Management of Recurrent Infections in Children

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Family physicians and pediatricians are besieged daily by swarms of children with running noses and coughing, with aching ears and throats, occasional fevers, diarrhea, skin infections, wheezing bronchitis, and finally pneumonia. They are usually accompanied by nervous mothers who expect a cure on the spot.

Most of these children suffer from viral intercurrent or bacterial benign infections, without any significant underlying disease. They will gradually become relatively immune to most of these pathogens and "outgrow" their infections. However, in a minority with various immune defects the infections will recur and worsen in intensity. Thus, what we need are guidelines to help us formulate a simple plan of action, leading to an early identification and appropriate management of those few whose infections represent a true immune deficiency, transient or not.

First we have to define qualitatively and quantitatively the designation "recurrent infections." The criteria are:

- Six to eight respiratory infections or two bouts of pneumonia/year
- Recurrent or persistent sinusitis
- Recurrent or persistent diarrhea and malabsoption
- Failure to thrive
- Skin eczema/infections
- Oral and perianal candidiasis
- Paucity of lymph nodes or generalized lymphadenopathy and hepatosplenomegaly

Immune defects may be primary congenital – mostly of genetic origin or due to intrauterine infections, or secondary – usually after a viral infection, such as Epstein-Barr virus or cytomegalovirus. The frequency of pediatric infectious diseases varies markedly between countries and ethnic groups, but it averages 1:100,000. They may be roughly divided into four groups, leading to certain types of infections and symptoms:

- The most common are humoral – 50% antibody and immunoglobulin production defects and 2% complement deficiencies – resulting mainly in bacterial pyogenic infections.
- 10% are cellular – essentially of T cell origin – associated with viral, fungal, mycobacterial and intracellular parasitic infections, malabsorption and failure to thrive.
- 20% are combined humoral and cellular infections of all types, and failure to thrive.
- 18% are phagocytic – disseminated bacterial and fungal infections.

Simple diagnostic screening tests may be applied upon arousal of the suspicion index for an immune defect:

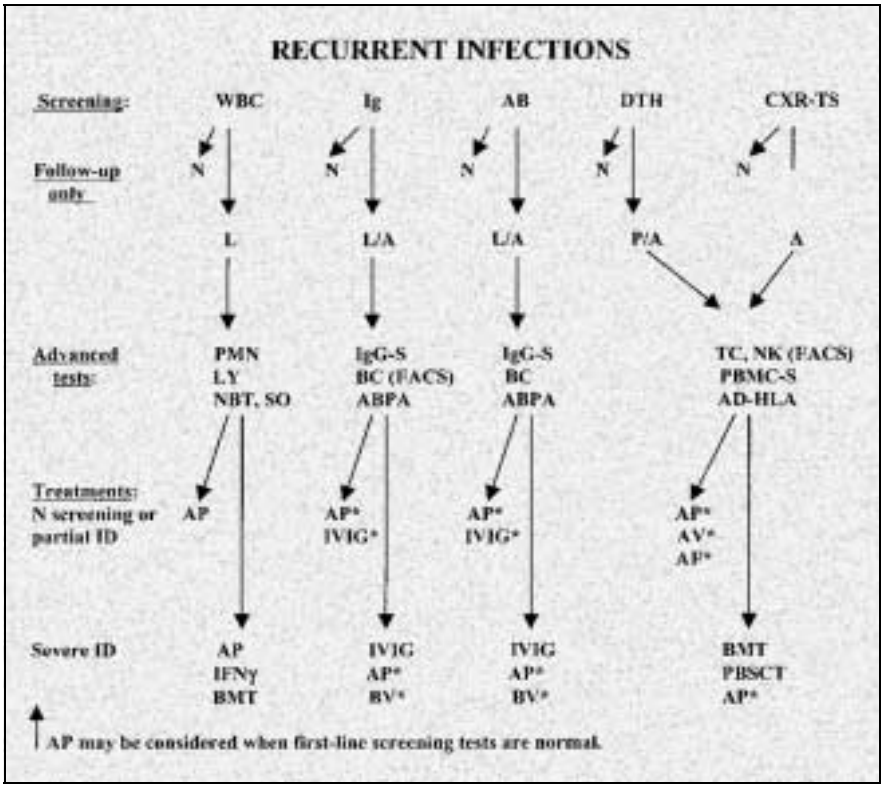
- Differential white blood cell count will reveal percentages and absolute numbers of lymphocytes and neutrophils; it should be remembered that values are age dependent and differ from those in adults.
- Serum levels of the immunoglobulin isotypes.
- Serum levels of the C3, C4 complement components and the total hemolytic activity will determine the integrity of the complement system.
- Intradermal assay of delayed type hypersensitivity to purified protein derivative tetanus toxoid, candidin, measles vaccine and others. Anergy will occur in cellular and combined defects.
- Presence or absence of isohemagglutinins, anti-tetanus and anti-measles antibodies will testify to the qualitative capacity of antibody production.
- Chest X-ray will reveal the presence or absence of a thymic shadow in the anterior mediastinum.

Upon a suspicious clinical picture and some defective screening assays, the patient should be referred to a specialized center where more sophisticated tests may be performed. These may include:

- Screening of lymphocyte subpopulations for percentages of B cells, T cell subsets and natural killer cells, using fluorescent monoclonal anti-membrane antibodies by flow-cytometry analysis (FACS instrument).
- Assaying of cell membrane adhesion and HLA molecules, as above.
- Proliferation of peripheral blood mononuclear cells in response to mitogenic (such as phytohemagglutinin, pokeweed mitogen, or concanavalin-A) or antigenic stimulus (PBMC-S).
- Screening of the capacity of phagocytic cells to produce oxygen-radicals, using the nitroblue tetrazolium-dye test. If negative, to be followed by

measurements of superoxide formation. Phagocytosis and chemotaxis assays to be added.
- Measurement of IgG-subclasses serum levels.
- Measurement of anti-bacterial polysaccharide antibodies, especially after *Haemophilus influenzae* type B and *Streptococcus pneumoniae* (Pneumovax) booster vaccination.

On the basis of these explanatory notes an algorithm of simple guidelines may be drawn:



AB = antibodies, ABPA = anti-bacterial polysaccharide antibodies, AD-HLA = cell membrane adhesion and HLA molecules, AP = antibiotic prophylaxis, AF = anti-fungals, AV = anti-virals, BC = B cells, BMT = bone marrow transplant, BV = booster vaccinations, CTX = chest X-ray, DTH = delayed-type hypersensitivity, FACS = fluorescence-activated cell sorter, ID = immunodeficiency, Ig = immunoglobulin, IVIG = intravenous immunoglobulin, IFN = interferon gamma, IgG-S = immunoglobulin G subclasses, LY = lymphocytes, NBT = nitroblue tetrazolium-dye test, NK = natural killer cells, PBSCT = peripheral blood stem cells transplant, PBMC-S = peripheral blood mononuclear cells stimulus, PMN = neutrophils, SO = superoxide, TC = T cells, TS = thymic shadow, WBC = white blood cells, A = absent, L = low, N = normal, P = poor, * = if indicated.

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I fear we have only awakened a sleeping giant, and his reaction will be terrible

Isoroku Yamamoto, Japanese admiral (1884-1943), after the Japanese attack on Pearl Harbor in 1942, which he devised