Isolated factor H deficiency
D. T-cell or combined immunodeficiency
E. Isolated terminal complement deficiency

ORIGINAL SOURCE TABLE | Table 164.6 | PDF p. 1270 | printed p. 1257

Table 164.6 Clinical Aids to the Diagnosis of Immunodeficiency

SUGGESTIVE OF B-CELL DEFECT (HUMORAL IMMUNODEFICIENCY)
Recurrent bacterial infections of the upper and lower respiratory tracts
Recurrent skin infections, meningitis, osteomyelitis secondary to encapsulated bacteria *(Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Neisseria meningitidis)*
Severe *Giardia lamblia* infections
Paralysis after vaccination with live attenuated poliovirus
Reduced levels of immunoglobulins
SUGGESTIVE OF T-CELL DEFECT (COMBINED IMMUNODEFICIENCY)
Systemic illness after vaccination with any live virus or BCG
Unusual life-threatening complication after infection with benign viruses (giant cell pneumonia with measles; varicella pneumonia)
Chronic oral candidiasis after 6 mo of age
Chronic mucocutaneous candidiasis
Graft versus host disease after blood transfusion
Reduced lymphocyte counts for age
Low level of immunoglobulins
Absence of lymph nodes and tonsils
Small thymus
Chronic diarrhea
Failure to thrive
Recurrent infections with opportunistic organisms
Generalized, recurrent, recalcitrant warts
SUGGESTIVE OF MACROPHAGE DYSFUNCTION
Disseminated atypical mycobacterial infection, recurrent *Salmonella* infection
Fatal infection after BCG vaccination
CONGENITAL SYNDROMES WITH IMMUNODEFICIENCY
Ataxia-telangiectasia: ataxia, telangiectasia
Autoimmune polyglandular syndrome: hypofunction of one or more endocrine organs, chronic mucocutaneous candidiasis
Cartilage-hair hypoplasia: short-limbed dwarfism, sparse hair, neutropenia
Wiskott-Aldrich syndrome: thrombocytopenia, male gender, eczema
Chédiak-Higashi syndrome: oculocutaneous albinism, nystagmus, recurrent bacterial infections, peripheral neuropathies
DiGeorge syndrome (22q deletion syndrome): unusual facies, heart defect, hypocalcemia
CHARGE syndrome: coloboma, heart defects, atresia choanae, retarded growth, genital hypoplasia, ear anomalies/deafness
Short-limb skeletal dysplasia with combined immune deficiency: metaphyseal dysplasia, ADA deficiency, or Omenn syndrome
X-linked agammaglobulinemia with growth hormone deficiency: hypogammaglobulinemia, growth hormone deficiency
Kabuki syndrome: long palpebral fissures, prominent eyelashes, congenital heart disease
Timothy syndrome: prolonged QT, congenital heart disease, developmental delay
PTEN tumor hamartoma syndrome: multiple hamartomas, cancer
SUGGESTIVE OF ASPLENIA
Heterotaxia, complex congenital heart disease, Howell-Jolly bodies on blood smear, sickle cell anemia

ADA, Adenosine deaminase; BCG, bacille Calmette-Guérin.
From Verbsky JW, Routes JM. Recurrent fever, immune deficiency, and autoinflammatory disorders. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*. 2nd ed. Philadelphia: Elsevier; 2023.Table 54.7, p. 1028.

An infant has eczema, recurrent infections, and thrombocytopenia with unusually small platelets. Which syndrome is most consistent with the physical-feature table?

A. DiGeorge syndrome
B. Wiskott–Aldrich syndrome
C. Ataxia–telangiectasia
D. Chédiak–Higashi syndrome
E. Cartilage–hair hypoplasia

ORIGINAL SOURCE TABLE | Table 164.7 | PDF p. 1271 | printed p. 1258

Table 164.7 Special Physical Features Associated with Immunodeficiency Disorders

CLINICAL FEATURES	DISORDERS
DERMATOLOGIC	
Eczema	Wiskott-Aldrich syndrome, IPEX, hyper-IgE syndromes, hypereosinophilia syndromes, IgA deficiency
Sparse and/or hypopigmented hair	Cartilage-hair hypoplasia, Chédiak-Higashi syndrome, Griscelli syndrome
Ocular telangiectasia	Ataxia-telangiectasia
Oculocutaneous albinism	Chédiak-Higashi syndrome
Severe dermatitis	Omenn syndrome
Erythroderma	Omenn syndrome, SCID, graft versus host disease, Comèl-Netherton syndrome
Recurrent abscesses with pulmonary pneumatoceles	Hyper-IgE syndromes
Recurrent organ granulomas or abscesses, lung, liver, and rectum especially	CGD
Recurrent abscesses or cellulitis	CGD, hyper-IgE syndrome, leukocyte adhesion defect
Cutaneous granulomas	Ataxia telangiectasia, SCID, CVID, RAG deficiency
Oral ulcers	CGD, SCID, congenital neutropenia
Periodontitis, gingivitis, stomatitis	Neutrophil defects
Oral or nail candidiasis	T-cell immune defects, combined defects (SCIDs); mucocutaneous candidiasis; hyper-IgE syndromes; IL-12, IL-17, and IL-23 deficiencies; *CARD9* deficiency; STAT1 deficiency
Vitiligo	B-cell defects, mucocutaneous candidiasis
Alopecia	B-cell defects, mucocutaneous candidiasis
Chronic conjunctivitis	B-cell defects
EXTREMITIES	
Clubbing of nails	Chronic lung disease caused by antibody defects
Arthritis	Antibody defects, Wiskott-Aldrich syndrome, hyper-IgM syndrome
ENDOCRINOLOGIC	
Hypoparathyroidism	DiGeorge syndrome, mucocutaneous candidiasis
Endocrinopathies (autoimmune)	Mucocutaneous candidiasis
Diabetes, hypothyroid	IPEX and IPEX-like syndromes
Growth hormone deficiency	X-linked agammaglobulinemia
Gonadal dysgenesis	Mucocutaneous candidiasis
HEMATOLOGIC	
Hemolytic anemia	B- and T-cell immune defects, ALPS
Thrombocytopenia, small platelets	Wiskott-Aldrich syndrome
Neutropenia	Hyper-IgM syndrome, Wiskott-Aldrich variant, CGD
Immune thrombocytopenia	B-cell immune defects, ALPS
SKELETAL	
Short-limb dwarfism	Short-limb dwarfism with T-cell and/or B-cell immune defects
Bony dysplasia	ADA deficiency, cartilage-hair hypoplasia

ADA, Adenosine deaminase; ALPS, autoimmune lymphoproliferative syndrome; CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; IPEX, X-linked immune dysfunction enteropathy polyendocrinopathy; SCID, severe combined immunodeficiency.
From Goldman L, Ausiello D, ed. *Cecil Textbook of Medicine*. 22nd ed. Philadelphia: Saunders; 2004. p 1599.

An infant has severe early enteropathy, endocrinopathy, and immune dysregulation. Which X-linked gene in the enteropathy table is most relevant?

A. EPCAM
B. MYO5B
C. STX3
D. TTC37
E. FOXP3

ORIGINAL SOURCE TABLE | Table 164.9 | PDF p. 1273 | printed p. 1260

Table 164.9 Early-Onset Enteropathy (Not Gluten Sensitive)

CONDITION	GENE	INHERITANCE	ENTEROPATHY FREQUENCY	OTHER FEATURES
Microvillous inclusion disease	*MYO5B*	AR	Always	Neonatal onset
Microvillous inclusion disease	*STX3*	AR	Always	Neonatal onset
Tufting enteropathy	*EPCAM*	AR	Always	Neonatal onset
Tufting enteropathy	*SPINT2*	AR	Always	Keratitis, anal/choanal atresia
Trichohepatoenteric syndrome	*SKIV2L*	AR	Always	Trichorrhexis nodosa, IUGR
Trichohepatoenteric syndrome	*TTC37*	AR	Always	Trichorrhexis nodosa, IUGR
Multiple intestinal atresia	*TTC7A*	AR	High	Lymphopenia, IA
Immune dysregulation	*CARD11*	AD	Low	CVID, alopecia, atopy
Immune dysregulation	*CTLA4*	AD	Medium (broad age of onset)	LP, CVID, infections
Immune dysregulation	*DEF6*	AR	Medium	Cardiomyopathy, infections
Immune dysregulation	*FOXP3*	XL	Always	Diabetes
Immune dysregulation	*ICOS*	AR	Medium (broad age of onset)	LP, CVID, infections
Immune dysregulation	*IL2RA*	AR	Low	Lymphopenia, infections, LP
Immune dysregulation	*LRBA*	AR	Medium (broad age of onset)	LP, CVID, infections
Immune dysregulation	*MALT1*	AR	High	Infections, LP, eczema
Immune dysregulation	*RLTPR*	AR	Medium	Infections, EBV
Immune dysregulation	*STAT1*	AD (GOF)	High	*Candida*, diabetes
Immune dysregulation	*STAT3*	AD (GOF)	High	Short, LP
Immune dysregulation	*XIAP*	XL	High	EBV, HLH
MHC class II deficiency	*RFXANK*	AR	Low	Infection, cytopenias
MHC class II deficiency	*CIITA*	AR	Low	Infection, cytopenias
MHC class II deficiency	*RFX5*	AR	Low	Infection, cytopenias
MHC class II deficiency	*RFXAP*	AR	Low	Infection, cytopenias

AD, Autosomal dominant; AR, autosomal recessive; CVID, Common variable immune deficiency; EBV, Epstein-Barr virus; GOF, gain of function; HLH, hemophagocytic lymphohistiocytosis; IA, intestinal atresia and fibrosis; IUGR, intrauterine growth retardation; LP, lymphocytic infiltrates in multiple organs; MHC, major histocompatibility complex; XL, X-linked

A young child has autoimmune enteropathy, cytopenias, and other organ-specific autoimmunity. Which T-cell tolerance gene in the table is X-linked?

A. STAT3
B. AIRE
C. FOXP3
D. CTLA4
E. LRBA

ORIGINAL SOURCE TABLE | Table 164.10 | PDF p. 1274 | printed p. 1261

Table 164.10 Pleomorphic Autoimmunity (Autoimmunity Not Limited to a Single Organ)

PATHWAY	GENE	INHERITANCE	MAIN ORGANS INVOLVED	NONIMMUNE FEATURES	INFECTIONS
B-cell tolerance	*AID*	AR	Lymphoid hyperplasia, cytopenias, GI		High IgM, frequent infections
T-cell tolerance	*AIRE*	AR/AD	Endocrine organs, lung, skin	Nail dystrophy	*Candida*
T-cell tolerance	*ARPC1B*	AR	Cytopenias, GI	Thrombocytopenia	Frequent infections
T-cell tolerance	*CTLA4*	AD	GI, lung, CNS		Frequent infections
T-cell tolerance	*COPA*	AD	Lung, joint, renal		
T-cell tolerance	*FOXP3*	XL	GI, endocrine, skin		
T-cell tolerance	*HAVCR2*	AR	HLH, panniculitis, SLE-like, joint	Lymphoma	
T-cell tolerance	*IL2RA*	AR	Skin, GI, endocrine		Viral
T-cell tolerance	*IL2RB*	AR	GI, skin		Viral
T-cell tolerance	*ITCH*	AR	Joints, lung, enteropathy	Developmental delay	
T-cell tolerance	*JAK1*	AD (GOF)	Skin, renal, GI		
T-cell tolerance	*LRBA*	AR	GI, lung, CNS		
T-cell tolerance	*ORAI1*	AR	Cytopenias, vasculitis	Myopathy, poor dental enamel	Frequent infections
T-cell tolerance	*PRKCD*	AR	SLE-like		Frequent infections
T-cell tolerance	*PTEN*	AD	Cytopenias, GI, endocrine	Malignancy, macrocephaly, developmental delay	
T-cell tolerance	*STAT1*	AD (GOF)	GI, endocrine		*Candida*
T-cell tolerance	*STAT3*	AD (GOF)	GI, lung, endocrine	Short stature	
T-cell tolerance	*STIM1*	AR	Cytopenias, Sjögren syndrome	Myopathy, poor dental enamel	Frequent infections
T-cell tolerance	*TPP2*	AR	Hematopoietic	CNS	Viral
T-cell tolerance	*WAS*	XL	Cytopenias, GI	Thrombocytopenia	Frequent infections
T-cell tolerance	*WIP*	AR	Cytopenias, GI	Thrombocytopenia	Frequent infections
Inflammatory pathway	*RBCK1*	AR	Joints, skin, GI	Amylopectin deposits in muscle	Frequent infections
Inflammatory pathway	*RIPK1*	AD	GI, joint	HSM episodic	Fevers
Inflammatory pathway	*RNF31*	AR	Joints, skin	Amylopectin deposits in muscle	Frequent infections, CVID-like
Inflammatory pathway	*TNFAIP3*	AD	Mucosal ulcers, GI, arthritis, skin		Fevers
Lysinuric protein intolerance	*SLC7A7*	AR	HLH, SLE, PAP	HSM, poor growth, osteoporosis, renal	Infections trigger metabolic decompensation

AD, Autosomal dominant; AR, autosomal recessive; CNS, central nervous system; CVID, common variable immune deficiency; GI, gastrointestinal, GOF, gain of function; H hemophagocytic lymphohistiocytosis; HSM, hepatosplenomegaly; PAP, pulmonary alveolar proteinosis; SLE, systemic lupus erythematosus; XL, X-linked.

A boy with severe combined immunodeficiency has absent T cells, preserved B cells, and absent NK cells. Which molecular defect is a classic fit?

A. Common gamma-chain (CD132) deficiency
B. RAG1 deficiency
C. Adenosine deaminase deficiency
D. Artemis deficiency
E. DNA ligase IV deficiency

ORIGINAL SOURCE TABLE | Table 165.1 | PDF p. 1276 | printed p. 1263

Table 165.1 Genetic Basis of Severe Combined Immunodeficiency and SCID Variants

DISEASE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
T⁻B⁻ SCID				
Reticular dysgenesis	AR	Impaired mitochondrial energy metabolism and leukocyte differentiation	Severe neutropenia, deafness Pathogenic variants in adenylate kinase 2	GCSF, HSCT
Reticular dysgenesis	AD	Impaired hematopoiesis	Severe neutropenia but no deafness, gain-of-function variant in RAC2	HSCT
Adenosine deaminase deficiency	AR	Accumulation of toxic purine nucleosides	Neurologic, hepatic, renal, lung, skeletal, bone marrow abnormalities	HSCT, PEG-AD gene therapy
RAG1 and RAG2 deficiency	AR	Defective V(D)J recombination	None	HSCT
Artemis deficiency	AR	Defective V(D)J recombination, radiation sensitivity	*DCLERE1C* pathogenic gene variants	HSCT
DNA-PK deficiency	AR	Defective V(D)J recombination	None	HSCT
DNA ligase IV deficiency	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, bone marrow abnormalities, lymphoid malignancies	HSCT
Cernunnos-XLF	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, birdlike facies, bone defects	HSCT
T⁻B⁺ SCID				
γ_c (CD132) deficiency	XL	Abnormal signaling via γ_c-ILRs (IL-2, 4, 7, 9, 15, 21)	None	HSCT, gene therapy
Jak3 deficiency	AR	Abnormal signaling downstream of γ_c	None	HSCT
IL-7Rα deficiency	AR	Abnormal IL-7R signaling	Thymus absent	HSCT
CD45 deficiency	AR		None	HSCT
CD3δ deficiency	AR	Arrest of thymocytes differentiation at $CD4^-CD8^-$ stage	Thymus size may be normal	HSCT
CD3ε deficiency	AR	Arrest of thymocytes differentiation at $CD4^-CD8^-$ stage	γ/δ T cells absent	HSCT
CD3ζ deficiency	AR	Abnormal signaling	None	HSCT
Coronin-1A deficiency	AR	Abnormal T-cell egress from thymus and lymph nodes	Normal thymus size Attention deficit disorder	HSCT
LAT deficiency	AR	Defective T-cell development in the thymus	Autoimmune disease	HSCT
SLP76	AR	Abnormal signaling	Neutrophil defect, skin abscesses, rash, autoimmunity	HSCT attempt

γ_c, Common gamma chain; AD, Autosomal dominant; AR, Autosomal recessive; GCSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; IL, interleukin; Jak3, Janus kinase 3; PEG-ADA, polyethylene glycol-modified adenosine deaminase; R, receptor; RAG1, RAG2, recombinase-activating genes 1 and 2; SCID, severe combined immune deficiency; V(D)J, variable, diversity, joining domains; XL, X-linked.

Adapted from Roifman CM, Grunebaum E. Primary T-cell immunodeficiencies. In: Rich RR, Fleisher TA, Shearer WT, et al., eds. *Clinical Immunology*. 4th ed. Philadelphia: Saunder

A child has short-limbed skeletal dysplasia, sparse hair, and recurrent infection. Which immunoosseous dysplasia is most likely?

A. Roifman syndrome
B. MYSM1 deficiency
C. EXTL3 deficiency
D. Cartilage–hair hypoplasia
E. Schimke immunoosseous dysplasia

ORIGINAL SOURCE TABLE | Table 165.4 | PDF p. 1281 | printed p. 1268

Table 165.4 Immunoosseous Dysplasias

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
Cartilage hair hypoplasia	*RMRP*	AR	Normal to severely decreased T-cell counts Decreased T-cell proliferation	Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure, autoimmunity, susceptibility to lymphoma and other cancers, impaired spermatogenesis, neuronal dysplasia of the intestine	HSCT for the immunodeficiency
Schimke immuno-osseous dysplasia	*SMARCAL1*	AR	Decreased T cells	Short stature, spondyloepiphyseal dysplasia, intrauterine growth restriction; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure	HSCT for the immunodeficiency
MYSM1 deficiency	*MYSM1*	AR	Decreased T cells, naïve T cells, and NK cells B-cell deficiency with hypogammaglobulinemia	Short stature; recurrent infections; congenital bone marrow failure, myelodysplasia; immunodeficiency affecting B cells and granulocytes; skeletal anomalies; cataracts; developmental delay	HSCT for the immunodeficiency
MOPD1 deficiency (Roifman syndrome)	*RNU4ATAC*	AR	Decreased NK cell function Decreased total and memory B cells Hypogammaglobulinemia, variably decreased specific antibodies	Recurrent bacterial infections; lymphadenopathy; spondyloepiphyseal dysplasia, extreme intrauterine growth restriction; retinal dystrophy; facial dysmorphism; may present with microcephaly; short stature	HSCT for the immunodeficiency
Immunoskeletal dysplasia with neurodevelopmental abnormalities (*EXTL3* deficiency)	*EXTL3*	AR	Decreased T cells, decreased to normal Ig levels	Short stature; cervical spinal stenosis, neurodevelopmental impairment; eosinophilia; may have early infant mortality	HSCT for the immunodeficiency

AR, Autosomal recessive; HSCT, hematopoietic stem cell transplantation; Ig, immunoglobulin; NK, natural killer; SCID, severe combined immune deficiency.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

A newborn with conotruncal heart disease, hypocalcemia, and low T cells has suspected thymic hypoplasia. Which table-listed condition best fits?

A. Properdin deficiency
B. 22q11.2 deletion syndrome
C. Cartilage–hair hypoplasia
D. X-linked agammaglobulinemia
E. Chediak–Higashi syndrome

ORIGINAL SOURCE TABLE | Table 165.6 | PDF p. 1283 | printed p. 1270

Table 165.6 Thymic Disorders

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
DiGeorge/Velocardio-facial syndrome/ chromosome 22Q11.2 deletion syndrome *TBX1* deficiency	22Q11.2del including *TBX1*, *TBX1* Unknown	AD (Unknown defects are sporadic)	Variable T-cell counts, may have low TRECs at NBS, may have hypogammaglobulinemia	Conotruncal cardiac defects, hypoparathyroidism, abnormal facies, velopalatal insufficiency, intellectual disability, autoimmunity	Thymic transplant for severe T-cell deficiency
CHARGE syndrome	*CHD7* *SEMA3E* Unknown	AD AD	Variable T-cell counts, may have low TRECs at NBS, may have hypogammaglobulinemia	Coloboma of eye; heart anomaly; choanal atresia; intellectual disability; genital and ear anomalies (CHARGE), CNS malformation	Thymic transplant for severe T-cell deficiency
Winged helix nude *FOXN1* deficiency	*FOXN1*	AR	Very low T cells, decreased Ig levels	Severe infections, abnormal thymic epithelium, congenital alopecia, nail dystrophy, neural tube defect	Thymic transplant attempted
FOXN1 haploinsufficiency	*FOXN1*	AD	Severe T-cell lymphopenia at birth, normal by adulthood	Recurrent, viral and bacterial respiratory tract infections; (eczema, dermatitis), nail dystrophy	
Chromosome 10p13-p14 deletion syndrome (10p13-p14DS)	10p13-p14del	AD	T-cell lymphopenia rarely with decreased proliferation to mitogens and antigens, may have hypoplastic thymus	Hypoparathyroidism, renal disease, deafness, growth retardation, facial dysmorphism, cardiac defects may be present, may have recurrent infections	
Chromosome 11q deletion syndrome (Jacobsen syndrome)	11q23del	AD	T-, B-, and NK cell lymphopenia, low switched memory B cells, variable Ig levels and antibody responses	Recurrent respiratory infections; multiple warts; facial dysmorphism, growth retardation	Ig replacement for antibody deficiency
PAX1	*PAX1*	AR	Absent thymus	Omenn-like syndrome	HSCT attempted, thymic transplantation attempted

AD, Autosomal dominant; AR, Autosomal recessive; del, deletion; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; TREC, T-cell receptor excision circle; NBS, newborn screening; Ig, immunoglobulin.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473–1507.

A child with eczema, recurrent skin infections, very high IgE, and severe persistent cutaneous viral infections is evaluated for a hyper-IgE syndrome. Which gene is table-listed and clinically relevant?

A. BTK
B. C2
C. ELANE
D. FOXP3
E. DOCK8

ORIGINAL SOURCE TABLE | Table 165.7 | PDF p. 1284 | printed p. 1271

Table 165.7 Hyper IgE Syndromes

DISEASE	GENE	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	TREATMEN
HIE (Job syndrome)	*STAT3*	AD (DN LOF)	Decreased response to *STAT3*-activating cytokines; decreased Th17, T follicular helper, MAIT, NKT cells, reduced memory B cells, elevated IgE	Coarse facial features, broad nasal bridge; staphylococcal abscesses, eczema, pneumatoceles, pulmonary *Aspergillus,* PJP, mucocutaneous candidiasis; hyperextensible joints, osteoporosis and bone fractures, scoliosis, retained primary teeth; coronary and cerebral aneurysms	Bacterial and fungal prophylaxi
DOCK8 deficiency	*DOCK8*	AR	T-cell lymphopenia with poor proliferation, few Tregs with poor function, reduced MAIT and NKT cells, very high IgE	Low NK cells with poor function Eosinophilia, recurrent infections, cutaneous viral, fungal and staphylococcal infections, severe atopy/allergic disease, cancer diathesis	HSCT
IL-6 receptor deficiency	*IL6R*	AR	Decreased switched memory B cells, very high IgE	Recurrent pyogenic infections, cold abscesses, elevated IL-6 levels	Bacterial prophylaxi
IL-6 signal transducer (IL6ST) deficiency	*IL6ST*	AR	Decreased Th17 cells, reduced memory B cells, high IgE, variable antibody responses	Bacterial infections, abscesses, eczema, pulmonary abscesses, pneumatoceles; bone fractures; scoliosis; retention of primary teeth; craniosynostosis	Bacterial prophylaxi
IL6ST	*IL6ST*	AD (DN)	Increased Th2, naïve T cells, low memory T and B cells, low to normal NK cell counts, elevated IgE with normal or low IgG	Similar to AD HIE syndrome: dermatitis/eczema, eosinophilia, recurrent skin infections, pneumonia, bronchiectasis, pneumatoceles, pulmonary aspergillosis, connective tissue defects (scoliosis, face, joints, fractures, palate, tooth retention)	Bacterial and fungal prophylaxi
IL6ST	*IL6ST*	AR (LOF)	Death in utero or in neonatal period	Fatal Stuve-Wiedemann-like syndrome; skeletal dysplasia, lung dysfunction, renal abnormalities, thrombocytopenia, dermatitis, eczema, defective acute phase response, complete unresponsiveness to IL-6 family cytokines	None
ZNF341 deficiency	*ZNF341*	AR	Decreased Th17 and NK cells, reduced memory B cells, decreased response to *STAT3*-activating cytokines	Similar to AD-HIE: mild facial dysmorphism; early-onset eczema, mucocutaneous candidiasis, bacterial skin infections, *Staphylococcus aureus* abscesses, recurrent bacterial respiratory infections, pneumatoceles; hyperextensible joints; bone fractures and retention of primary teeth	Bacterial and fungal prophylaxi
ERBIN deficiency	*ERBB2IP*	AD	Increased Treg, moderate increased IgE	Susceptibility to *S. aureus,* eczema, recurrent respiratory infections, hyperextensible joints, scoliosis, arterial dilatation in some patients	Bacterial prophylaxi
Loeys-Dietz syndrome	*TGFBR1, TGFBR2*	AD	Elevated IgE	Recurrent respiratory infections; eczema, food allergies; hyperextensible joints, scoliosis, retention of primary teeth; aortic aneurysms	Bacterial prophylaxi
Comèl-Netherton syndrome	*SPINK5*	AR	Low memory B cells, elevated IgE and IgA, variable antibody responses	Congenital ichthyosis, bamboo hair, atopic diathesis, bacterial infections, failure to thrive	Bacterial prophylaxis replacemer for antibo deficiency
PGM3 deficiency	*PGM3*	AR	May have low T cells, B cells, memory B cells, normal or elevated IgG, IgA, and high IgE, eosinophilia	Severe atopy; autoimmunity; bacterial and viral infections; short stature, brachydactyly, dysmorphic facial features; intellectual disability and cognitive impairment, delayed CNS myelination in some patients	
CARD11 deficiency	*CARD11 DN LOF*	AD	Defective T-cell activation and proliferation, high IgE, Th2 skewing, poor specific antibody production, impaired activation of the NF-κB and mTORC1 pathways	Variable atopy, eczema, food allergy, eosinophilia; cutaneous viral infections, recurrent respiratory infections; lymphoma; CID	Ig replaceme for antibo deficiency

AD, Autosomal dominant; AR, Autosomal recessive; CID, combined immunodeficiency; CNS, central nervous system; DN, dominant negative; HIE, hyper-IgE; Ig, immunoglobulir IL, interleukin; IL6ST, gp130 common signal transducer of the IL-6 cytokine family; LOF, loss of function; MAIT, mucosal-associated invariant T cells; NKT, natural killer T cells; PJ *Pneumocystis jiroveci*; Th, T helper; Treg, regulatory T cells.
Adapted from Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societi

A boy has nearly absent circulating B cells and profoundly low serum immunoglobulins. Which gene in the common antibody-deficiency table causes agammaglobulinemia?

A. C5
B. ELANE
C. BTK
D. CTLA4
E. FOXP3

ORIGINAL SOURCE TABLE | Table 166.1 | PDF p. 1291 | printed p. 1278

Table 166.1 Genetic Basis of the Most Common Primary Antibody Deficiency Disorders

GENE	PHENOTYPE	DISORDER
BAFFR	CVID	Hypogammaglobulinemia
CD19	CVID	Hypogammaglobulinemia
CD20	CVID	Hypogammaglobulinemia
CD21	CVID	Hypogammaglobulinemia
CD81	CVID	Hypogammaglobulinemia
CTLA4	CVID	Hypogammaglobulinemia, pronounced lymphoproliferation and autoimmunity
ICOS	CVID	Hypogammaglobulinemia, autoimmunity, neoplasia
LRBA	CVID	Hypogammaglobulinemia, pronounced lymphoproliferation and autoimmunity
NFKB2	CVID	Hypogammaglobulinemia, autoimmunity
NFKB1	CVID	Hypogammaglobulinemia, autoimmunity
PIK3CD (AD)	CVID	Hypogammaglobulinemia, adenopathy
PI3KR1 (AD)	CVID	Hypogammaglobulinemia
TNFRSF13B	CVID	Hypogammaglobulinemia, low penetrance of disease
Unknown	CVID	Hypogammaglobulinemia, autoimmunity Majority of patients with CVID have no known gene variant
Unknown	IgG subclass deficiency	Variable association with infection
Unknown	Specific antibody deficiency	Normal immunoglobulin levels with poor vaccine responses
Unknown	Transient hypogammaglobulinemia of infancy	Vaccine responses are usually preserved, and most children outgrow this by age 3yr
Unknown	Selective IgA deficiency	Low or absent IgA; low concentrations of all immunoglobulins and of switched memory B cells in CVID
BLNK	Agammaglobulinemia	Absence of antibody production, lack of B cells
BTK	Agammaglobulinemia	Absence of antibody production, lack of B cells, X-linked agammaglobulinemia
CD79A	Agammaglobulinemia	Loss of the Igα required for signal transduction, absence of antibody production, lack of B cells
CD79B	Agammaglobulinemia	Loss of the Igβ required for signal transduction, absence of antibody production, lack of B cells
IGHM	Agammaglobulinemia	Loss of the Ig heavy chain, absence of antibody production, lack of B cells
IGLL1	Agammaglobulinemia	Loss of the surrogate light chain, absence of antibody production, lack of B cells
PI3KR1 (AR)	Agammaglobulinemia	Loss of signal transduction through the B-cell receptor, absence of antibody production, lack of B cells
PIK3CD δ (AR)	Agammaglobulinemia	Severely impaired signal transduction through B-cell receptor, absence of antibody production, lack of B cells
SLC39A7	Agammaglobulinemia	Impaired signal transduction through the B-cell receptor, absence of antibody production, lack of B cells
TCF3	Agammaglobulinemia	Loss of a key transcription factor for B-cell development, absence of antibody production, lack of B cells
AID	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
CD40	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, *Pneumocystis* and *Cryptosporidium* susceptibility
CD154	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, *Pneumocystis* and *Cryptosporidium* susceptibility
INO80	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
MSH6	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, malignancy
UNG	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
CD27	EBV lymphoproliferation	Memory B-cell deficiency Hypogammaglobulinemia
NEMO	Anhidrotic ectodermal dysplasia with immunodeficiency	Phenotype highly variable but includes specific antibody deficiency and CVID

AD, autosomal dominant; AR, autosomal recessive; CVID, common variable immunodeficiency; EBV, Epstein-Barr virus.

A mother is a carrier of X-linked agammaglobulinemia. Which gene in the inheritance table defines the classic X-linked form?

A. BTK
B. IGHM
C. CD79A
D. BLNK
E. IGLL1

ORIGINAL SOURCE TABLE | Table 166.2 | PDF p. 1293 | printed p. 1280

Table 166.2 Patterns of Inheritance for Different Forms of Agammaglobulinemia

DISEASE	GENE/PROTEIN AFFECTED	PATTERN OF INHERITANCE
XLA	Btk	X-linked
IGHM	μ heavy chain	Autosomal recessive
Igα	CD79a	Autosomal recessive
Igβ	CD79b	Autosomal recessive
λ5	IGLL1	Autosomal recessive
BLNK	BLNK scaffolding protein	Autosomal recessive
PIK3R1	PIK3 regulatory subunit	Autosomal recessive
PIK3CD	PIK3 regulatory subunit	Autosomal recessive
SLC39A7	Zinc transporter protein ZIP7	Autosomal recessive
TCF3	Transcription factors E12 and E47	Autosomal recessive or autosomal dominant
LRRC8	LRRC8 deficiency	Autosomal dominant
Hoffman syndrome	TOP2B	Autosomal dominant

XLA, X-linked agammaglobulinemia.

A child with recurrent bacterial respiratory infections also develops a serious enterovirus infection. Which primary antibody-deficiency phenotype in the table best matches?

A. Isolated IgG subclass deficiency
B. Selective polysaccharide antibody deficiency
C. Transient hypogammaglobulinemia of infancy
D. Agammaglobulinemia
E. Selective IgA deficiency

ORIGINAL SOURCE TABLE | Table 166.3 | PDF p. 1295 | printed p. 1282

Table 166.3 Main Phenotypes of Primary Antibody Deficiencies

PHENOTYPE	MAIN CLINICAL FEATURES	MAIN B-CELL FEATURES
Agammaglobulinemia	Bacterial infections (in respiratory tract) and enterovirus infections	Absence of CD19 B cells
Common variable immunodeficiency	Bacterial infections (in respiratory tract and gut), autoimmunity, cancer, and increased risk of granuloma	Highly variable; may see decreased memory B cells
Class switch defects	Bacterial and opportunistic infections	Decreased frequency of memory B cells
Selective IgA deficiency	Most often asymptomatic	Normal
IgG subclass deficiency	Frequent bacterial infections; diagnosis after age 2yr	B-cell subsets normal
Selective polysaccharide antibody deficiency	Bacterial infections (after age 2yr)	Normal IgG (including IgG2 and IgG4) levels, normal B-cell subsets

A boy has low IgG, IgA, and IgM, nearly absent CD19-positive B cells, and poor protein and polysaccharide antibody titers. Which laboratory phenotype fits?

A. Isolated T-cell lymphocytopenia
B. X-linked or autosomal recessive agammaglobulinemia
C. Selective IgA deficiency
D. Specific antibody deficiency with normal immunoglobulins
E. Isolated complement deficiency

ORIGINAL SOURCE TABLE | Table 166.4 | PDF p. 1295 | printed p. 1282

Table 166.4 Antibody Deficiency Disorders with Laboratory Evaluation

LABORATORY VALUES	XLA/AR AGAMMA	SELECTIVE IgA	SPECIFIC ANTIBODY DEFICIENCY	COMMON VARIABLE IMMUNODEFICIENCY	TRANSIENT HYPOGAMMA-GLOBULINEMIA
IgG	Decreased	Normal	Normal	Decreased to normal	Decreased
IgA	Decreased	Decreased	Normal	Decreased to normal	Normal
IgM	Decreased	Normal	Normal	Varies	Normal
LYMPHOCYTES					
B $CD19^+$	Decreased to absent	Normal	Normal	Decreased to normal memory B cells	Normal
T $CD4^+/CD3^+$	Normal to increased	Normal	Normal	Normal	Normal
$CD8^+/CD3^+$	Normal to increased	Normal	Normal	Normal	Normal
NK $16^+/56^+$	Normal to increased	Normal	Normal	Normal	Normal
SPECIFIC ANTIBODY TITERS					
Protein	Decreased	Normal	Normal	Decreased to normal	Normal
Polysaccharide	Decreased	Normal	Decreased	Decreased to normal	Normal

AR, Autosomal recessive; NK, natural killer; XLA, X-linked agammaglobulinemia.

pneumococcal vaccines (PCV-7, PCV-13, PCV-10, PCV-15, PCV-20) ... memory phenotype, also dependent on age, is defined as an adequate

A child has persistent eosinophilia, wheezing, and travel exposure with possible tissue-invasive helminth infection. Which listed pathogen is a plausible cause?

A. Neisseria meningitidis
B. Streptococcus pneumoniae
C. Mycoplasma pneumoniae
D. Staphylococcus epidermidis
E. Strongyloides stercoralis

ORIGINAL SOURCE TABLE | Table 169.1 | PDF p. 1308 | printed p. 1295

Table 169.1 Causes of Eosinophilia

ALLERGIC DISORDERS
Allergic rhinitis
Asthma
Acute and chronic urticaria
Atopic dermatitis
Angioedema
Hypersensitivity drug reactions (drug rash with eosinophilia and systemic symptoms [DRESS])
Eosinophilic gastrointestinal disorders
Interstitial nephritis
Mastocytosis

INFECTIOUS DISEASES
Tissue-Invasive Helminth Infections and Other Infections
Trichinosis
Toxocariasis
Strongyloidiasis
Ascariasis
Filariasis
Schistosomiasis
Echinococcosis
Amebiasis
Malaria
Scabies
Toxoplasmosis
Pneumocystis jirovecii
Scarlet fever
Allergic bronchopulmonary aspergillosis (ABPA)
Coccidioidomycosis
Human immunodeficiency virus (HIV)

MALIGNANT DISORDERS
Hodgkin disease and T-cell lymphoma
Acute myelogenous leukemia
Myeloproliferative disorders
Eosinophilic leukemia
Brain tumors

GASTROINTESTINAL DISORDERS
Inflammatory bowel disease
Peritoneal dialysis
Chronic active hepatitis
Eosinophilic Gastrointestinal Disorders
Eosinophilic esophagitis
Eosinophilic gastritis
Eosinophilic enteritis
Eosinophilic colitis

RHEUMATOLOGIC DISEASE
Rheumatoid arthritis
Eosinophilic fasciitis
Scleroderma
Dermatomyositis
Systemic lupus erythematosus
IgG4-related disease
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculit

IMMUNODEFICIENCY/IMMUNE DYSREGULATION DISEASE
Hyperimmunoglobulin E syndromes
Wiskott-Aldrich syndrome
Graft-versus-host disease
Omenn syndrome
Severe congenital neutropenia
Autoimmune lymphoproliferative syndromes (ALPS)
Immune dysregulation, polyendocrinopathy, X-linked (IPEX) and IPEX-like syndrome
Transplant rejection (solid organ)

MISCELLANEOUS
Thrombocytopenia with absent radii
Hypersensitivity pneumonitis
Adrenal insufficiency
Postirradiation of abdomen
Histiocytosis with cutaneous involvement
Hypereosinophilic syndromes
Cytokine infusion
Pemphigoid

by demonstrating a clonal interstitial deletion on chromosome 4q12

An infant has recurrent omphalitis and marked neutrophilia, with delayed umbilical cord separation. Which phagocyte disorder fits the infection-pattern table and context?

A. Hereditary angioedema
B. Isolated CD8 deficiency
C. Leukocyte adhesion deficiency
D. Selective IgA deficiency
E. C1-inhibitor deficiency

ORIGINAL SOURCE TABLE | Table 170.1 | PDF p. 1310 | printed p. 1297

Table 170.1 Infections and White Blood Cell Defects: Features That Can Be Seen in Phagocyte Disorders

SEVERE INFECTIONS		RECURRENT INFECTIONS		SPECIFIC INFECTIONS		UNUSUALLY LOCATED INFECTIONS	
TYPE OF INFECTION	DIAGNOSIS TO CONSIDER	SITE OF INFECTION	DIAGNOSIS TO CONSIDER	MICRO-ORGANISM	DIAGNOSIS TO CONSIDER	SITE OF INFECTION	DIAGNOSIS TO CONSID
Cellulitis	Neutropenia, LAD, CGD, HIES	Cutaneous	Neutropenia, CGD, LAD, HIES	*Staphylococcus epidermidis*	Neutropenia, LAD	Umbilical cord	LAD
Colitis	Neutropenia, CGD	Gums	LAD, neutrophil motility disorders	*Serratia marcescens, Nocardia, Burkholderia cepacia*	CGD	Liver abscess	CGD
Osteomyelitis	CGD, MSMD pathway defects	Upper and lower respiratory tract	Neutropenia, HIES, functional neutrophil disorders	*Aspergillus*	Neutropenia, CGD, HIES	Gums	LAD, neutrop motility disorders
		Gastrointestinal tract	CGD, MSMD pathway defects (salmonella)	Nontuberculous mycobacteria, BCG	MSMD pathway defects, SCID, CGD		
		Lymph nodes	CGD, MSMD pathway defects (mycobacteria)	*Candida*	Neutropenia, CGD, MPO		
		Osteomyelitis	CGD, MSMD				

BCG, Bacille Calmette-Guérin; CGD, chronic granulomatous disease; HIES, hyper-IgE syndrome; LAD, leukocyte adhesion deficiency; MPO, myeloperoxidase; MSMD, mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency.
From Leung DYM. *Pediatric Allergy: Principles and Practice*. 2nd ed. Philadelphia: Saunders; 2010. p. 134.

A newborn has delayed cord separation, recurrent bacterial soft-tissue infection, and marked neutrophilia. Which molecule is deficient in classic LAD type 1?

A. CD18 beta-2 integrin chain
B. BTK tyrosine kinase
C. C1 esterase inhibitor
D. FOXP3 transcription factor
E. C5 complement component

ORIGINAL SOURCE TABLE | Table 170.3 | PDF p. 1313 | printed p. 1300

Table 170.3 Leukocyte Adhesion Deficiency Syndromes

LEUKOCYTE ADHESION DEFICIENCY (LAD)	TYPE 1 (LAD-1)	TYPE 2 (LAD-2 OR CDG-IIc)	TYPE 3 (LAD-3)	E-SELECTIN DEFICIENCY	Rac2 DEFICIENCY
OMIM	116920	266265	612840	131210	602049
Inheritance pattern	Autosomal recessive	Autosomal recessive	Autosomal recessive	Unknown	Autosomal dominant
Affected protein(s)	β_2-Integrin common chain (CD18)	Fucosylated proteins (e.g., sialyl-Lewis X, CD15s)	Kindlin 3	Endothelial E-selectin expression	Rac2
Neutrophil function affected	Chemotaxis, tight adherence	Rolling, tethering	Chemotaxis, adhesion, superoxide production	Rolling, tethering	Chemotaxis, superoxide production
Delayed umbilical cord separation	Yes (severe phenotype only)	Yes	Yes	Yes	Yes
Leukocytosis/neutrophilia	Yes	Yes	Yes	No (mild neutropenia)	Yes

CDG-IIc, Congenital disorder of glycosylation IIc, OMIM, Online Mendelian Inheritance in Man.
From Leung DYM. *Pediatric Allergy: Principles and Practice*. 2nd ed. Philadelphia: Saunders; 2010. p. 139.

A boy has chronic granulomatous disease caused by a gp91phox defect. Which inheritance is assigned to that component?

A. Mitochondrial
B. Multifactorial only
C. Maternal imprinting
D. X-linked
E. Autosomal dominant

ORIGINAL SOURCE TABLE | Table 170.4 | PDF p. 1315 | printed p. 1302

Table 170.4 Classification of Chronic Granulomatous Disease

COMPONENT AFFECTED	INHERITANCE	SUBTYPE*	FLAVOCYTOCHROME b SPECTRUM	NBT SCORE (% POSITIVE)	INCIDENCE (% OF CASES)
$gp91^{phox}$	X	$X91^{0}$	0	0	60
		$X91^{-}$	Low	80-100 (weak)	5
		$X91^{-}$	Low	5-10	<1
		$X91^{+}$	0	0	1
$p22^{phox}$	A	A220	0	0	4
		$A22^{+}$	N	0	<1
$p47^{phox}$	A	A470	N	0†	25
$p67^{phox}$	A	A670	N	0	5
		$A67^{+}$	N	0	<1
$p40^{phox}$	A	$A40^{-}$	N	100	<1

*In this nomenclature, the first letter represents the mode of inheritance (X-linked [X] or autosomal recessive [A]), whereas the number indicates the *phox* component that is genetically affected. The superscript symbols indicate whether the level of protein of the affected component is undetectable (^{0}), diminished ($^{-}$), or normal ($^{+}$), as measured by immunoblot analysis.
†Can be weakly positive.

A child has persistent severe neutropenia documented on three separate blood counts. Which next evaluation appears in the diagnostic approach table?

A. A single serum IgE level as definitive testing
B. Bone marrow examination with cytogenetics
C. No further assessment until adulthood
D. Isolated skin-prick allergy testing
E. Routine echocardiography as the sole test

ORIGINAL SOURCE TABLE | Table 171.1 | PDF p. 1318 | printed p. 1305

Table 171.1 Diagnostic Approach for Patients with Leukopenia

EVALUATION	ASSOCIATED CLINICAL DIAGNOSES
INITIAL EVALUATION	
History of acute or chronic leukopenia	
General medical history including prior serious, recurrent or unusual infections and malignancy	Congenital syndromes (severe congenital neutropenia, cyclic neutropenia Shwachman-Diamond, Wiskott-Aldrich, Fanconi anemia, dyskeratosis congenita, glycogen storage disease type Ib, disorders of vesicular transport, GATA2 haploinsufficiency, and primary immunodeficiencies)
Physical examination: stomatitis, gingivitis, dental defects, warts, lymphedema, congenital anomalies	
Spleen size	Hypersplenism
History of drug exposure	Drug-associated neutropenia
Complete blood count with differential and reticulocyte counts	Neutropenia, aplastic anemia, autoimmune cytopenias
IF ANC <1,000/μL	
Evaluation of Acute-Onset Neutropenia	
Repeat blood counts in 3-4 wk	Transient myelosuppression (e.g., viral)
Serology and cultures for infectious agents	Active or chronic infection with viruses (e.g., EBV, CMV), bacteria, mycobacteria, rickettsia
Discontinue drug(s) associated with neutropenia	Drug-associated neutropenia
Test for antineutrophil antibodies	Autoimmune neutropenia
Measure quantitative immunoglobulins (IgG, IgA, IgM, IgE), lymphocyte subsets	Neutropenia associated with disorders of immune function
IF ANC <500/μL ON THREE SEPARATE TESTS	
Bone marrow aspiration and biopsy, with cytogenetics	Severe congenital neutropenia, cyclic neutropenia, Shwachman-Diamond syndrome, myelokathexis; chronic benign or idiopathic neutropenia; reticular dysgenesis
Glucocorticoid stimulation test	Chronic benign or idiopathic neutropenia, some autoimmune neutropeni
Serial CBCs (3/wk for 6 wk)	Cyclic neutropenia
Exocrine pancreatic function	Shwachman-Diamond syndrome
Skeletal radiographs	Shwachman-Diamond syndrome, cartilage-hair hypoplasia, Fanconi anem
IF ALC <1,000/μL	
Repeat blood counts in 3-4 wk	Transient leukopenia (e.g., viral)
IF ALC <1,000/μL THREE SEPARATE TESTS	
HIV antibody or RNA test	HIV infection, AIDS
Quantitative immunoglobulins (IgG, IgA, IgM, IgE), vaccine titers, lymphocyte subsets; qualitative lymphocyte proliferation to mitogens/antigens	Congenital or acquired disorders of immune function
IF THERE IS PANCYTOPENIA	
Bone marrow aspiration and biopsy	Bone marrow replacement by malignancy, fibrosis, granulomata, storage cells; aplastic anemia
Bone marrow cytogenetics and flow cytometry	Myelodysplasia, leukemia
Copper, vitamin B12 and folate levels	Vitamin deficiencies

ALC, Absolute lymphocyte count; ANC, absolute neutrophil count; CBC, complete blood count; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

A child develops neutropenia after a new anticonvulsant. Which etiologic category is listed among causes extrinsic to marrow myeloid cells?

A. Congenital maturation arrest
B. Cyclic neutropenia from ELANE
C. Myelokathexis due to CXCR4
D. Schwachman–Diamond syndrome
E. Drug-induced neutropenia

ORIGINAL SOURCE TABLE | Table 171.2 | PDF p. 1319 | printed p. 1306

Table 171.2 Causes of Neutropenia Extrinsic to Marrow Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Infection	Viruses, bacteria, protozoa, rickettsia, fungi	Clinical features and laboratory findings of the infectious agent
Drug induced	Phenothiazines, sulfonamides, anticonvulsants, penicillins, aminopyrine	Usually none; occasional hypersensitivity reaction (fever, lymphadenopathy, rash, hepatitis, nephritis, pneumonitis, aplastic anemia) or antineutrophil antibody
Immune neutropenia	Alloimmune, autoimmune	Myeloid hyperplasia with left shift in bone marrow (may appear to be "arrested" at metamyelocyte or band stage)
Reticuloendothelial sequestration	Hypersplenism	Anemia, thrombocytopenia
Bone marrow replacement	Myelofibrosis, malignancy (leukemia, lymphoma, metastatic solid tumor, etc.)	Anemia, thrombocytopenia, marrow fibrosis, malignant cells in bone marrow sites of extramedullary hematopoiesis
Cancer chemotherapy or radiation therapy	Suppression of myeloid cell production	Anemia, thrombocytopenia, bone marrow hypoplasia

A child with neutropenia has macrocytosis and restrictive eating with malnutrition. Which acquired myeloid cause in the table should be assessed?

A. C1 inhibitor deficiency
B. A terminal complement defect
C. Vitamin B12, copper, or folate deficiency
D. Inherited ELANE mutation as the required cause
E. Congenital CD18 deficiency

ORIGINAL SOURCE TABLE | Table 171.3 | PDF p. 1319 | printed p. 1306

Table 171.3 Acquired Disorders of Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Aplastic anemia	Stem cell destruction and depletion	Pancytopenia
Vitamin B_{12}, copper, or folate deficiency	Malnutrition; congenital deficiency of B_{12} absorption, transport, and storage; vitamin avoidance	Megaloblastic anemia, hyper-segmented neutrophils
Acute leukemia, chronic myelogenous leukemia	Bone marrow replacement with malignant cells	Pancytopenia, leukocytosis
Myelodysplasia	Dysplastic maturation of stem cells	Bone marrow hypoplasia with megaloblastoid red cell precursors, thrombocytopenia
Prematurity with birthweight <2 kg	Impaired regulation of myeloid proliferation and reduced size of postmitotic pool	Maternal preeclampsia
Chronic idiopathic neutropenia	Impaired myeloid proliferation and/or maturation	None
Paroxysmal nocturnal hemoglobinuria	Acquired stem cell defect secondary to *PIGA* gene variant	Pancytopenia, thrombosis (hepatic vein thrombosis)

A child has an acute influenza infection and transient neutropenia. Which etiologic group includes influenza in the infection table?

A. Viral infections
B. Protozoan infections
C. Fungal infections
D. Rickettsial infections
E. Helminth infections

ORIGINAL SOURCE TABLE | Table 171.4 | PDF p. 1319 | printed p. 1306

Table 171.4 Infections Associated with Neutropenia

Viral	Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella, HHV-6, SARS-CoV-2
Bacterial	*Brucella*, paratyphoid, pertussis, tuberculosis (disseminated), tularemia, *Shigella*, typhoid; any form of sepsis
Fungal	Histoplasmosis (disseminated)
Protozoan	Malaria, leishmaniasis (kala-azar)
Rickettsial	*Anaplasma* (formerly *Ehrlichia*) *phagocytophilum*, psittacosis, Rocky Mountain spotted fever, typhus, rickettsialpox

HHV-6, Human herpesvirus-6.

Neutropenia appears abruptly after a medication exposure and promptly recurs after a small rechallenge. Which mechanism in the table is suggested?

A. Nutritional copper deficiency
B. Cyclic neutropenia
C. Postviral marrow recovery
D. Immunologic drug-induced neutropenia
E. Chronic inherited marrow failure

ORIGINAL SOURCE TABLE | Table 171.5 | PDF p. 1320 | printed p. 1307

Table 171.5 Forms of Drug-Induced Neutropenia

	IMMUNOLOGIC	TOXIC	HYPERSENSITIVITY
Paradigm drugs	Aminopyrine, propylthiouracil, penicillins	Phenothiazines, clozapine	Phenytoin, phenobarbital
Time to onset	Days to weeks	Weeks to months	Weeks to months
Clinical appearance	Acute, often explosive symptoms	Often asymptomatic or insidious onset	May be associated with fever, rash, nephritis, pneumonitis, or aplastic anemia
Rechallenge	Prompt recurrence with small test dose	Latent period; high doses required	Latent period; high doses require
Laboratory findings	Antineutrophil antibody may be positive; bone marrow myeloid hyperplasia	Bone marrow myeloid hypoplasia	Bone marrow myeloid hypoplasi

for example to chloramphenicol, are unpredictable with regard to

by abnormal macrophages filled with blue-staining pigment gr

A child has recurrent episodes of profound neutropenia at regular intervals. Which gene in the intrinsic myeloid-disorder table is linked to cyclic neutropenia?

A. CD40LG
B. ELANE
C. FOXP3
D. BTK
E. C1QA

ORIGINAL SOURCE TABLE | Table 171.6 | PDF p. 1322 | printed p. 1309

Table 171.6 Intrinsic Disorders of Myeloid Precursor Cells

SYNDROME	INHERITANCE *(GENE)*	CLINICAL FEATURES (INCLUDING STATIC NEUTROPEN UNLESS OTHERWISE NOTED)
PRIMARY DISORDERS OF MYELOPOIESIS		
Cyclic neutropenia	AD *(ELANE)*	Periodic oscillation (21-day cycles) in ANC
Severe congenital neutropenia	AD (primarily *ELANE*, also *GFI1* and others)	Risk of MDS/AML
	AR *(G6PC3, HAX1, JAGN1, CSF3R)* (*HAX1* = Kostmann syndrome)	*G6PC3:* cardiac and urogenital anomalies, venous angioectasi *HAX1:* neurologic abnormalities, risk of MDS/AML
	XL *(WAS)*	Neutropenic variant of Wiskott-Aldrich syndrome
DISORDERS OF MOLECULAR PROCESSING		
Shwachman-Diamond syndrome	Ribosomal defect: AR *(SBDS, DNAJC21, EFL1, SRP54)*	Pancreatic insufficiency, metaphyseal dysostosis, bone marr failure, MDS/AML
Telomere biology disorders/ dyskeratosis congenita	Telomere length abnormality: XL *(DKC1)*, AD or AR *(ACD, RTEL1, TERC, TERT)*, AD *(NAF1, TINF2)*, AR *(CTC1, NHP2, NOP10, PARN, STN1, WRAP53)*	Nail dystrophy, leukoplakia, abnormal and carious teeth, lacey reticulated hyperpigmentation of the skin, bone marrow failure, various malignancies, Coats plus syndrom (*CTC1* and *STN1*)
DISORDERS OF VESICULAR TRAFFICKING		
Chédiak-Higashi syndrome	AR *(LYST)*	Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired NK cell function, HLH
Griscelli syndrome, type II	AR *(RAB27a)*	Partial albinism, impaired NK cell function, neurologic impairment, HLH
Cohen syndrome	AR *(COH1)*	Partial albinism, pigmentary retinopathy, developmental delay, facial dysmorphism
Hermansky-Pudlak syndrome, type II	AR *(AP3B1)*	Cyclic neutropenia, partial albinism, HLH
p14 deficiency	AR *(MAPBPIP)*	Partial albinism, coarse facial features, decreased B and T cells
VPS45 defects	AR *(VPS45)*	Neutrophil dysfunction, bone marrow fibrosis, nephromeg
DISORDERS OF METABOLISM		
Glycogen storage disease, type 1b	AR *(G6PT1)*	Hepatic enlargement, growth retardation, impaired neutrop motility
Methylmalonic/propionic acidemia/ aciduria	AR (*CLPB*) Mutase or cobalamin transporters/ propionyl coenzyme A carboxylase	Ketoacidosis, metabolic stroke, depressed consciousness, megaloblastic anemia
3-Methylglutaconic aciduria	AR (*CLPB*)	Nonspecific finding indicative of mitochondrial dysfunctior or associated with known syndromes
Barth syndrome	XL *(TAZ)*	Episodic neutropenia, dilated cardiomyopathy, methylglutacor aciduria
Pearson syndrome	Mitochondrial (DNA deletions)	Episodic neutropenia, pancytopenia; defects in exocrine pancreas, liver, and kidneys
NEUTROPENIA IN DISORDERS OF IMMUNE FUNCTION		
Common variable immunodeficiency	Familial, sporadic *(TNFRSF13B)*	Hypogammaglobulinemia, other immune system defects
IgA deficiency	Unknown (Unknown or *TNFRSF13B*)	Decreased IgA
Severe combined immunodeficiency	AR, XL (multiple loci)	Absent humoral and cellular immune function
Hyper-IgM syndrome	XL *(HIGM1)*	Absent IgG, elevated IgM, autoimmune cytopenias
WHIM syndrome	AD *(CXCR4)*	Warts, hypogammaglobulinemia, infections, myelokathexi
Cartilage-hair hypoplasia	AR *(RMRP)*	Lymphopenia, short-limbed dwarfism, metaphyseal chondrodysplasia, fine sparse hair
Schimke immunoosseous dysplasia	AR *(SMARCAL1)*	Lymphopenia, pancytopenia, spondyloepiphyseal dysplasi growth retardation, renal failure
X-linked agammaglobulinemia	XL (Bruton tyrosine kinase (*BTK*))	Agammaglobulinemia, neutropenia in ~25%
GATA2 haploinsufficiency	AD (*GATA2*)	Pulmonary alveolar proteinosis, lymphedema, monocytopenia, decreased B and NK cells, risk for sever fungal/mycobacterial/viral infections, susceptibility to leukemia/MDS, MonoMAC syndrome

AD, Autosomal dominant; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; AR, autosomal recessive; HLH, hemophagocytic lymphohistiocytosis; MDS, myelodysplas syndrome; NK, natural killer; XL, X-linked.

A child has congenital neutropenia and exocrine pancreatic insufficiency. Which syndrome does the organ-feature table favor?

A. WHIM syndrome
B. Barth syndrome
C. Wiskott–Aldrich syndrome
D. Cohen syndrome
E. Shwachman–Diamond syndrome

ORIGINAL SOURCE TABLE | Table 171.7 | PDF p. 1324 | printed p. 1311

Table 171.7 Main Organ Associated Features and Genetic Subtypes of Congenital Neutropenia

SYSTEM	HEMATOLOGIC OR ASSOCIATED FEATURES	DISEASE	GENE
Blood/bone marrow maturation	Maturation arrest	Severe congenital neutropenia Severe congenital neutropenia Wiskott-Aldrich syndrome *Neutropenia G6PC3* *G-CSF receptor*	*ELANE* *HAX1* *WAS* *G6PC3* Extracellular domain of *CSF3R*
	No maturation arrest	GSDIb WHIM Shwachman Diamond disease Cohen disease Hermansky-Pudlak type 2	*G6PT1* *CXCR4* *SBDS* *VPS13B* *AP3B1*
	Myelokathexis	WHIM	*CXCR4*
Pancreas	External pancreatic insufficiency	Shwachman Diamond disease	*SBDS*
Eyes	Congenital cataract	Charcot-Marie-Tooth	*Dynamin 2*
	Retinochoroidal dystrophy	Cohen disease	*VPS13B*
Heart	Heart: arrhythmias	Neutropenia G6PC3	*G6PC3*
	Dilated cardiomyopathy	Barth diseases	*TAZ*
	Cardiomyopathy	Shwachman Diamond disease	*SBDS*
	Various cardiac abnormalities	Shwachman Diamond disease WHIM Neutropenia G6PC3	*SBDS* *CXCR4* *G6PC3*
Skin	Skin xerosis eczema	Shwachman Diamond disease	*SBDS*
	Skin: prominent superficial veins	Neutropenia G6PC3	*G6PC3*
	Skin poikiloderma	SCN with poikiloderma type Clericuzio	*16ORF57*
	Skin: Partial or complete albinism	Hermansky-Pudlak type 2 AP14 defect Chédiak Higashi disease Griscelli disease	*AP3B1* *AP14* *LYST* *RAB27A*
	Hair: fine, sparse, and light-colored	Cartilage-hair hypoplasia	*RMRP*
Bone	Metaphyseal dysplasia	Shwachman Diamond disease Cartilage-hair hypoplasia	*SBDS* *RMRP*
	Facial dysmorphia	Cohen disease	*VPS13B*
Central nervous system	Mental retardation	Kostmann disease Shwachman Diamond disease Cohen disease	*HAX1* *SBDS* *VPS13B*
Muscle	Weakness	Neutropenia G6PC3 Axonal Charcot-Marie-Tooth disease	*G6PC3* *Dynamin 2*
Metabolic pathway	Fasting intolerance and glycogenosis	Glycogen storage disease type Ib	*SLC37A4*
Inner ear	Inner ear defect	GFI 1/severe chronic neutropenia Reticular dysgenesia	*GFI1* *AK2*
Urogenital tract	Uropathy	Neutropenia G6PC3	*G6PC3*
	Cryptorchidism	Cohen disease Neutropenia G6PC3	*VPS13B* *G6PC3*

G-CSF, Granulocyte colony-stimulating factor; SCN, severe congenital neutropenia; WHIM, warts, hypogammaglobulinemia, infections, myelokathexis.
From Donadieu J, Fenneteau O, Beaupain B, Mahlaoui N, Chantelot CB. Congenital neutropenia: diagnosis, molecular bases and patient management. *Orphanet J Rare Dis.* 2011;6:26. Table 2.

A child has lymphocytopenia in the setting of a protein-losing enteropathy. Which category in the causes table applies?

A. Primary neutrophil oxidative-burst defect
B. Hereditary C1 inhibitor deficiency
C. Acquired systemic disease
D. Inherited absence of lymphopoietic stem cells
E. Isolated terminal complement deficiency

ORIGINAL SOURCE TABLE | Table 171.8 | PDF p. 1325 | printed p. 1312

Table 171.8 Causes of Lymphocytopenia

ACQUIRED	
Infectious diseases	AIDS, hepatitis, influenza, sepsis, tuberculosis, typhoid, COVID-19
Iatrogenic	Corticosteroids, cytotoxic chemotherapy, high-dose PUVA, immunosuppressive therapy, radiation, thoracic duct drainage/ chylothorax
Systemic diseases	Hodgkin disease, lupus erythematosus, myasthenia gravis, protein-losing enteropathy, renal failure, sarcoidosis
Other	Aplastic anemia, dietary deficiencies, thermal injury
INHERITED	
Aplasia of lymphopoietic stem cells	Cartilage-hair hypoplasia, ataxia-telangiectasia, SCID, thymoma, Wiskott-Aldrich syndrome

PUVA, Psoralen and ultraviolet A irradiation; SCID, severe combined immunodeficiency.

A child with a severe burn has transient neutrophilia. Which category in the table includes this presentation?

A. Acute acquired neutrophilia
B. Chronic acquired neutrophilia
C. Lifelong congenital neutrophilia
D. Primary lymphocytopenia
E. Monocyte-specific proliferation

ORIGINAL SOURCE TABLE | Table 172.1 | PDF p. 1327 | printed p. 1314

Table 172.1 Causes of Neutrophilia

TYPE	CAUSE	EXAMPLE
Acute acquired	Bacterial infections	
	Neutrophil disorder	Leukocyte adhesion defects
	Surgery	
	Acute stress	Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise
	Drugs	Corticosteroids, epinephrine, hematopoietic growth factors, lithium
Chronic acquired	Chronic inflammation	Inflammatory bowel disease, rheumatoid arthritis, vasculitis, cigarette exposure
	Persistent infection	Tuberculosis
	Persistent stress	Chronic blood loss, hypoxia, sickle cell and other chronic hemolytic anemias
	Drugs	Corticosteroids, lithium; rarely ranitidine, quinidine
	Other	Postsplenectomy, tumors, Hodgkin disease, pregnancy, Sweet syndrome
Lifelong	Congenital asplenia	
	Hereditary disorders	Familial cold urticaria, hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes

A toddler has persistent monocytosis, splenomegaly, and concern for a myeloid malignancy. Which listed malignancy is particularly relevant?

A. Retinoblastoma
B. Wilms tumor
C. Neuroblastoma
D. Juvenile myelomonocytic leukemia
E. Ewing sarcoma

ORIGINAL SOURCE TABLE | Table 172.2 | PDF p. 1327 | printed p. 1314

Table 172.2 Causes of Monocytosis

CAUSE	EXAMPLE
Infections	
Bacterial	Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis, typhoid
Nonbacterial	Fungal infections, kala-azar, malaria, Rocky Mountain spotted fever, typhus
Hematologic disorders	Congenital and acquired neutropenias, hemolytic anemias
Malignant disorders	Acute myelogenous leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphomas, preleukemia
Chronic inflammatory diseases	Inflammatory bowel disease, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus
Miscellaneous	Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression

A child has recurrent meningococcal infection. Which complement components form the membrane attack complex in the component table?

A. CD46, CD55, and CD59 only
B. C5 through C9
C. C1q, C1r, and C1s only
D. Factor B and factor D only
E. C3a and C5a receptors

ORIGINAL SOURCE TABLE | Table 173.2 | PDF p. 1328 | printed p. 1315

Table 173.2 Components of Complement System

SERUM COMPONENTS THAT ARE THE CORE OF THE COMPLEMENT SYSTEM
Classical pathway: C1q, C1r, C1s, C4, C2, C3
Alternative pathway: factor B, factor D
Lectin pathway: Mannose-binding lectin (MBL), ficolins 1/2/3, MBL-associated serine proteases (MASPs) 1/2/3
Membrane attack complex: C5, C6, C7, C8, C9
Regulatory protein, enhancing: properdin
Regulatory proteins, downregulating: C1 inhibitor (C1-INH), C4-binding protein (C4-bp), factor H, factor I, vitronectin, clusterin, carboxypeptidase N (anaphylatoxin inactivator)
MEMBRANE REGULATORY PROTEINS
CR1 (CD35), membrane cofactor protein (MCP; CD46), decay-accelerating factor (DAF, CD55), CD59 (membrane inhibitor of reactive lysis)
MEMBRANE RECEPTORS
CR1 (CD35), CR2 (CD21), CR3 (CD11b/CD18), CR4 (CD11c/CD18)
C3a receptor, C5a receptor, C1q receptors, complement receptor of the immunoglobulin superfamily (CRIg)

A child has recurrent Neisseria meningitidis infections and suspected terminal complement deficiency. Which strategy in the evaluation table should be used first?

A. Measure serum IgE alone
B. Perform a neutrophil oxidative-burst test as the sole evaluation
C. Diagnose terminal deficiency from total IgG alone
D. Use lymphocyte proliferation to exclude complement disease
E. Screen complement pathway function before targeted component testing

ORIGINAL SOURCE TABLE | Table 173.3 | PDF p. 1331 | printed p. 1318

Table 173.3 The Steps for Complement System Evaluation

COMPLEMENT EVALUATION	EXAMPLES
Total complement activity	CH50, AP50, lectin pathway
Quantification of single components	C3, C4, MBL, properdin
Functional activity of single components	Functional C1 inhibitor
Products of complement activation	C3d; C3dg
Autoantibodies to complement components	Anti-C1q; nephritic factor
Cell surface expression	CD55; CD59; CR3/4
Tissue deposition of complement proteins or fragments	Deposition of C3 or factor H in injury burns
Genetic evaluation	Next generation sequencing or specific gene panels

urticarial vasculitis and/or proliferative systemic lupus erythematosus

A child develops recurrent invasive Neisseria infections with otherwise unremarkable immune testing. Which group of deficiencies is most consistent with the pathway table?

A. BTK deficiency
B. ELANE deficiency
C. C5–C9 terminal component deficiencies
D. C1-inhibitor deficiency alone
E. FOXP3 deficiency

ORIGINAL SOURCE TABLE | Table 173.4 | PDF p. 1332 | printed p. 1319

Table 173.4 Pathway Deficiencies of Complement System

DEFICIENCY	INHERITANCE	ASSOCIATED SYMPTOMS/DISORDERS
C1q, C1r/s (often combined), C2, C4 (total C4 deficiency)	AR	SLE, systemic infections with encapsulated organisms; heterozygo C2 deficiency may have a reduced CH50 but remain asymptoma
C4A or C4B	Complex	Susceptibility to infections and/or autoimmunity (SLE); mostly asymptomatic
C3 GOF	AD	aHUS (2–10% of the cases)
C3	AR	Pyogenic infections, neisserial infections, glomerulonephritis, AMD
C5, C6, C7, C8α–γ/C8β	AR	Neisserial infections; recurrent meningitis
C9	AR	Neisserial infections (mostly asymptomatic)
Factor B	AR*	Neisserial and pneumococcal infections, aHUS (1–4% of the cases)
Factor D	AR	Bacterial infections
MBL	Polymorphism	Bacterial infections (mostly asymptomatic) and susceptibility to autoimmunity in some cases
Ficolin-3 (H-ficolin)	Polymorphism	Various clinical phenotypes
MASP-1	AR	3MC syndrome
MASP-2	AR	Respiratory infections, mostly asymptomatic

*AR, Autosomal recessive non-codominant.
AR, Autosomal recessive; AD, Autosomal dominant; C4A and C4B, isotypes encoded by C4A and C4B genes, respectively; GOF, gain of function; SLE, systemic lupus erythemato aHUS, atypical hemolytic uremic syndrome; AMD, aging macular degeneration; 3MC, Mingarelli, Malpuech, Michels and Carnevale.

A child has recurrent swelling without urticaria and low functional C1 inhibitor. Which inheritance pattern does the regulator-deficiency table list?

A. Autosomal dominant
B. X-linked recessive
C. Mitochondrial
D. Y-linked
E. Autosomal recessive in every case

ORIGINAL SOURCE TABLE | Table 173.5 | PDF p. 1335 | printed p. 1322

Table 173.5 Protein Regulators and Receptor Deficiencies of Complement System

DEFICIENCY	INHERITANCE	ASSOCIATED SYMPTOMS/DISORDERS
C1 inhibitor	AD	HAE with C1-INH deficiency
C4-binding protein	Unknown	Atypical Morbus Behçet, angioedema, protein S deficit
Properdin	X-linked recessive	Meningitis (*Neisseria*)
Factor H	AR	Membranoproliferative glomerulonephritis, AMD, aHUS (20–30% of the cases)
Factor I	AR	Pyogenic infections, neisserial infections, glomerulonephritis, aHUS (5–10% of the cases), central nervous system inflammation
CFHR1 (FHR3)	Complex	aHUS, C3G, AMD, RA, SLE
Thrombomodulin (CD141)	AD	aHUS (3–5% of the cases)
CD46/MCP	Most often heterozygous or compound heterozygous pathogenic variants	aHUS (10–15% of the cases)
CD55/DAF	AR	Protein losing enteropathy
CD55 (DAF) or CD59	AR	PNH
CD59	AR	Chronic hemolysis and relapsing peripheral demyelinating disease, cerebral infarction
CR2 (CD21)	AR	Infections, associated with CVID
CR3 (CD18/CD11b); CR4 (CD18/CD11c, LFA-1)	AR	LAD

CFHR1, Complement factor H related 1; MCP, membrane cofactor protein; DAF, decay-accelerating factor; LFA-1, integrin called lymphocyte function-associated antigen 1; AR, autosomal recessive; AD, autosomal dominant; aHUS, atypical hemolytic uremic syndrome; C3G, C3 glomerulopathy; SLE, systemic lupus erythematosus; AMD, aging macular degeneration; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; PNH, paroxysmal nocturnal hemoglobinuria; CVID, common variable immunodeficiency; LAD, leukocyte adhesion deficiency.

A boy has severe early enteropathy, eczema, and type 1 diabetes with immune dysregulation. Which gene is listed for the classic X-linked Tregopathy?

A. CTLA4
B. BACH2
C. STAT3
D. FOXP3
E. LRBA

ORIGINAL SOURCE TABLE | Table 174.1 | PDF p. 1338 | printed p. 1325

Table 174.1 Tregopathies

GENE (PROTEIN)	DISORDER	INHERITANCE	CLINICAL PHENOTYPE	DEFINITIVE OR DISEAS SPECIFIC TREATMENT
FOXP3	IPEX syndrome	XL	Enteropathy, type 1 diabetes, eczema, FTT, autoimmune cytopenias, thyroiditis, hepatitis	Tacrolimus, cyclosporine Allogeneic HCT
IL2RA	CD25 deficiency	AR	Enteropathy, eczema, lymphoproliferation, recurrent infections	Allogeneic HCT
CTLA-4 ALPSV	CTLA4 haploinsufficiency	AD	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Sirolimus Abatacept, belatacept Allogeneic HCT
LRBA	LRBA deficiency	AR	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Abatacept, belatacept Allogeneic HCT
BACH2	BACH2 deficiency	AD	Enteropathy, lymphoproliferation, recurrent respiratory tract infections, infections	Allogeneic HCT
STAT3	STAT3 GOF	AD, GOF	Enteropathy, autoimmune cytopenias, lymphoproliferation, type 1 diabetes, recurrent infections	Jakinibs Allogeneic HCT
STAT5B	STAT5B	AD, AR	Eczema, growth hormone deficiency, infections, enteropathy, JIA, ITP, chronic lung disease	Symptom specific therapy HCT

IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked; XL, X-linked; FTT, failure to thrive; HCT, hematopoietic cell transplant; AR, autosomal recessive; CTLA, cytotoxic T-lymphocyte protein; ALPSV, autoimmune lymphoproliferative disease V; AD, autosomal dominant; LRBA, lipopolysaccharide-responsive and beigelike anchor protei BACH, broad complex-tramtrack-bric a brac and Cap'n'collar homology; STAT, signal transducer and activator of transcription; GOF, gain of function; JIA, juvenile idiopathic arthrit ITP, immune thrombocytopenic purpura.

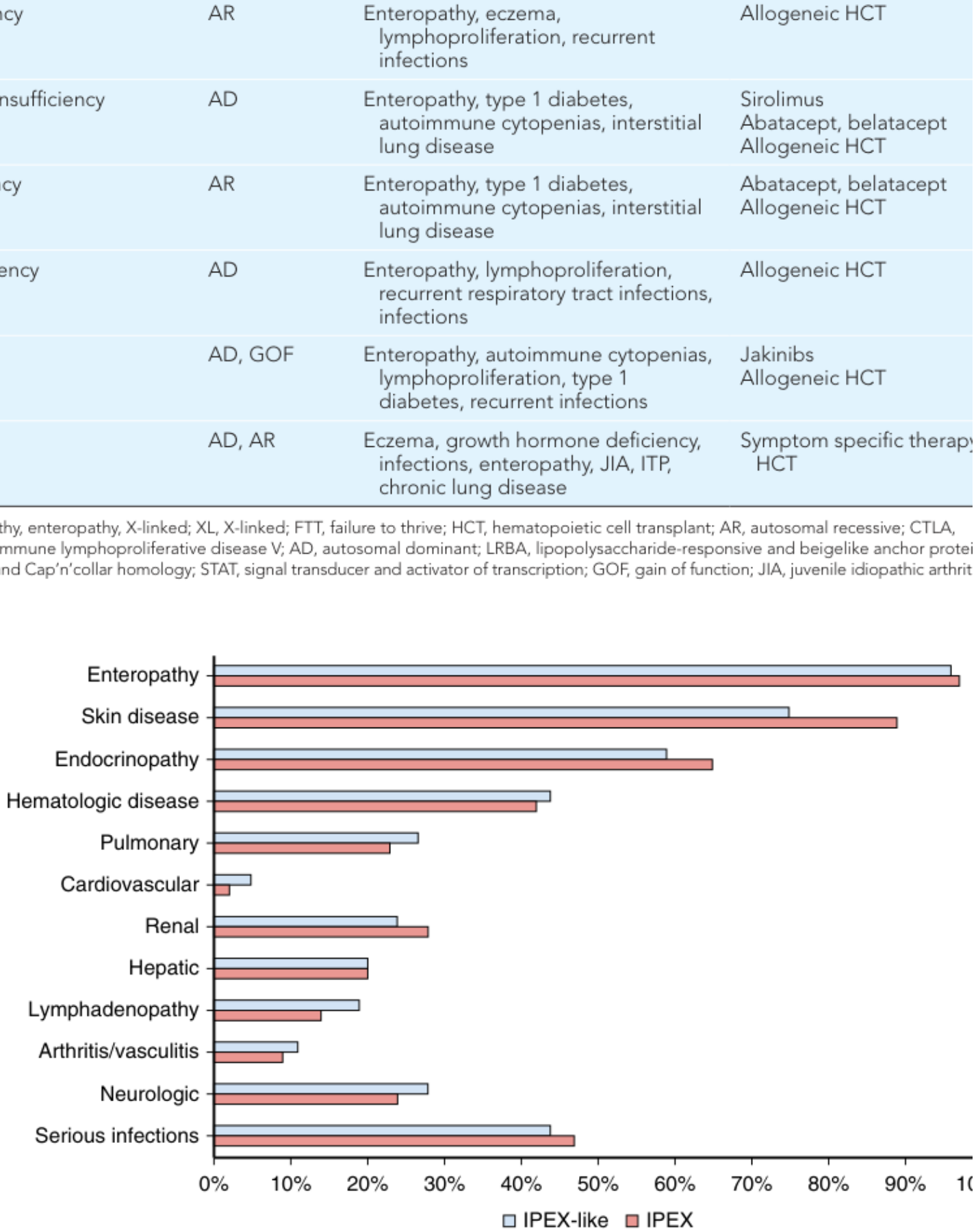

Fig. 174.2 Clinical manifestations in the IPEX-like cohorts. (*Modified from Gambineri E, Ciullini Mannurita S, Hagin D, et al. Clinical, immunological, and molecular heterogeneity of 173 patients with the phenotype of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. Front Immunol. 2018;9:2411. Fig. 5.*)

A boy has severe EBV disease with lymphoproliferation, hypogammaglobulinemia, and an X-linked magnesium transport defect. Which gene is listed?

A. RASGRP1
B. MAGT1
C. ITK
D. CD70
E. CTPS1

ORIGINAL SOURCE TABLE | Table 174.2 | PDF p. 1340 | printed p. 1327

Table 174.2 Primary or Genetic EBV Susceptibility Disorders

GENE (PROTEIN)	DISORDER	INHERITANCE	PATHOGENESIS	ADDITIONAL FEATURES	DEFINITIVE OR DISEASE-SPECIF TREATMENT*
MAGT1	XMEN (X-linked immunodeficiency w/Mg^{2+} defect, EBV infection and neoplasia)	XL	Defective Mg^{2+} transporter; ↓ NKG2D expression results in defective cytotoxicity	Chronic EBV infection rather than full-scale HLH, viral infections, lung infections, autoimmune cytopenia, lymphoma	Allogeneic HCT
ITK	Lymphoproliferative syndrome 1	AR	Defective tyrosine kinase function; defective cytotoxic T-cell expansion, and cytolytic capacity; ↓ iNKT cells	Chronic EBV infection, lung infections, PJP, autoimmune cytopenia, lymphoma	Allogeneic HCT
CD27	Lymphoproliferative syndrome 2	AD	CD27 is a co-stimulatory molecule on T cells; required for normal T-cell proliferation and cytotoxicity against EBV-infected B cells; ↓ iNKT cells	Chronic EBV infection, lung infections, uveitis, oral and anal ulcers, hypogammaglobulinemia, lymphoma	Allogeneic HCT
CD70	Lymphoproliferative syndrome 3	AR	CD70 expressed by EBV-infected B cells interacts with CD27 on T cells; required for normal expansion and cytotoxicity of T cells; ↓ NKG2D and 2B4 expression; ↓ iNKT cells	Chronic EBV infection, lung infections, lymphoma	Allogeneic HCT
CTPS1	CTPS1 deficiency	AR	Enzyme involved in de novo synthesis of cytidine nucleotide triphosphate (CTP); deficiency leads to impaired T-cell proliferation; ↓ iNKT cells	Chronic EBV infection, viral infections, lung infections, meningitis, eczema, lymphoma	Allogeneic HCT
CORO1A	CORO1A deficiency	AR	Actin regulator; T lymphopenia, impaired immunologic synapse formation and intracellular signaling; ↓ iNKT cells	Chronic EBV infection rather than HLH, viral infections, lung infections, neurologic involvement, lymphoma	Allogeneic HCT
RASGRP1	RASGRP1 deficiency	AR	Activates RAS, which leads to MAPK pathway activation; defects in T-cell activation, proliferation, and migration; ↓ iNKT cells	Chronic EBV infection, viral infections, lung infections, autoimmune cytopenia, EBV negative lymphoproliferative disease, lymphoma	Allogeneic HCT

*Treatment should include HLH-directed therapy, treatment of infections and malignancy, and other supportive care measures as appropriate.
EBV, Epstein-Barr virus; AR, autosomal recessive; XL, X-linked; AD, autosomal dominant; TNF, tumor necrosis factor; iNKT, invariant NK T cell; CNS, central nervous system; HSM, hepatosplenomegaly; PJP, *Pneumocystis jiroveci* pneumonia; HCT, hematopoietic cell transplantation.

A child has mononucleosis-like symptoms for more than three months and elevated EBV PCR. Which additional evidence is required by the CAEBV diagnostic table?

A. A positive heterophile antibody alone
B. A history of one uncomplicated EBV infection
C. Isolated tonsillar enlargement alone
D. Normal EBV testing in affected tissue
E. EBV infection of T or NK cells and exclusion of other diagnoses

ORIGINAL SOURCE TABLE | Table 174.3 | PDF p. 1341 | printed p. 1328

Table 174.3 Chronic Active EBV (CAEBV) Diagnostic Criteria

All 4 criteria must be present:

1. Sustained or recurrent infectious mononucleosis-like symptoms persisting for >3 mo
2. EBV PCR $>10^{2.5}$ copies/μg DNA in the peripheral blood or tissue lesion
3. Evidence of EBV infection of T or NK cells in the peripheral blood or affected tissues
4. Exclusion of other diagnoses: primary EBV infection, primary or secondary immunodeficiency, malignancy, autoimmune disease

EBV, Epstein-Barr virus; NK, natural killer; PCR, polymerase chain reaction.

or pathways, including upregulation of co-stimulatory molecules that

A child has autoimmune cytopenias, enteropathy, and recurrent infection. Which listed gene can cause CTLA-4 haploinsufficiency?

A. C9
B. CYBB
C. CTLA4
D. ELANE
E. BTK

ORIGINAL SOURCE TABLE | Table 174.4 | PDF p. 1343 | printed p. 1330

Table 174.4 Monogenic Causes of Autoimmune Cytopenias and Primary Immunodeficiency

GENE (PROTEIN)	DISORDER	MOI	CLINICAL PHENOTYPE	IMMUNE FEATURES	DEFINITIVE OR DISEASE-SPECIFIC TREATMENT
PIK3 defects	Activated PI3K-delta syndrome	AD, LOF AD, GOF AD	Insulin resistance, short stature, nodular lymphoid hyperplasia, lymphoma, bronchiectasis	High IgM, low IgG, low CD4/CD45RA	Allogeneic HCT *Leniolisib, sirolimus
STAT3	STAT3 GOF	AD, GOF	Enteropathy, autoimmune cytopenias, lymphoproliferation, recurrent infections	Elevated DNTs Variable decreases in IgG, IgA, IgM, B- and T-cell quantities	Jakinibs Allogeneic HCT
STAT1	STAT1 GOF	AD, GOF	Chronic mucocutaneous candidiasis, cerebral aneurysms, interstitial lung disease, enteropathy, colitis	Variable decreases in IgG, IgA, IgM, B- and T-cell quantities	Jakinibs Allogeneic HCT
CTLA-4	CTLA4 haploinsufficiency	AD	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Low IgG, low T-cell quantities	Sirolimus Abatacept, belatacept Allogeneic HCT
LRBA	LRBA deficiency	AR	Enteropathy, type 1 diabetes, autoimmune cytopenias, interstitial lung disease	Low IgG, low T-cell quantities	Abatacept, belatacept Allogeneic HCT
TNFRSF6 *TNFSF6* *FADD* *CASP8* *CASP10*	ALPS	AR GOF	Lymphadenopathy, lymphoma	Elevated DNTs	Mycophenolate mofetil Sirolimus

PI3K, Phosphoinositide 3 kinase; AD, autosomal dominant; LOF, loss of function; AD, autosomal dominant; GOF, gain of function; HCT, hematopoietic cell transplant; STAT, signal transducer and activator of transcription; CTLA, cytotoxic T-lymphocyte protein; LRBA, lipopolysaccharide-responsive and beigelike anchor protein; ALPS, autoimmune lymphoproliferative syndrome; DNT, double negative T cell.

A child has chronic noninfectious lymphadenopathy and splenomegaly with elevated alpha-beta double-negative T cells. Which diagnosis is supported by the required criteria?

A. Autoimmune lymphoproliferative syndrome
B. Isolated selective IgA deficiency
C. Chronic granulomatous disease
D. Terminal complement deficiency
E. Hereditary angioedema

ORIGINAL SOURCE TABLE | Table 174.5 | PDF p. 1344 | printed p. 1331

Table 174.5 Revised Diagnostic Criteria for Autoimmune Lymphoproliferative Syndrome*

REQUIRED

1. Chronic (>6 mo), nonmalignant, noninfectious lymphadenopathy, splenomegaly or both
2. Elevated $CD3^+$ $TCR\alpha\beta^+$ $CD4^-CD8^-$ DNT cells (≥1.5% of total lymphocytes or 2.5% of $CD3^+$ lymphocytes) in the setting of normal or elevated lymphocyte counts

ACCESSORY

Primary

1. Defective lymphocyte apoptosis (in two separate assays)
2. Somatic or germline pathogenic mutation in *FAS*, *FASLG*, or *CASP10*

Secondary

1. Elevated plasma sFasL levels (>200 pg/mL) OR elevated plasma interleukin-10 levels (>20 pg/mL) OR elevated serum or plasma vitamin B_{12} levels (>1500 ng/L) OR elevated plasma interleukin-18 levels >500 pg/mL
2. Typical immunohistologic findings as reviewed by an experienced hematopathologist
3. Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) AND elevated immunoglobulin G levels (polyclonal hypergammaglobulinemia)
4. Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity

*A *definitive* diagnosis is based on the presence of both required criteria plus one primary accessory criterion. A *probable* diagnosis is based on the presence of both required criteria plus one secondary accessory criterion.

DNT, Double-negative T cell; TCR, T-cell receptor.

A patient with recurrent infection and immune dysregulation has alopecia, vitiligo, and central adrenal insufficiency. Which pathway-gene entry best fits?

A. IKBKG
B. BTK
C. ELANE
D. NFKB2
E. NFKB1

ORIGINAL SOURCE TABLE | Table 174.7 | PDF p. 1347 | printed p. 1334

Table 174.7 Defects of Nuclear Factor-κB Pathways Associated with Immune Dysregulation

PROTEIN	INHERITANCE	AUTOIMMUNE OR INFLAMMATORY COMPLICATIONS	OTHER MANIFESTATIONS	IMMUNOLOGIC PHENOTYPE
IKBKG (NEMO)	XL	Colitis	• Ectodermal dysplasia • Osteopetrosis • Lymphedema • Bacterial infections • Opportunistic infections • DNA viral infections	• Hypogammaglobulinemia • Hyper-IgM • Hyper-IgA • Hyper-IgD • Poor antibody responses • Decreased NK cell function • Decreased TLR responses
NF-κB1	AD	• Pyoderma gangrenosum • Lymphoproliferation • Cytopenia • Hypothyroidism • Alopecia areata • Enteritis • LIP • NRH	• Atrophic gastritis • Squamous cell carcinoma • Respiratory tract infections • Superficial skin infections • Lung adenocarcinoma • Respiratory insufficiency • Aortic stenosis • Non-Hodgkin lymphoma	• Hypogammaglobulinemia • IgA deficiency
NF-κB2	AD	• Alopecia totalis • Trachyonychia • Vitiligo • Autoantibodies: thyroid peroxidase, glutamate decarboxylase, thyroglobulin • Central adrenal insufficiency	• Viral respiratory infections • Pneumonias • Sinusitis • Otitis media • Recurrent herpes • Asthma • Type 1 Chiari malformation • Interstitial lung disease	• Early-onset hypogamma-globulinemia • Low vaccine responses • Variable B-cell counts • Low switched memory B cells ($CD19^+CD27^+IgD^-$) • Low marginal zone B cells ($CD19^+CD27^+IgD^+$)

XL, X-linked; AD, autosomal dominant; LIP, lymphocytic interstitial pneumonitis; NRH, nonregenerative hyperplasia; TLR, toll like receptor.

A child has disseminated bacille Calmette–Guérin infection after vaccination. Which signaling axis is central to the table of Mendelian susceptibility to mycobacteria?

A. FOXP3/T-regulatory cells only
B. IL-12/interferon-gamma
C. C5–C9 membrane attack
D. C1 inhibitor/bradykinin
E. BTK/B-cell receptor only

ORIGINAL SOURCE TABLE | Table 175.1 | PDF p. 1349 | printed p. 1336

Table 175.1 Medelian Susceptibility to Mycobacterial Disease Defects

	GENE/INHERITANCE	CLINICAL PHENOTYPE	TREATMENT
Complete IFNgR1/R2 deficiency	*IFNgR1* or I*FNgR2*/AR	Early-onset disseminated NTM or BCG	Antimycobacterials; HSCT
Autosomal dominant IFNgR1 deficiency	IFNgR1/AD	NTM or BCG osteomyelitis, disseminated *Salmonella*, disseminated endemic mycoses	Antimycobacterials; adjuvant IFN-γ
IL-12RB1 deficiency	*IL12RB1*/AR	Disseminated NTM, BCG, *Salmonella* Mucocutaneous candidiasis Variable penetration	Antimycobacterials; consider IFN-γ with careful monitoring
IL-12p40 deficiency	*IL12B*/AR	Disseminated NTM, BCG, *Salmonella* Variable penetration	Antimycobacterials; consider IFN-γ with careful monitoring
IL-12Rb2 deficiency	*IL12RB2*/AR	NTM, BCG, and tuberculosis	Antimycobacterials
IL-23R deficiency	*IL23R*/AR	NTM, BCG, and tuberculosis	Antimycobacterials
STAT1 LOF	*STAT1*/AD	Disseminated BCG/NTM, often osteomyelitis	Antimycobacterials; consider IFN-γ
SPPL2a deficiency	*SPPL2A*/AR	Disseminated BCG	Antimycobacterials
TYK2 deficiency	*TYK2*/AR	Disseminated BCG, tuberculosis, viral infections	Antimycobacterials
Macrophage gp91 phox deficiency	*CYBB*/XL; distinct variants than those causing CGD	Disseminated BCG	Antimycobacterials
IRF8 deficiency (dominant)	*IRF8*/AD	Disseminated BCG, NTM	Antimycobacterials
IRF8 deficiency (recessive)	*IRF8*/AR	Viral, mycobacterial, mucocutaneous candidiasis	Antimicrobials, consider HSCT
ISG15 deficiency	*ISG15*/AR	Disseminated BCG	Antimycobacterials
RORγt deficiency	*RORC*/AR	Disseminated BCG and mucocutaneous candidiasis	Antimicrobials
JAK1 LOF	*JAK1*/AR	Bacterial, viral, and disseminated NTM	Antimicrobials

AD, Autosomal dominant; AR, autosomal recessive; BCG, bacilli Calmette-Guérin; CGD, chronic granulomatous disease; HSCT, hematopoietic stem cell transplantation; IFN, interferon; LOF, loss of function; NTM, nontuberculous mycobacteria.

A previously healthy child has recurrent herpes simplex encephalitis. Which innate antiviral gene appears in the viral-susceptibility table?

A. BTK
B. ELANE
C. C6
D. CD18
E. TLR3

ORIGINAL SOURCE TABLE | Table 175.2 | PDF p. 1352 | printed p. 1339

Table 175.2 Defects with Predominant Susceptibility to Viral Infections

GENE/INHERITANCE	CLINICAL PHENOTYPE	SPECIFIC TREATMENT	GENE/INHERITANCE
Epidermodysplasia verruciformis	*EVER1, EVER2, CIB1*/AR	Diffuse flat warts, with increased skin cancers	Avoid UV/radiation exposure, sk cancer screening.
WHIM syndrome	*CXCR4*/AD	Warts, squamous cell cancer, sinopulmonary infections, neutropenia, hypogammaglobulinemia	G-CSF, IgRT, plerixafor
IFNAR1 deficiency	*IFNAR1*/AR	Severe disease after live viral vaccination (MMR, yellow fever), herpesviruses	Avoid live viral vaccination, consider HSV/VZV prophylaxis
IFNAR2 deficiency	*IFNAR2*/AR	Severe disease after live viral vaccination (MMR, yellow fever), herpesviruses	Avoid live viral vaccination, consider HSV/VZV prophylaxis
Complete STAT1 deficiency	*STAT1*/AR	Early-onset severe viral and disseminated *Mycobacteria*	Early HSCT
STAT2 deficiency	*STAT2*/AR	Severe respiratory viruses, enterovirus; some live viral vaccine disease	Avoid live viral vaccines
IRF9 deficiency	*IRF9*/AR	Severe respiratory viruses, enterovirus; some live viral vaccine disease	Avoid live viral vaccines
IRF7 deficiency	*IRF7*/AR	Severe influenza	Influenza vaccination*
MDA5 deficiency	*IFIH1*/AR or AD	Severe respiratory tract infections	Influenza vaccination
RNA polymerase III deficiency	*POL3A,POL3C, POL3F*/AD	Severe varicella-zoster	Antiviral prophylaxis
CD16 deficiency	*FCGR31*/AR	Herpes family infections, HPV	Antiviral prophylaxis
IL-18BP deficiency	*IL18BP/AR*	Fulminant hepatitis A	Hepatitis A vaccination
TLR3 deficiency	*TLR3*/AD and AR	HSV encephalitis, severe influenza, zoster	Antiviral prophylaxis
TRAF3 deficiency	*TRAF3*/AD	HSV encephalitis	Antiviral prophylaxis
TRIF deficiency	*TRIF*/AD and AR	HSV encephalitis	Antiviral prophylaxis
UNC93B1 deficiency	*UNC93B1*/AR	HSV encephalitis	Antiviral prophylaxis
TBNK1 deficiency	*TBNK1*/AD	HSV encephalitis	Antiviral prophylaxis
IRF3 deficiency	*IRF3*/AD	HSV encephalitis	Antiviral prophylaxis
DRB1 deficiency	*DRB1*/AR	Brainstem encephalitis	Antiviral prophylaxis

*Although influenza vaccination is highlighted for certain inborn errors of immunity (IEIs), influenza vaccination should be given to all those with IEIs and their close contacts unles there is a contraindication. In addition, HPV vaccination should be given per the recommended schedule. Vaccination at an earlier age can be considered for certain defects wi HPV predisposition.

AD, Autosomal dominant; AR, autosomal recessive; G-CSF, granulocyte colony-stimulating factor; HPV, human papillomavirus; HSCT, hematopoietic stem cell transplantation; HS

A child has persistent mucocutaneous candidiasis with no obvious acquired cause. Which signaling pathway is emphasized by the listed inborn errors?

A. BTK-dependent class switching
B. Neutrophil CD18 adhesion alone
C. IL-17 signaling
D. C5–C9 terminal complement
E. C1-inhibitor control

ORIGINAL SOURCE TABLE | Table 175.4 | PDF p. 1356 | printed p. 1343

Table 175.4 Chronic Mucocutaneous Candidiasis Associated Inborn Errors of Immunity

SYNDROME	GENE	INHERITANCE	FUNGAL SPECIES	OTHER MANIFESTATIONS
CARD9 deficiency (30% CMC)	*CARD9*	AR	*Candida* spp. (often CNS involvement), CMC *Aspergillus* spp. (extrapulmonary), dermatophytes, phaeohyphomycosis	Some with increased IgE and eosinophilia
IL-17F deficiency (67% CMC)	*IL17F*	AD	CMC	Asthma, folliculitis
IL-17RA deficiency (100% CMC)	*IL17RA*	AR	CMC	Folliculitis, susceptibilit to *Staphylococcus aureus* (skin) bacterial infections
IL-17RC (100% CMC)	*IL17RC*	AR	CMC	None
ACT1 (100%)	*TRAF3IP2*	AR	CMC	Seborrheic dermatitis
STAT1 GOF (95% CMC)	*STAT1*	AD	CMC, *Histoplasma capsulatum*, *Coccidioides* spp. *Talaromyces marneffei*, *Trichophyton*, *Cryptococcus*, *Aspergillus*, *Mucorales*	Herpes viral infections, bacterial sinopulmonar and skin infections, mycobacterial pulmona and disseminated infections, CNS aneurysms, autoimmur

AD, Autosomal dominant; AR, autosomal recessive; CMC, chronic mucocutaneous candidiasis; CNS, central nervous system; GOF, gain of function; IL, interleukin.

often helpful to clear the infection because some IFN-γ signaling remains more focal NTM or BCG infections, often with osteomyelitis, sin

An infant with newly diagnosed severe combined immunodeficiency is due for a live attenuated vaccine. Which principle follows the immunization table?

A. Avoid live vaccines in complete combined immunodeficiency
B. Give all live vaccines on the standard schedule regardless of immune status
C. Replace inactivated vaccines with oral poliovirus vaccine
D. Use BCG to test T-cell function
E. Infer vaccine safety solely from normal total IgE

ORIGINAL SOURCE TABLE | Table 176.1 | PDF p. 1358 | printed p. 1345

Table 176.1 Immunizations in Patients with Primary Immunodeficiency Diseases

PRIMARY DEFECT	EXAMPLE OF SPECIFIC IMMUNODEFICIENCY	NOT RECOMMENDED	RECOMMENDED
Predominantly antibody deficiencies	Hypogammaglobulinemias (X-linked agammaglobulinemia, common variable immunodeficiency) Other antibody deficiencies (selective IgA deficiency, IgG subclass deficiencies, specific antibody deficiency with normal immunoglobulins)	Live-attenuated vaccines excluding BCG Live-attenuated influenza, OPV, adenovirus, typhoid, yellow fever	Inactivated vaccines All vaccines likely effective Pneumococcal and *Hib*
Combined immunodeficiencies	Complete defects (SCID, complete DiGeorge syndrome) Partial defects (partial DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia)	All live vaccines Live-attenuated influenza, OPV, rotavirus, adenovirus, smallpox, typhoid, yellow fever, BCG	All vaccines likely ineffective Inactivated vaccines, live-attenuated MMR, varicella, anc herpes zoster if documentation of adequate T-cell number*
Complement		None	All routine vaccines, especially pneumococcal and meningococ vaccines
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defects	Live-attenuated influenza, adenovirus, typhoid, BCG	All inactivated vaccines, other liv attenuated viral vaccines
IFN-γ-IL-12 pathway defects		BCG	

*Age-related levels of immunocompetence proposed by the CDC: <1 yr, 1500; 1-5 yr, 1,000; and >6 yr, 500 $CD4^+$ T cells/mm^3 for HIV may also be used.
BCG, Bacille Calmette-Guérin; OPV, oral poliovirus vaccine; SCID, severe combined immune deficiency; MMR, measles, mumps, rubella; IFN-γ, interferon gamma; IL-12, interleukin-1
Data from Medical Advisory Committee of the Immune Deficiency Foundation, Shearer WT, Fleisher TA, et al. Recommendations for live viral and bacterial vaccines in immunode cient patients and their close contacts. *J Allergy Clin Immunol*. 2014;133(4):961–966.

A child has repeatedly normal total IgG but proven specific antibody deficiency with clinically significant infections. Which table principle is relevant when considering Ig replacement?

A. A single elevated IgE establishes an indication
B. The route of administration is fixed for every child
C. Replacement is limited to a single infusion after diagnosis
D. Normal total IgG alone does not exclude a documented antibody-production indication
E. Only absent total IgG can justify replacement

ORIGINAL SOURCE TABLE | Table 176.3 | PDF p. 1362 | printed p. 1349

Table 176.3 Guiding Principles for Effective Use of IgRT for Patients with Primary Immunodeficiency

GUIDING PRINCIPLE	RATIONALE
Indication for IgRT	IgG is indicated as replacement therapy for patients with PI characterized by absent or deficient antibody production; PI is an FDA-approved indication for IgRT
Diagnoses	A large number of PI diagnoses exist for which IgRT is indicated and recommended; many diagnoses have low total IgG levels, but some have a normal level with documented specific antibody deficiency
Frequency of IgRT	Treatment is indicated as ongoing replacement therapy for PI; treatment should not be interrupted once a definitive diagnosis has been established
Dose	IVIG is indicated for PI patients at a starting dose of 400-600 mg/kg every 3-4 wk; SCIG is generally used at a starting dose of 100-200 mg/kg/wk; SCIG dosing frequency is flexible
IgG trough levels	IgG trough levels can be useful in some diagnoses to guide care but should not be a consideration in access to IgRT
Site of care	The decision to infuse IgRT in a hospital, outpatient infusion center, community office, or home-based setting must be based on patient clinical characteristics
Route	Administration route must be based on patient characteristics; throughout life, certain patients may be more appropriate for IV or SC therapy depending on many factors, and patients should have access to either route as needed
Product	IVIG/SCIG are not generic drugs and products are not interchangeable; a specific product needs to be matched to patient characteristics to ensure patient safety; product change should only occur with active participation of the prescribing physician

IgRT, Immunoglobulin replacement therapy; IgG, immunoglobulin G; PI, primary immunodeficiency; FDA, US Food and Drug Administration; SCIG, subcutaneous immunoglobulin; IV, intravenous; SC, subcutaneous; IVIG, intravenous immunoglobulin.
Data from Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin

A child has severe acquired aplastic anemia and is referred for stem-cell transplant consideration. Which transplant type lists this condition as an indication?

A. A renal transplant
B. Allogeneic hematopoietic stem-cell transplantation
C. Autologous transplant as the sole standard category
D. Isolated granulocyte transfusion
E. Pancreatic islet transplantation

ORIGINAL SOURCE TABLE | Table 177.1 | PDF p. 1365 | printed p. 1352

Table 177.1 Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Diseases

MALIGNANCY
ALL
- First complete remission for patients at very high risk of relapse
- T-cell immunophenotype and poor response to corticosteroid therapy
- Not in remission at the end of the induction phase
- Marked hypodiploidy (<43 chromosomes)
- Minimal residual disease at the end of consolidation therapy

High-risk infant ALL
- Second complete remission
- Third or later complete remission

Acute myeloid leukemia in first complete remission or in advanced-disease phase
Philadelphia chromosome–positive chronic myeloid leukemia
Myelodysplastic syndromes
Hodgkin and non-Hodgkin lymphomas
Selected solid tumors
- Metastatic neuroblastoma
- Rhabdomyosarcoma refractory to conventional treatment
- Very high risk Ewing sarcoma
- High-risk CNS tumors

ANEMIAS
Severe acquired aplastic anemia
Fanconi anemia
Paroxysmal nocturnal hemoglobinemia
Congenital dyskeratosis
Diamond-Blackfan anemia
Thalassemia major
Sickle cell disease
Shwachman-Diamond syndrome

IMMUNOLOGIC DISORDERS
Variants of severe combined immunodeficiency
Hyper-IgM syndrome
Leukocyte adhesion deficiency
Omenn syndrome
Zap-70 kinase deficiency
Cartilage-hair hypoplasia
PNP deficiency
CD40 ligand deficiency
MHC class II deficiency
Wiskott-Aldrich syndrome
Chédiak-Higashi syndrome
Kostmann syndrome (infantile malignant agranulocytosis)
Chronic granulomatous disease
Autoimmune lymphoproliferative syndrome
X-linked lymphoproliferative disease (Duncan syndrome)
IPEX syndrome
Interleukin-10 receptor deficiency
Hemophagocytic lymphohistiocytosis
Interferon-γ receptor deficiency
Griscelli disease
Granule deficiency

OTHER DISORDERS
Selected severe variants of platelet function disorders (e.g., Glanzmann thrombasthenia, congenital amegakaryocytic thrombocytopenia)
Selected types of mucopolysaccharidosis (e.g., Hurler disease) or other liposomal/peroxisomal disorders (e.g., Krabbe disease, adrenoleukodystrophy)
Infantile malignant osteopetrosis
Life-threatening cytopenia unresponsive to conventional treatments

ALL, Acute lymphoblastic leukemia; CNS, central nervous system; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MHC, major histocompatibility complex; PNP, purine nucleoside phosphorylase.

A child with high-risk neuroblastoma is being evaluated for high-dose chemotherapy with stem-cell rescue. Which transplant approach appears in the indication table?

A. Allogeneic transplant for every stage of neuroblastoma
B. Cord-blood transplant for all low-risk patients
C. Granulocyte transfusion only
D. Pancreatic islet transplantation
E. Autologous hematopoietic stem-cell transplantation

ORIGINAL SOURCE TABLE | Table 178.1 | PDF p. 1369 | printed p. 1356

Table 178.1 Indications for Autologous Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Relapsed Hodgkin or non-Hodgkin lymphoma
- Stage IV or relapsed neuroblastoma
- High-risk, relapsed, or resistant brain tumors
- Stage IV Ewing sarcoma
- Life-threatening autoimmune diseases resistant to conventional treatments

inhibitory receptors for self–MHC class I molecules, autologous cells are not killed. When faced with mismatched allogeneic targets. NK cells

After HSCT, a child develops an erythematous rash covering 30% of body surface area, without liver or gastrointestinal involvement. Which skin stage is assigned in the acute GVHD table?

A. Stage 3
B. Stage 4
C. Stage 2
D. Stage 0
E. Stage 1

ORIGINAL SOURCE TABLE | Table 179.1 | PDF p. 1371 | printed p. 1358

Table 179.1 Clinical Staging and Grading* of Acute Graft-Versus-Host Disease

STAGE	SKIN (ACTIVE ERYTHEMA ONLY)	LIVER (BILIRUBIN)	UPPER GI	LOWER GI (STOOL OUTPUT/DAY)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	*Adult:* <500 mL/day or <3 episodes/day *Child:* <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	*Adult:* 500-999 mL/day or 3-4 episodes/day *Child:* 10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25–50% BSA	3.1-6 mg/dL		*Adult:* 1,000-1,500 mL/day or 5-7 episodes/day *Child:* 20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL		*Adult:* >1,500 mL/day or >7 episodes/day *Child:* >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

*Overall clinical grade (based on most severe target organ involvement):
Grade 0: no stage 1-4 of any organ.
Grade I: stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade II: stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.

Months after HSCT, a child develops dry eyes, lichen-planus-like oral changes, and sclerotic skin. Which complication fits the findings table?

A. Chronic graft-versus-host disease
B. Acute isolated neutropenia
C. Immediate transfusion hemolysis
D. Veno-occlusive disease alone
E. Primary complement deficiency

ORIGINAL SOURCE TABLE | Table 179.2 | PDF p. 1371 | printed p. 1358

Table 179.2 Clinical Findings in Chronic Graft-Versus-Host Disease

ORGAN SYSTEM	SYMPTOMS AND SIGNS
Systemic	Immunodeficiency and recurrent infections
Skin	Lichen planus, scleroderma, hyperpigmentation or hypopigmentation, erythema, freckling, ichthyosis, ulcerations Flexion contractures Vaginal scars Onycholysis Nail loss
Hair	Alopecia; scarring or nonscarring
Mouth	Sicca syndrome, lichen planus, depapillation of tongue with variegations, scalloping of lateral margins, xerostomia, mucocele
Joints	Diffuse myositis/tendonitis, arthritis, contractures
Eyes	Decreased tearing, injected sclerae, scarring conjunctivitis, keratopathy
Liver	Increased enzymes, cholestasis, hepatomegaly, cirrhosis
Gastrointestinal	Failure to thrive, malabsorption, chronic diarrhea Esophageal strictures
Lung	Cough, dyspnea, wheezing Bronchiolitis obliterans, chronic rales, pneumothorax, fibrosis
Hematology	Thrombocytopenia, eosinophilia, Howell-Jolly bodies (splenic dysfunction)

A child develops ascites, weight gain, and kidney dysfunction after HSCT. Which post-transplant complication is graded by these findings in the table?

A. Isolated selective IgA deficiency
B. X-linked agammaglobulinemia
C. Leukocyte adhesion deficiency
D. Sinusoidal obstructive syndrome
E. Chronic graft-versus-host disease

ORIGINAL SOURCE TABLE | Table 179.3 | PDF p. 1373 | printed p. 1360

Table 179.3 Severity Grading Thresholds of Sinusoidal Obstructive Syndrome Among Children, Adolescents, and Young Adults

	MILD	MODERATE	SEVERE	VERY SEVERE
ALT, AST, GLDH (mg/dL)	<2× normal	2-5× normal	2-5× normal	>5× normal
Bilirubin (mg/dL)	<2	<2	≥2	Bilirubin doubles in 48 hr
Coagulopathy (not responsive to vitamin K administration; INR)	<1.5	1.5-1.9	>2	Need for replacement of coagulation factors
Ascites	Mild (minimal fluid by liver, spleen or pelvis)	Moderate (<1 cm fluid)	Severe (fluid in all 3 regions with >1 cm fluid in at least 2 regions)	Requires paracentesis
Weight gain (from baseline)	2.5%	5–10% despite diuretic use	>10%	Persistent rise
Renal function score	KDIGO 1: serum creatinine 1.5-1.9× baseline or ≥0.3 mg/dL (≥26.5 mmol/L) increase or urine output <0.5 mL/kg/hr for 6-12 hr	KDIGO 2: serum creatinine 2.0-2.9× baseline or urine output <0.5 mL/kg/hr for ≥12 hr	KDIGO 3: serum creatinine 3.0× baseline or increase in serum creatinine ≥4.0-mg/dL (≥353.6 mmol/L) or initiation of renal replacement therapy or decrease in eGFR to <35 mL/min per 1.73 m^2 (patients <18 years) or urine output <0.3 mL/kg/hr for ≥24 hr or anuria for ≥12 hr (patients <18 years)	Persistent need for renal replacement therapy
Encephalopathy	CAPD <9	CAPD <9	CAPD ≥9	CAPD ≥9
Persistent RT	<3 days	3-7 days	—	>7 days
Pulmonary function	<2 L	<2 L	NIV/IMV	IMV

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; GLDH, glutamate dehydrogenase; INR, international normalized ratio; KDIGO, Kidney Disease: Improving Global Outcomes score; eGFR, estimated glomerular infiltration rate; CAPD, Cornell Assessment of Pediatric Delirium; RT, refractory thrombocytopenia; NIV, noninvasive ventilation; IMV, invasive mechanical ventilation.
From Mahadeo KM, Bajwa R, Abdel-Azim H, et al. Diagnosis, grading, and treatment recommendations for children, adolescents, and young adults with sinusoidal obstructive syn-

A survivor of childhood HSCT received total-body irradiation and now needs long-term surveillance. Which late effect appears among irradiation-associated risks?

A. Chronic mucocutaneous candidiasis as a necessary effect
B. Hypothyroidism
C. Delayed umbilical cord separation
D. Congenital asplenia
E. Neonatal omphalitis

ORIGINAL SOURCE TABLE | Table 181.1 | PDF p. 1379 | printed p. 1366

Table 181.1 Summary of Late Effects After Hematopoietic Stem Cell Transplantation in Childhood

EXPOSURE	LATE EFFECT*
HSCT experience in general	Dental abnormalities Renal toxicity Hepatic toxicity Low BMD Avascular necrosis Increased risk of second cancers Adverse psychosocial/quality-of-life effects Mental health disorders, risk behaviors Psychosocial disability caused by pain or fatigue
TRANSPLANTATION CONDITIONING	
Alkylating agent	Cataract (busulfan) Pulmonary fibrosis (busulfan) Renal toxicity Urinary tract toxicity Gonadal dysfunction Therapy-related AML/MDS Bladder cancer
Epipodophyllotoxin†	Therapy-related AML/MDS
DNA intersecting and cross linking agents (i.e., platinum, heavy metal)	Ototoxicity Renal toxicity Gonadal toxicity
TBI‡	Neurocognitive deficits Leukoencephalopathy Cataract Dental abnormalities GH deficiency Hypothyroidism, thyroid nodule Pulmonary toxicity Breast tissue hypoplasia Cardiac toxicity Renal toxicity Gonadal dysfunction Uterine vascular insufficiency Diabetes Dyslipidemia Musculoskeletal growth problems Second cancers
PRETRANSPLANTATION EXPOSURES (NOT LISTED ABOVE)	
Anthracycline/anthraquinone	Cardiac toxicity Therapy-related AML/MDS
Bleomycin	Pulmonary toxicity
Cytarabine	Neurocognitive deficits Leukoencephalopathy
Methotrexate	Neurocognitive deficits Leukoencephalopathy Renal toxicity Low BMD
Corticosteroid	Cataract Low BMD Avascular necrosis
Cranial radiation§	Neurocognitive deficits Leukoencephalopathy Cerebrovascular disease Cataract Craniofacial abnormalities Dental abnormalities, xerostomia GH deficiency Hypothyroidism thyroid nodule Increased obesity Precocious puberty Brain tumor
Spinal radiation (in addition to cranial dose)	Cardiac toxicity Scoliosis/kyphosis, musculoskeletal problems
AFTER TRANSPLANTATION (NOT LISTED ABOVE)	
Chronic GVHD	Xerophthalmia Xerostomia, dental abnormalities Pulmonary toxicity Gastrointestinal strictures Genitourinary strictures Skin and joint changes Immunodeficiency Second cancers, especially skin, oral, cervical, lymphoma
Tyrosine kinase inhibitor	Acute cardiac toxicity reported, but not known to cause late cardiotoxicity
OTHER EXPOSURES	
Blood transfusions	Hepatitis C, HIV

*Focused on those late effects that can develop or persist even after cessation of therapy.
†Includes etoposide, teniposide.
‡At given total dose, risks greater for single-fraction vs fractionated total body irradiation (TBI); single-fraction myeloablative TBI (>500 cGy) now rarely used.
§Effects listed are those more likely to be associated with doses used in HSCT survivors (e.g., those given for leukemia treatment, <25 Gy); late effects are more likely if TBI also given.

Answer key and teaching notes

01. D | Table 164.1 | PDF p. 1265, printed p. 1252

Why: The antibody-defect row links sinopulmonary infection with Giardia and other gastrointestinal infections.
Closest distractor: Complement defects may cause invasive encapsulated bacterial infection but do not best explain this combined pattern.

02. B | Table 164.2 | PDF p. 1266, printed p. 1253

Why: The table lists T–B+NK– among cellular and humoral severe combined immunodeficiencies.
Closest distractor: Selective IgA deficiency is an antibody defect without this T- and NK-cell phenotype.

03. E | Table 164.3 | PDF p. 1267, printed p. 1254

Why: Herpes simplex encephalitis is linked to TLR3 and related antiviral signaling genes in the sentinel-infection table.
Closest distractor: Terminal complement deficiency instead points toward invasive Neisseria infection.

04. C | Table 164.4 | PDF p. 1268, printed p. 1255

Why: Asplenia is explicitly one of the conditions in the recurrent invasive pneumococcal infection table.
Closest distractor: Thymic hyperplasia is not the table-listed anatomic explanation.

05. A | Table 164.5 | PDF p. 1269, printed p. 1256

Why: The table catalogs primary immune deficiency disorders that confer risk of HLH.
Closest distractor: An infectious trigger does not exclude a primary immune defect.

06. D | Table 164.6 | PDF p. 1270, printed p. 1257

Why: The table groups persistent candidiasis after 6 months, chronic diarrhea, failure to thrive, and lymphopenia under T-cell defects.
Closest distractor: Humoral defects chiefly cause recurrent bacterial sinopulmonary infections.

07. B | Table 164.7 | PDF p. 1271, printed p. 1258

Why: Small-platelet thrombocytopenia and eczema are listed features of Wiskott–Aldrich syndrome.
Closest distractor: Chédiak–Higashi syndrome is associated with hypopigmentation rather than small-platelet thrombocytopenia.

08. E | Table 164.9 | PDF p. 1273, printed p. 1260

Why: FOXP3 is the X-linked immune-dysregulation cause of early-onset enteropathy.
Closest distractor: EPCAM is listed for tufting enteropathy, an epithelial rather than IPEX-like immune disorder.

09. C | Table 164.10 | PDF p. 1274, printed p. 1261

Why: The pleomorphic-autoimmunity table identifies FOXP3 as an X-linked T-cell tolerance defect.
Closest distractor: CTLA4 is also relevant to autoimmunity but is listed as autosomal dominant.

10. A | Table 165.1 | PDF p. 1276, printed p. 1263

Why: The SCID genetics table lists common gamma-chain deficiency as X-linked T–B+ SCID; the nearby discussion identifies its NK– phenotype.
Closest distractor: RAG1 deficiency has a T–B– pattern rather than preserved B cells.

11. D | Table 165.4 | PDF p. 1281, printed p. 1268

Why: The immunoosseous table identifies cartilage–hair hypoplasia, with RMRP, as a skeletal disorder with immune deficiency.
Closest distractor: Schimke dysplasia is a different immunoosseous disorder, without the characteristic cartilage–hair combination.

12. B | Table 165.6 | PDF p. 1283, printed p. 1270

Why: The thymic-disorders table lists DiGeorge/22q11.2 deletion syndrome.
Closest distractor: X-linked agammaglobulinemia is a B-cell maturation defect and does not explain the congenital thymic phenotype.

13. E | Table 165.7 | PDF p. 1284, printed p. 1271

Why: DOCK8 deficiency is included in the hyper-IgE syndromes table and is associated with combined immune defects.
Closest distractor: BTK is an agammaglobulinemia gene and not a hyper-IgE syndrome in this table.

14. C | Table 166.1 | PDF p. 1291, printed p. 1278

Why: BTK is listed among the agammaglobulinemia genes.
Closest distractor: CTLA4 is listed in the CVID-associated category and does not best match absent B cells.

15. A | Table 166.2 | PDF p. 1293, printed p. 1280

Why: The inheritance table identifies XLA with Btk.
Closest distractor: IGHM is among the other agammaglobulinemia forms in the table.

Answer key and teaching notes

16. D | Table 166.3 | PDF p. 1295, printed p. 1282

Why: The phenotype table specifically includes enterovirus infections with agammaglobulinemia.
Closest distractor: Selective IgA deficiency is often asymptomatic and is less consistent with this severe pattern.

17. B | Table 166.4 | PDF p. 1295, printed p. 1282

Why: The laboratory table pairs decreased immunoglobulins and absent B cells with agammaglobulinemia.
Closest distractor: Selective IgA deficiency preserves IgG and circulating B cells.

18. E | Table 169.1 | PDF p. 1308, printed p. 1295

Why: Strongyloidiasis appears under tissue-invasive helminth causes of eosinophilia.
Closest distractor: Neisseria infection is not listed as a typical helminth-associated eosinophilia cause.

19. C | Table 170.1 | PDF p. 1310, printed p. 1297

Why: The infection-pattern table includes LAD among severe skin/soft-tissue infection and gum infection causes; delayed cord separation supports LAD.
Closest distractor: Selective IgA deficiency does not produce the characteristic adhesion phenotype.

20. A | Table 170.3 | PDF p. 1313, printed p. 1300

Why: The LAD table identifies the common beta-2 integrin chain CD18 in LAD-1.
Closest distractor: C1 inhibitor deficiency causes hereditary angioedema rather than defective tight leukocyte adherence.

21. D | Table 170.4 | PDF p. 1315, printed p. 1302

Why: The CGD classification table identifies gp91phox as the X-linked component.
Closest distractor: The p47phox and several other components are classified as autosomal.

22. B | Table 171.1 | PDF p. 1318, printed p. 1305

Why: The leukopenia approach includes marrow aspiration and biopsy with cytogenetics for ANC below 500/µL on three tests.
Closest distractor: A single IgE level cannot assess persistent severe neutropenia.

23. E | Table 171.2 | PDF p. 1319, printed p. 1306

Why: The extrinsic-neutropenia table lists anticonvulsants under drug-induced causes.
Closest distractor: ELANE-associated cyclic neutropenia is an intrinsic inherited myeloid disorder.

24. C | Table 171.3 | PDF p. 1319, printed p. 1306

Why: The acquired-myeloid table lists vitamin B12, copper, and folate deficiency, including malnutrition-related mechanisms.
Closest distractor: ELANE disease is an inherited myeloid condition, not the nutritional explanation.

25. A | Table 171.4 | PDF p. 1319, printed p. 1306

Why: Influenza is explicitly among viral infections associated with neutropenia.
Closest distractor: Protozoan examples in the table include malaria and leishmaniasis, not influenza.

26. D | Table 171.5 | PDF p. 1320, printed p. 1307

Why: The immunologic drug-neutropenia column describes rapid recurrence with a small rechallenge and acute onset.
Closest distractor: Cyclic neutropenia has periodic episodes independent of drug rechallenge.

27. B | Table 171.6 | PDF p. 1322, printed p. 1309

Why: Cyclic neutropenia is listed with autosomal dominant ELANE in the intrinsic myeloid table.
Closest distractor: BTK affects B-cell maturation rather than periodic neutrophil production.

28. E | Table 171.7 | PDF p. 1324, printed p. 1311

Why: The congenital-neutropenia feature table associates exocrine pancreatic insufficiency with Shwachman–Diamond syndrome.
Closest distractor: WHIM syndrome is associated with myelokathexis rather than exocrine pancreatic failure.

29. C | Table 171.8 | PDF p. 1325, printed p. 1312

Why: Protein-losing enteropathy is listed among acquired systemic causes of lymphocytopenia.
Closest distractor: Inherited lymphopoietic aplasia is a separate category.

30. A | Table 172.1 | PDF p. 1327, printed p. 1314

Why: Burns and acute stress appear in the acute acquired neutrophilia group.
Closest distractor: Chronic acquired neutrophilia is linked to persistent inflammation or infection.

Answer key and teaching notes

31. D | Table 172.2 | PDF p. 1327, printed p. 1314

Why: Juvenile myelomonocytic leukemia is listed among malignant causes of monocytosis.
Closest distractor: Neuroblastoma is not the myelomonocytic neoplasm highlighted in this table.

32. B | Table 173.2 | PDF p. 1328, printed p. 1315

Why: The membrane attack complex is composed of C5, C6, C7, C8, and C9 in the table.
Closest distractor: C1 components initiate the classical pathway rather than form the terminal complex.

33. E | Table 173.3 | PDF p. 1331, printed p. 1318

Why: The evaluation table organizes screening of complement pathways followed by targeted component assessment.
Closest distractor: Serum IgE does not test the terminal complement pathway.

34. C | Table 173.4 | PDF p. 1332, printed p. 1319

Why: The pathway table includes C5–C9 deficiencies, which are linked in the chapter to Neisseria susceptibility.
Closest distractor: C1 inhibitor deficiency causes angioedema rather than the terminal-pathway infection phenotype.

35. A | Table 173.5 | PDF p. 1335, printed p. 1322

Why: The table lists C1 inhibitor deficiency as autosomal dominant.
Closest distractor: Properdin deficiency, not classic C1 inhibitor deficiency, is listed as X-linked recessive.

36. D | Table 174.1 | PDF p. 1338, printed p. 1325

Why: FOXP3 is the X-linked IPEX gene in the Tregopathies table.
Closest distractor: LRBA is an autosomal recessive IPEX-like immune-dysregulation defect.

37. B | Table 174.2 | PDF p. 1340, printed p. 1327

Why: The EBV susceptibility table identifies MAGT1 with X-linked XMEN syndrome.
Closest distractor: ITK deficiency also predisposes to EBV disease but is listed as autosomal recessive.

38. E | Table 174.3 | PDF p. 1341, printed p. 1328

Why: The CAEBV criteria require evidence of EBV in T or NK cells and exclusion of alternative diagnoses along with sustained symptoms and elevated viral load.
Closest distractor: A heterophile test alone does not establish the required cellular infection and exclusion criteria.

39. C | Table 174.4 | PDF p. 1343, printed p. 1330

Why: CTLA4 haploinsufficiency appears among monogenic causes of autoimmune cytopenias and immune deficiency.
Closest distractor: ELANE primarily causes congenital or cyclic neutropenia, not the CTLA-4 phenotype.

40. A | Table 174.5 | PDF p. 1344, printed p. 1331

Why: The two required ALPS criteria are chronic nonmalignant/noninfectious lymphoproliferation and elevated alpha-beta double-negative T cells.
Closest distractor: Selective IgA deficiency does not explain this characteristic cell population.

41. D | Table 174.7 | PDF p. 1347, printed p. 1334

Why: The NF-κB table lists alopecia, vitiligo, and central adrenal insufficiency in the NF-κB2 row.
Closest distractor: NF-κB1 has a different cluster of inflammatory and autoimmune manifestations in the table.

42. B | Table 175.1 | PDF p. 1349, printed p. 1336

Why: The table lists IL12RB1, IL12B, and IFN-gamma receptor defects among Mendelian susceptibility disorders.
Closest distractor: Terminal complement deficiency chiefly predisposes to invasive Neisseria.

43. E | Table 175.2 | PDF p. 1352, printed p. 1339

Why: TLR3 deficiency is listed among disorders with predominant viral susceptibility, including HSV encephalitis in the chapter.
Closest distractor: BTK deficiency predominantly causes antibody deficiency rather than isolated HSV encephalitis.

44. C | Table 175.4 | PDF p. 1356, printed p. 1343

Why: The chronic mucocutaneous candidiasis table lists IL17F, IL17RA, IL17RC, and related signaling defects.
Closest distractor: Terminal complement defects have a different invasive bacterial infection phenotype.

45. A | Table 176.1 | PDF p. 1358, printed p. 1345

Why: The immunization table distinguishes complete combined defects such as SCID and their contraindications to live vaccines.
Closest distractor: A standard live-vaccine schedule cannot be presumed safe in SCID.

Answer key and teaching notes

46. D | Table 176.3 | PDF p. 1362, printed p. 1349

Why: The IgRT principles state that some indicated diagnoses have normal total IgG with documented specific antibody deficiency.
Closest distractor: The table does not require every eligible patient to have low total IgG.

47. B | Table 177.1 | PDF p. 1365, printed p. 1352

Why: Severe acquired aplastic anemia is included in the allogeneic HSCT indications table.
Closest distractor: Autologous stem cells would not replace the diseased hematopoietic compartment in the same way.

48. E | Table 178.1 | PDF p. 1369, printed p. 1356

Why: The autologous-HSCT chapter and table include high-risk neuroblastoma among relevant indications.
Closest distractor: Allogeneic transplant is not the routine stem-cell rescue approach described for this scenario.

49. C | Table 179.1 | PDF p. 1371, printed p. 1358

Why: A maculopapular rash affecting 25–50% of body surface area is skin stage 2.
Closest distractor: Stage 1 is limited to less than 25% of body surface area.

50. A | Table 179.2 | PDF p. 1371, printed p. 1358

Why: Sicca eye changes, oral lichen-planus changes, and sclerotic skin are listed manifestations of chronic GVHD.
Closest distractor: Sinusoidal obstruction chiefly affects the liver and does not explain this mucocutaneous cluster.

51. D | Table 179.3 | PDF p. 1373, printed p. 1360

Why: The pediatric sinusoidal-obstructive-syndrome grading table uses ascites, weight gain, and renal function among severity domains.
Closest distractor: Chronic GVHD has a distinct multisystem clinical findings table and is not graded by this SOS scale.

52. B | Table 181.1 | PDF p. 1379, printed p. 1366

Why: The late-effects table lists hypothyroidism among total-body-irradiation-associated outcomes.
Closest distractor: Delayed cord separation is a congenital adhesion-defect feature rather than a late transplant exposure effect.

Table selection log

01. Table 164.1 | PDF p. 1265 | printed p. 1252 | Completed
02. Table 164.2 | PDF p. 1266 | printed p. 1253 | Completed
03. Table 164.3 | PDF p. 1267 | printed p. 1254 | Completed
04. Table 164.4 | PDF p. 1268 | printed p. 1255 | Completed
05. Table 164.5 | PDF p. 1269 | printed p. 1256 | Completed
06. Table 164.6 | PDF p. 1270 | printed p. 1257 | Completed
07. Table 164.7 | PDF p. 1271 | printed p. 1258 | Completed
08. Table 164.9 | PDF p. 1273 | printed p. 1260 | Completed
09. Table 164.10 | PDF p. 1274 | printed p. 1261 | Completed
10. Table 165.1 | PDF p. 1276 | printed p. 1263 | Completed
11. Table 165.4 | PDF p. 1281 | printed p. 1268 | Completed
12. Table 165.6 | PDF p. 1283 | printed p. 1270 | Completed
13. Table 165.7 | PDF p. 1284 | printed p. 1271 | Completed
14. Table 166.1 | PDF p. 1291 | printed p. 1278 | Completed
15. Table 166.2 | PDF p. 1293 | printed p. 1280 | Completed
16. Table 166.3 | PDF p. 1295 | printed p. 1282 | Completed
17. Table 166.4 | PDF p. 1295 | printed p. 1282 | Completed
18. Table 169.1 | PDF p. 1308 | printed p. 1295 | Completed
19. Table 170.1 | PDF p. 1310 | printed p. 1297 | Completed
20. Table 170.3 | PDF p. 1313 | printed p. 1300 | Completed
21. Table 170.4 | PDF p. 1315 | printed p. 1302 | Completed
22. Table 171.1 | PDF p. 1318 | printed p. 1305 | Completed
23. Table 171.2 | PDF p. 1319 | printed p. 1306 | Completed
24. Table 171.3 | PDF p. 1319 | printed p. 1306 | Completed
25. Table 171.4 | PDF p. 1319 | printed p. 1306 | Completed
26. Table 171.5 | PDF p. 1320 | printed p. 1307 | Completed
27. Table 171.6 | PDF p. 1322 | printed p. 1309 | Completed
28. Table 171.7 | PDF p. 1324 | printed p. 1311 | Completed
29. Table 171.8 | PDF p. 1325 | printed p. 1312 | Completed
30. Table 172.1 | PDF p. 1327 | printed p. 1314 | Completed
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32. Table 173.2 | PDF p. 1328 | printed p. 1315 | Completed
33. Table 173.3 | PDF p. 1331 | printed p. 1318 | Completed
34. Table 173.4 | PDF p. 1332 | printed p. 1319 | Completed
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36. Table 174.1 | PDF p. 1338 | printed p. 1325 | Completed
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Table selection log

39. Table 174.4 | PDF p. 1343 | printed p. 1330 | Completed

40. Table 174.5 | PDF p. 1344 | printed p. 1331 | Completed

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42. Table 175.1 | PDF p. 1349 | printed p. 1336 | Completed

43. Table 175.2 | PDF p. 1352 | printed p. 1339 | Completed

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45. Table 176.1 | PDF p. 1358 | printed p. 1345 | Completed

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47. Table 177.1 | PDF p. 1365 | printed p. 1352 | Completed

48. Table 178.1 | PDF p. 1369 | printed p. 1356 | Completed

49. Table 179.1 | PDF p. 1371 | printed p. 1358 | Completed

50. Table 179.2 | PDF p. 1371 | printed p. 1358 | Completed

51. Table 179.3 | PDF p. 1373 | printed p. 1360 | Completed

52. Table 181.1 | PDF p. 1379 | printed p. 1366 | Completed

Table 164.8 | PDF p. 1272 | Excluded: Continues onto PDF p. 1273

Table 165.2 | PDF p. 1279 | Excluded: Continues onto PDF p. 1280

Table 165.3 | PDF p. 1280 | Excluded: Continues onto PDF p. 1281

Table 165.5 | PDF p. 1282 | Excluded: Continues onto PDF p. 1283

Table 168.1 | PDF p. 1303 | Excluded: Basic cell kinetics; limited board decision value

Table 170.2 | PDF p. 1310 | Excluded: Continues onto PDF p. 1311

Table 173.1 | PDF p. 1328 | Excluded: Basic nomenclature; limited clinical value

Table 173.6 | PDF p. 1336 | Excluded: Detailed treatment and dose table; requires current guideline review

Table 174.6 | PDF p. 1345 | Excluded: Continues onto PDF p. 1346

Table 175.3 | PDF p. 1354 | Excluded: Wide genetic listing; source image not reliably readable at page size

Table 176.2 | PDF p. 1360 | Excluded: Continues onto PDF p. 1361 and product listing is time sensitive

Table 180.1 | PDF p. 1375 | Excluded: Continues onto PDF p. 1376

Total: 52 completed + 12 excluded = 64 tables in Part XII.

Last completed: Table 181.1, PDF p. 1379. Part XIII Allergy begins PDF p. 1380.

Clinical review: consult current guidance before applying treatment or vaccination tables.

CDC: https://www.cdc.gov/vaccines/hcp/imz-best-practices/altered-immunocompetence.html