Current Paediatrics (2006) **16**, 16–28

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Impaired immunity in children

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KEYWORDS
Primary immunodeficiency;
Recurrent infections;
Opportunistic infections;
Severe combined immunodeficiency;
Antibody deficiency;
Immunoglobulin treatment

Summary
All young children are excessively susceptible to infections by virtue of immaturities in their immune mechanisms and a lack of prior antigen exposure. This results in an increased frequency of infections and, potentially, more severe infections than at older ages. Inherited primary deficiencies of the immune system may result not only in infections with common pathogens, but also atypical infections with opportunistic organisms. Most of these disorders are rare, but it is important to diagnose them early since treatments are more likely to be effective at that stage. Elucidation of the molecular basis of these disorders provides an insight into the working of the immune system as well as providing the means for genetic counselling, prenatal diagnosis and 'potentially' corrective gene therapy. The most common infections in children with antibody disorders are bacterial sino-pulmonary infections. Early diagnosis and immunoglobulin-replacement therapy can help to prevent long-term morbidity from chronic sinusitis and bronchiectasis. Defects of cell-mediated immunity are, almost invariably, associated with defective antibody production and are best termed combined immunodeficiencies. These may predispose to infections with both common and opportunistic pathogens. Persistent lymphopenia is often present and should not be ignored. Some immunodeficiencies are syndromic and associated with other defects. For many children with combined immunodeficiencies, bone marrow transplantation is the only option offering the potential for cure, although gene therapy approaches have reached the clinical trial stage for some disorders.
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Practice points

- Young children have an excess susceptibility to infection because of their immature immunity
- Some children with recurrent infections show a delayed maturation of antibody production
- The early recognition of primary immunodeficiency disorders has an important influence on outcome
- Immunoglobulin-replacement therapy for antibody deficiency syndromes confers an excellent prognosis if commenced before organ damage has occurred
- Persistent lymphopenia in infancy should arouse the suspicion of a possible combined immunodeficiency disorder
- Children with combined immunodeficiency disorders often require bone marrow transplantation

Introduction

All young children are excessively susceptible to infection by virtue of immaturities in their immune mechanisms and a

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doi:10.1016/j.cupe.2005.12.002

lack of prior antigen exposure. This results in an increased frequency of infections and, potentially, more severe infections than at older ages. Inherited primary deficiencies of the immune system may result not only in infections with common pathogens, but also atypical infections with opportunistic organisms. Secondary immunodeficiency in childhood is seen following human immunodeficiency virus infection, immunosuppressive treatment, including that following organ transplantation, and chemotherapy for malignant disease.

Developmental aspects of immunity

Physiological immunodeficiency of immaturity

Although the neonate has a normal number of circulating lymphocytes, these cells are relatively hyporesponsive. Neutrophil number increases during labour to normal levels shortly after birth, but bone marrow reserves are low so that, in the face of sepsis, the neutrophil count will often fall in neonates. As a result of these immaturities, serious infection can occur with common viruses such as herpes and enteroviruses, as well as invasive bacterial infections. True opportunistic infections such as *Pneumocystis* pneumonia do not, however, occur.

Transferred maternal IgG helps to protect the infant during this vulnerable period. The initial production of antibody is predominantly IgM, and class switching to IgG begins to occur shortly after birth. Although B cells expressing surface IgA are present at birth, the production of this isotype is often delayed, and indeed it takes until late childhood /adolescence to reach adult levels (Fig. 1). Premature delivery does not affect T-cell and B-cell numbers or responsiveness. Maternally transferred IgG is, however, markedly reduced before 33 weeks of gestation.

The maturation of immune responses occurs quite rapidly after birth, but the ability to handle pathogens normally matures at different rates for different microbes (Fig. 2). B cells in the neonate are of an immature phenotype, and lymph nodes lack germinal centres; these develop soon after antigen exposure in the early weeks of life. The ability to class-switch from IgM to IgG develops relatively early, and good IgG responsiveness to protein antigens is acquired by the time of the infant vaccine schedule at 2 months of age. It has, however, been observed that the magnitude of the antibody response to tetanus toxoid is inversely related to the level of passively transferred maternal IgG, which means that, in general, antibody responses are lower the earlier the immunization programme is started. Nevertheless, protective levels are achieved in the great majority of children immunized at 2, 3 and 4 months, and good immunological memory is generated.

Evidence in relation to hepatitis B vaccination suggests that infants generate better immunological memory than adults. The ability to make antibodies against polysaccharide antigens develops more slowly. Although immunogenicity varies between different polysaccharides, as a generalization, children under 2 years of age will not produce good antipolysaccharide responses. Conjugate vaccines, such as Hib conjugate, can overcome this immaturity in responsiveness and are immunogenic from 2 months of age, resulting in protective antibodies to the polysaccharide component. Recent work indicates, however, that after a 2-, 3- and

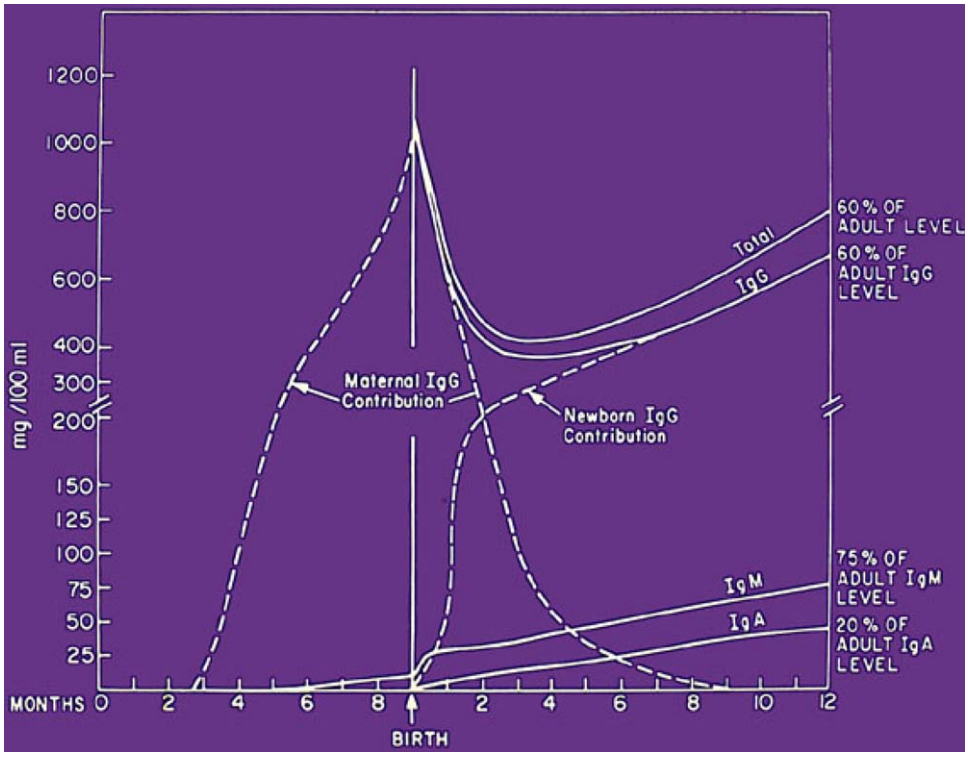

Figure 1 Immunoglobulin levels before birth and in the first year of life. (Reproduced with permission from Steihm et al.[5]).

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