Approach to the patient with recurrent infections

Table I – Factors that contribute to the risk of recurrent infections

Atopy/ allergic disease
Day care attendance
School age siblings
Second-hand tobacco smoke exposure
Gastroesophageal reflux
Anatomic abnormalities of upper or lower airways
Foreign body
Cystic fibrosis
Immotile cilia syndrome

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Approach to the patient with recurrent infections

Table II Critical elements of the history

Age of Onset

4-5 months	combined T/B cell immunodeficiency phagocytic disorder
7-9 months	B cell immunodeficiency

History of recurrent infections

Sites of infection

Types of infection

Gastrointestinal symptoms

Autoimmune disease

Family History

Adverse reaction to vaccines

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Table III Sites of infection

Sites of Infection	
Otitis media, recurrent mastoiditis	B cell deficiency
Sinusitis	B cell deficiency
Pneumonia bronchiectasis	B cell deficiency
Meningitis	B cell deficiency
Sepsis	B cell deficiency Complement pathway defect Neutropenia
Skin infections	B cell deficiency, Neutrophil/phagocyte defects
Gingivitis/stomatitis	Neutrophil/phagocyte defects
Organ abscesses	" "
Lymphadenitis	" "

Approach to the patient with recurrent infections

Table IV Microbiology of infections

Bacteria	
Mycobacteria	
Mycobacterium avium intracellulare	T cell deficiency NK cell defect IL-12/IFN-γ pathway defects
Enteric bacterial organisms Campylobacter Samonella species *Clostridium difficile*	B-cell immune deficiency
Encapsulated organisms *Streptococcus pneumoniae* *Hemophilus influenza* *Neisseria* species	B cell or complement deficiency
Catalase positive organisms *Staphlococcus aureus* *Burkholderia cepacia* Klebsiella Serratia	Neutrophil/phagocyte defects (CGD)
Viruses	
herpes, varicella, CMV	T cell deficiency, IL-12/IFN-γ pathway defects, NK cell defects
Epstein-Barr virus	XLP
Human papilloma virus (HPV) related diseases	T-cell WHIM syndrome
enteroviruses (echovirus, coxsackie)	B-cell deficiency
Rotavirus	B-cell deficiency
Fungi	
Candida	T cell deficiency
Aspergillus	T cell or phagocyte defects
Parasites	
Giardia lamblia	B cell deficiency
Toxoplasma gondii	T cell deficiency
Opportunistic infections	
Pneumocystis jiroveci	T cell deficiency
Cryptosporidium	T cell deficiency

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Table V – Gastrointestinal disturbances

Malabsorption, chronic diarrhea	
Failure to thrive	T cell or IPEX
Lactose intolerance	CVID, IgA deficiency
Celiac disease	CVID, IgA deficiency
Bacterial overgrowth small bowl	CVID, IgA deficiency
Parasites	CVID, IgA deficiency
Inflammatory bowl disease	B cell deficiency (CVID, IgA deficiency)
Nodular lymphoid hyperplasia	B cell deficiency (CVID, IgA deficiency)
Atrophic gastritis/ achlorhydria	CVID
Gastric carcinoma	CVID
Pancreatic insufficiency	neutrophil defect

Table VI – Autoimmune disorders

Rheumatic diseases	
Lupus erythematosus	early complement component deficiency
	CVID
Hemolytic-uremic syndrome	Factor H deficiency
Glomerulonephritis	C3 deficiency
	ALPS
	CVID
Autoimmune endocrinopathies	CVID, IgA deficiency
	APECED
	IPEX
Autoimmune neuropathies	
Guillain Barre syndrome	ALPS
Autoimmune hematologic diseases	
Hemolytic anemia	CVID
	ALPS
	Wiskott-Aldrich syndrome
Thrombocytopenia	CVID
	ALPS
Autoimmune neutropenia	CVID
	ALPS
	Wiskott-Aldrich syndrome
	Type 1 hyper IgM syndrome

Approach to the patient with recurrent infections

Table VII – Family history

Consanguinity of the parents

History of a sibling dying early in life of infections

Family history of an x-linked or autosomal recessive inheritance of a primary immune deficiency

Table VIII: Vaccine contraindications/precautions in patients with primary immunodeficiency[1,2]

Vaccine Type:	Avoid in:
Live virus vaccines	T- and B-cell deficiency
Oral polio vaccine	
Varicella vaccine[a]	
MMR vaccine[a]	
Intranasal influenza vaccine	
Rotavirus vaccine	
Smallpox vaccine	
Yellow fever vaccine	
Herpes zoster vaccine	
Live bacterial vaccines	T- and B-cell deficiency, CGD/LAD, IFN-γ pathway defects/NEMO
BCG vaccine	
Oral Salmonella typhi vaccine	

[a] Measles and varicella vaccination may be considered in some B-cell deficiencies

[1] Pickering LK et al, ed. Red book: 2009 report of the Committee on Infectious Diseases. 28th ed. American Academy of Pediatrics; 2009.

[2] CDC. General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2011;60:2.

Table IX: The Physical Examination in Patients with Recurrent Infection

Diagnosis and Physical Finding	Association
Growth Failure	T/B cell combined deficiency (SCID)
Dysmorphisms	
Micrognathia, short philtrum, ear anomalies	T cell deficiency (DiGeorge anomaly)
Short-limbed dwarfism	T cell deficiency (cartilage-hair hypoplasia)
Hypertelorism, epicanthal folds, flat nasal bridge	ICF syndrome
Ectodermal dysplasia	NEMO
Course facies	Hyper IgE syndrome
Skin and Oral Mucosa	
Rashes	
Lupus-like malar rash	early complement pathway defect
Dermatomyositis rash	XLA
Erythroderma	Omenn syndrome
Eczema	Wiskott-Aldrich, Hyper IgE syndrome
Petechiae	Wiskott-Aldrich syndrome
Pyoderma, abscesses	Neutrophil or B cell defects
Poor wound healing	Leukocyte adhesion defect
Candidiasis	T cell or T/B cell combined deficiency APECED, IPEX, CMCC
Telangiectasia	Ataxia-telangiectasia
Delayed umbilical cord separation	neutrophil adhesion defect
Abnormal hair	cartilage-hair hypoplasia NEMO Chediak-Higashi syndrome Griscelli syndrome
Ears, Nose,Throat and Mouth	
Chronic otitis media	B cell deficiency; mannose-binding
lectin deficiency	
dull tympanic membranes	
poor light reflex	
scarring	
perforations of the tympanic membrane	
Sinusitis	B cell deficiency
purulent nasal discharge	
purulent post-pharyngeal exudate	
pharyngeal cobblestoning	
Dentition, gums	
Conical teeth	NEMO

Approach to the patient with recurrent infections

Peridonditis	Leukocyte adhesion defects, neutropenia
Respiratory Tract	
Digital clubbing	Defect in any immune component
Rales	" "
Wheezing	B cell (IgA) deficiency
Cardiac	
Heart murmur (conotruncal abnormalities)	DiGeorge anomaly
Lymphatic System	
Absent tonsils, lymph nodes	Bruton's disease T/B cell combined deficiencies
Diffuse lymphoid hyperplasia	Common variable immunodeficiency Chronic granulomatous disease HIV infection ALPS XLP
Lymphadenitis	CGD
Musculoskeletal System	
Arthralgia/ arthritis	B cell deficiency
Dermatomyositis	B cell or complement deficiency
Lupus-like syndrome	Complement (early classical pathway), CVID or IgA deficiency
Short-limb dwarfism	Cartilage hair syndrome
Craniosynostosis	Hyper IgE syndrome
Neurological system	
Ataxia	Ataxia-telangiectasia
Enteroviral meningoencephalitis	B cell deficiency (Bruton's disease/XLA)
Neuropathies	Chediak-Higashi and Griscelli syndromes
Pernicious anemia	CVID

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Table X Screening Laboratory Evaluation of Innate Defense Factors

Absolute granulocyte count, cell morphology

Serum total hemolytic complement (CH50, alternative pathway AP50)

Nitroblue tetrazolium test (NBT) or flow cytometry using dihydrorhodamine dye test

Flow cytometry for leukocyte adhesion molecules (CD11/CD18, and CD15a)

Advanced testing –

Phagocytic assays

Chemotaxis assays

Analysis of toll-like receptor pathways

Molecular analysis for specific defects

Table XI: Screening Tests for T-Cell Immunity

Screening tests -

Newborn screening for TREC analysis (not available in all states)

Absolute lymphocyte count

Chest x-ray for thymus shadow in newborns

Delayed skin hypersensitivity to recall antigens

Quantification of T-cell subsets

Advanced testing -

Lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells (MLC)

Lymphocyte-mediated cytotoxicity - NK and ADCC activity

Production of cytokines

Functional response to cytokines

Signal transduction studies

Molecular analysis for specific defects

Table XII: Screening Laboratory Tests for the Evaluation of B-cell Immune Function

Screening-

Quantitative serum immunoglobulins
Specific antibodies to vaccine responses-
- Tetanus/diphtheria (IgG_1)
- Pneumococcal and meningococcal polysaccharides (IgG_2)
- Viral respiratory pathogens (IgG_1 and IgG_3)
- Other vaccines - hepatitis B, influenza, MMR, polio (killed vaccine)

Isohemagglutinins (IgM antibodies to A and B blood group antigens)
B-cell quantitation by flow cytometry

Advanced Testing-

In vitro B-cell immunoglobulin production
Regulation of immunoglobulin synthesis
CD40 ligand-CD40 interactions
Molecular analysis for gene deletions or mutations

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