what was found in this study. I found it discouraging that two thirds of the people who should have been receiving γ globulin were not.

**Recognition, Clinical Diagnosis and Management of Patients With Primary Antibody Deficiencies: A Systematic Review**  

**PURPOSE OF THE STUDY.** To create an evidence-based literature review of clinical diagnosis and management of primary antibody deficiency.

**METHODS.** Computer literature searches were conducted for randomized clinical trials in medical literature databases including the US National Library of Medicine (Medline), the Excerpta Medica database (EMBASE), the Cochrane Library, the Database of Abstracts of Reviews of Effects (DARE) of the Centre for Reviews and Dissemination (University of York), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) up to June 2006. Reports were rated on the basis of relevance and quality or type of evidence. Disease entities included were X-linked agammaglobulinemia, common variable immunodeficiency, hyper–immunoglobulin M (IgM) syndromes, IgG subclass deficiency with and without IgA deficiency, and specific antibody deficiency. Reports that involved only a limited number of patients were not included.

**RESULTS.** Individuals who present with recurrent respiratory infections of all types, especially with excessive frequency and severity, should be screened for antibody deficiency. In children, common associations included growth delay and failure to thrive, recurrent fevers without a source, and poor school attendance or performance. Chronic diarrhea was found in 40% to 60% of the patients at all ages. The median delay in diagnosis was 1 year but ranged to >10 years. Delayed diagnosis led to increased risk of bronchiectasis, pulmonary hypertension, and cor pulmonale. Randomized trials of the efficacy of γ-globulin replacement versus placebo do not currently exist. Many observational studies have confirmed the benefit of IgG therapy for reducing infectious morbidity. Higher IgG doses are associated with reduced incidence and severity of infections.

**CONCLUSIONS.** Delayed diagnosis was common as a result of lack of recognition of presenting symptoms and signs. Delay was less frequent when patients were referred to specialists. Delayed diagnosis led to delayed therapy (IgG) and a higher rate of infections and morbidity.

**HUMAN IMMUNODEFICIENCY VIRUS**

**Functional Patterns of HIV-1-Specific CD4 T-Cell Responses in Children Are Influenced by the Extent of Virus Suppression and Exposure**  

**PURPOSE OF THE STUDY.** HIV-specific CD4+ T cells seem to play a critical role in antiretroviral immunity and particularly in maintaining cytotoxic T-cell responses. The objective of this study was to evaluate the function of HIV-specific T cells in antiviral treated, HIV-infected children.

**STUDY POPULATION.** The researchers evaluated 23 HIV-infected children who were treated with antiretroviral therapy for a mean of 7 years.

**METHODS.** Flow-cytometric analysis was used to measure the ability of HIV-specific T cells to secrete interleukin 2 (IL-2) and interferon γ (IFN-γ) after stimulation of patient cells with p55 gag protein.

**RESULTS.** Three patterns of intracellular cytokine generation were identified: in 10 subjects, antigen-specific cytokine production was characterized by IL-2 production, 8 subjects’ CD4+ T cells expressed IL-2 and IFN-γ, and 5 subjects’ T cells expressed IFN-γ alone. These 3 groups were then analyzed for factors that might explain the different patterns. The patterns correlated with viral load at the time of functional analysis and over the previous 2 years. The group with dominant IFN-γ responses had high viremia levels, a pattern similar to that observed in patients with uncontrolled viral replication. Patients with combined IL-2 and IFN-γ production had relatively lower viral loads but had experienced viral “blips” over the 2 years before analysis. This pattern was similar to...
adults who were long-term nonprogressors or those whose conditions continued to progress despite antiretroviral therapy. The subjects with a dominant IL-2 response had very low levels of viremia and had not experienced viral “blips” over the previous 2 years. This pattern was similar to that generally observed in individuals who have cleared the infecting agent. It is important to note that this pattern has not been observed in HIV-infected adults.

CONCLUSIONS. Children with HIV have a higher frequency of HIV-specific CD4+ T cells compared with adults, and their recovery of an IL-2-secreting T-cell pattern indicates a greater capacity for immune restoration in children than adults.

REVIEWER COMMENTS. This elegant study provides a biological rationale for the clinical observation that young children started on antiretroviral therapy have the capacity for remarkable reconstitution of immune functions relative to those reported in adults and older children who have been infected for prolonged periods before antiretroviral therapy. Perhaps it is unfair to compare these results with findings in adults that included patients who were infected for many years before their initiation of therapy. A more appropriate comparative adult group would be those treated within 6 months of their diagnosis. Most importantly, this study demonstrates that children are “different” and that treatment early in infection allows excellent immune reconstitution if viral replication is completely controlled.

Identification of Host Proteins Required for HIV Infection Through a Functional Genomic Screen


PURPOSE OF THE STUDY. The HIV genome encodes only 15 proteins and, therefore, must use multiple host-cell collaborators for successful replication and transmission. Required host-derived proteins include CD4 as the primary virus receptor and chemokine receptors as coreceptors. This study identified multiple other host proteins required for HIV activity.

METHODS. Human cells known to be susceptible to HIV were exposed in vitro to HIV. Using small interfering RNAs able to inhibit each known gene in the human genome 1 at a time, the investigators tested whether HIV could establish an infection and copy itself. HIV dependence on >21 000 human genes was examined.

RESULTS. More than 250 human genes were identified to be required for efficient HIV replication. Termed “HIV-dependency factors,” the products of these genes are known to participate in a broad array of cellular functions and implicate unsuspected pathways in the virus life cycle.

CONCLUSIONS. The extraordinary dependence of HIV on human host proteins for efficient transmission and replication provides many new potential targets for antiretroviral therapy.

REVIEWER COMMENTS. An example of targeting host proteins is the use of chemokine receptor 5 (CCR5) inhibitors. Many people with CCR5 deficiency are very resistant to HIV infection yet have limited if any clinical consequences. Maraviroc CCR5 inhibitor is approved for treatment for HIV infection. This study identified many more such potential targets.

Proteinuria in Children Infected With the Human Immunodeficiency Virus


PURPOSE OF THE STUDY. Proteinuria is a common feature of HIV infection and a potential complication of therapy in adult patients. This study was performed to determine the prevalence of proteinuria in a group of children infected with HIV and to assess this process over time and the impact of antiretroviral therapy on it.

STUDY POPULATION. HIV-infected children (N = 286) were studied from 1998 through 2006.

METHODS. Proteinuria was determined by random urine protein/creatinine ratios, with “normal” defined as <0.2 and “nephrotic” defined as >1.0.

RESULTS. A total of 94 (33%) of the children had proteinuria at baseline. Of these, 32 had urine protein range ratios of ≥1.0. Clinically, the mortality rate was higher in those patients with proteinuria. It is important to note that 55 of the 94 patients with baseline proteinuria showed a good response to antiretroviral therapy, as indicated by a decrease in HIV viral load and a substantial reduction in the number of subjects who had proteinuria.

CONCLUSIONS. Control of HIV viremia with antiretroviral therapy reduces progression of HIV-associated proteinuria and improves the survival rate of infected children.

REVIEWER COMMENTS. Proteinuria is a common feature of HIV infection in children. Two features of this patient popu-
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