

systemic infection with *Candida albicans* and with *K pneumoniae*, which ultimately proved to be fatal despite aggressive and appropriate antimicrobial therapy. The second patient was born to consanguineous parents and did not receive the BCG vaccine, but at the age of 14 months she developed multiple adenopathies that stained for *Nocardia nova*; she also developed a positive blood culture for *K pneumoniae*. The initiation of appropriate antimicrobial agents and interferon γ resulted in resolution of her infections.

CONCLUSIONS. *Klebsiella* infections should be considered in patients with IL-12 receptor $\beta 1$ deficiency. In addition, IL-12 receptor $\beta 1$ should be considered in patients with unexplained klebsiellosis.

REVIEWER COMMENTS. This is another example of the expanding range of microbial pathogens that can be observed in patients with defects that affect the IL-12 pathway. The historical observation that these patients primarily are affected by mycobacterial and salmonella infections needs to be modified to include mucocutaneous disease with *C albicans* seen in up to 25% of these patients and now also *Klebsiella* infection. This again points out that clinicians should be wary of not considering a specific defect caused by an infectious organism that does not fit with the initial or "classical" description of infections associated with a genetic defect. These disorders should be considered a "work in progress" in terms of the clinical phenotype. As with all rare diseases, it is best to consult with an experienced clinical immunologist when a child presents with an unusually severe or persistent infection.

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Thomas A. Fleisher, MD
Bethesda, MD

Clinical Features and Outcome of Patients With IRAK-4 and MyD88 Deficiency

Picard C, von Bernuth H, Ghandil P, et al. *Medicine (Baltimore)*. 2010;89(6):403-425

PURPOSE OF THE STUDY. To describe the clinical features and outcomes of patients with autosomal recessive defects in the interleukin 1 receptor-associated kinase 4 (IRAK-4) and the myeloid differentiation factor 88 (MyD88).

STUDY POPULATION. The authors provided the cumulative data of 48 patients with IRAK-4 deficiency and 12 patients with MyD88 deficiency from 37 kindreds in 15 countries.

METHODS. The data for this report were collected on the basis of a detailed questionnaire filled out by the physician who cared for the enrolled patient.

RESULTS. The leading threat to these patients was invasive pneumococcal disease, which was seen in 41 of the 60 patients (68%) and caused 72 documented invasive infections (52.2%). Invasive infections with *Pseudomonas aeruginosa* and *Staphylococcus aureus* were observed in 13 patients each. Noninvasive infections, typically involving the skin and lungs associated with *Pseudomonas aeruginosa* and *Staphylococcus aureus*, were also seen frequently (52 of 60 patients). Signs of inflammation (fever, elevated C-reactive protein level) are usually weak or delayed. It is important to note that there were no instances of severe viral, fungal, or parasitic infections. The clinical outcome to date has been poor; there have been 24 infection-related deaths (38%), and in 10 cases death was associated with the first invasive episode. Antibiotic prophylaxis, antipneumococcal vaccination, and/or immunoglobulin infusions seem to have a beneficial effect on outcomes. It is also important to note that there were no deaths after the age of 8 years and no invasive infections after the age of 14 years, which indicates that once a child with these defects reaches adolescence, there might be little risk for infection and prophylactic therapy might not be needed at that point.

CONCLUSIONS. The authors concluded that patients and families should be informed of the risk of developing life-threatening infections, and empiric antibacterial treatment and immediate medical consultation were strongly recommended in cases of suspected infection or moderate fever. Prophylactic measures in childhood were considered beneficial until spontaneous improvement occurs in adolescence.

REVIEWER COMMENTS. This is the most complete account to date of the clinical features and outcome of these 2 defects, both of which target critical signaling pathways in the innate immune system involving Toll-like receptors and the interleukin 1 receptor. The authors clearly defined these signaling pathways as playing a critical role in the host defense against invasive bacterial infection earlier in life. This also suggests that the full maturation of adaptive immunity involving T and B cells that occurs during later childhood compensates for the innate defect and prevents susceptibility to invasive bacterial infection after reaching adolescence. The consistent finding that the inflammatory response is somewhat diminished represents a clinical clue in these disorders, and the therapeutic recommendations clearly seem to alter what is otherwise a serious primary immunodeficiency in terms of mortality.

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Thomas A. Fleisher, MD
Bethesda, MD

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