

Of the remaining patients, 26 children (16%) were found to have an immunologic abnormality, and a primary immunodeficiency was identified in 17 of these patients (10%). The majority of the patients with an identified immunodeficiency had a defect associated with antibody production, whereas there were also patients with complement defects ( $n = 3$ ), MyD88 deficiency ( $n = 1$ ), and congenital asplenia ( $n = 1$ ). Importantly, patients presenting with invasive pneumococcal disease aged  $>2$  years had a much higher risk of having a primary immunodeficiency (26% vs 2% in patients aged  $<2$  years at presentation).

**CONCLUSIONS.** Patients presenting with invasive pneumococcal disease should undergo an immunologic evaluation, particularly those who present with disease who are aged  $>2$  years.

**REVIEWER COMMENTS.** This study is the first prospective evaluation of immunized children presenting with invasive pneumococcal disease. The incidence during the first 4 years of the study (2005–2008) was 23 per 100 000 for children aged  $<2$  years and 5 per 100 000 for children aged  $>2$  years. Universal immunization with 7-valent pneumococcal conjugate vaccine was initiated in France in 2006, and this was switched to 13-valent pneumococcal conjugate vaccine in 2010, with vaccination coverage reaching  $\sim 93\%$  by 2011. The majority of the serotypes found in the patients with invasive pneumococcal disease were not found in the 7-valent pneumococcal conjugate vaccine, suggesting that “herd” immunity is at play regarding the serotype exposure among susceptible children. This study may actually underestimate the frequency of invasive pneumococcal disease because it did not include children missed who may have died of this infection. The take-home message from the study is that any child who develops invasive pneumococcal disease should undergo an immunologic evaluation focused on leukocyte count and differential, immunoglobulin levels, and complement (classic and alternative pathway) activity. In addition, these patients should be assessed for congenital asplenia as well as anatomic abnormalities that could be associated with infectious susceptibility. If results of all these studies are unrevealing, referral to a clinical immunologist with expertise in primary immunodeficiency disorders should be considered for evaluation of toll-like receptor function.

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### Deficiency of Innate and Acquired Immunity Caused by an IKBKB Mutation

Pannicke U, Baumann B, Fuchs S, et al. *N Engl J Med*. 2013;369(26):2504–2514

**PURPOSE OF THE STUDY.** The goal of this study was to characterize a form of severe combined immunodeficiency (SCID) that has previously been described.

**STUDY POPULATION.** The study included 4 patients of Northern Cree ancestry from Canada, who presented with normal numbers of T cells and B cells but very low levels of immunoglobulins, as well as a severe defect in activation of immune cells, which affected both the innate and adaptive immune-receptor pathways. These patients presented with oral candidiasis, *Escherichia coli* septicemia, parainfluenza virus type 1 pneumonia, *Listeria monocytogenes* septicemia, parainfluenza virus type 3 pneumonia, and *Serratia marcescens* bacteremia.

**METHODS.** Immunologic phenotyping, genetic and protein analyses, and functional investigations were performed.

**RESULTS.** The patients all had hypogammaglobulinemia or agammaglobulinemia, and peripheral blood B and T cells were almost exclusively of naive phenotype. Regulatory T cells and  $\gamma\delta$  T cells were absent. All 4 patients carried a homozygous duplication that led to loss of expression of IKK2, which is a component of the IKK-nuclear factor  $\kappa$ B pathway. Immune cells from these patients had impaired responses to stimulation through T-cell receptors, B-cell receptors, toll-like receptors, inflammatory cytokine receptors, and mitogens.

**CONCLUSIONS.** This form of SCID is characterized by normal lymphocyte development despite a loss of IKK2 function. This deficiency results in an impaired response to activation stimuli in a variety of immune cells, which leads to severe impairment of adaptive and innate immunity.

**REVIEWER COMMENTS.** SCID is rare, but most pediatricians will encounter this diagnosis sooner or later. It is important to be vigilant with children who have unusual, frequent, and persistent infections. In this case, the presence of normal numbers of T cells and B cells did not rule out the diagnosis of SCID.

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### Autosomal Recessive Phosphoglucomutase 3 (PGM3) Mutations Link Glycosylation Defects to Atopy, Immune Deficiency, Autoimmunity, and Neurocognitive Impairment

Zhang Y, Yu X, Ichikawa M, et al. *J Allergy Clin Immunol*. 2014;133(5):1400–1409. e1–5

**PURPOSE OF THE STUDY.** The goal of this study was to investigate the clinical, laboratory, and molecular characteristics of patients with similar findings, including immunodeficiency, significant atopy, immune dysregulation, and neurocognitive developmental defects.

**STUDY POPULATION.** Eight patients from 2 different families underwent clinical, laboratory, and genetic evaluation.

**METHODS.** Patients were assessed clinically followed by an immunologic evaluation and whole-exome sequencing,

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