Humoral and cellular immune responses to *Helicobacter pylori* in Bangladeshi children and adults that may be related to protection

Akademisk avhandling

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av

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Avhandlingen baseras på följande arbeten:

I. Bhuiyan TR, Qadri F, Bardhan PK, Ahmad MM, Kindlund B, Svennerholm AM, and Lundgren A: Comparison of mucosal B- and T-cell responses in *Helicobacter pylori*-infected subjects in a developing and a developed country.
FEMS Immunol Med Microbiol. 2008 Oct; 54(1): 70-9.

II. Bhuiyan TR, Qadri F, Saha A and Svennerholm AM: Infection by *Helicobacter pylori* in Bangladeshi children from birth to two years: relation to blood group, nutritional status and seasonality.
Pediatr Infect Dis J. 2009 Feb; 28(2): 79-85.

III. Bhuiyan TR, Saha A, Lundgren A, Qadri F and Svennerholm AM: Immune responses to *Helicobacter pylori* infection in Bangladeshi children during their first two years of life and relation between maternal antibodies and onset of infection.
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IV. Bhuiyan TR, Qadri F, Janzon A, Chowdhury MI, Lundin SB and Lundgren A: Th1 and Th17 responses to *Helicobacter pylori* in Bangladeshi children and adults.
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ABSTRACT

Humoral and cellular immune responses to *Helicobacter pylori* in Bangladeshi children and adults that may be related to protection

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Helicobacter pylori (Hp) colonizes the human gastric and duodenal mucosa and the infection may cause peptic ulcers and gastric adenocarcinoma. Half of the world's population is infected with Hp with the highest prevalence in developing countries. Hp infection is normally acquired during childhood, but comparatively little is known about immune responses to acute infection or potential differences in responses between individuals in Hp endemic and nonendemic countries. The overall aim of this thesis was to analyze humoral and cellular immune responses to Hp in children and adults living in a country with a high prevalence of Hp infections, i.e. Bangladesh.

T- and B-cell responses to Hp were analyzed in Hp infected adults from Bangladesh and Sweden. Comparable numbers of $CD19^+$ B cells and $CD4^+$ T cells and similar levels of Hp-specific IgA antibodies were found in gastric mucosa from Bangladeshi and Swedish subjects. However, higher numbers of $CD19^+$ B cells and higher levels of specific and total IgA antibodies were found in the duodenum of the Bangladeshis, possibly due to frequent enteric infections causing recruitment of Hp-specific and unspecific lymphocytes to this site. Furthermore, Bangladeshi subjects had about two-fold lower Hp-specific IgA and IgG serum antibody titers.

To determine the incidence of Hp infection during early childhood in a high endemic area and possible associations between infection and different host and environmental factors, a birth cohort (BC) study was undertaken in Bangladeshi children from birth up to 24 months. Using diagnostic methods suitable for use in less well-equipped laboratories, i.e. stool antigen test and serology, 50-60% of the children were found to be positive for Hp at 24 months. Most children were initially infected with Hp during spring or autumn and blood group A children had increased susceptibility to the infection. Serum and stool samples collected every third month from the BC children were analyzed for development of systemic and mucosal antibody responses to acute Hp infection. Almost all children mounted specific, ≥4-fold serum IgA and stool IgA responses following infection. Serum IgG levels at birth were comparable to the maternal antibody levels and decreased during the initial 6 months, whereafter they increased in response to infection. An association between spontaneous eradication of Hp infection (in approximately 10% of the children) and increased serum antibody responses was found. Pre-existing maternal IgG and breast milk IgA antibody levels were associated with delayed onset of Hp infection.

To analyze if certain T-cell responses (Th1 and Th17) may contribute to the immune responses against Hp, peripheral blood mononuclear cells were isolated and stimulated with Hp antigens. Cells from both Bangladeshi infants and adults responded with production of both IL-17 and IFN-γ, with higher IL-17 responses in infants. These results suggest that Th17 as well as Th1 type T-cell responses may be important for initial immune responses to Hp in young children.

These studies give important information regarding acquisition of Hp during early childhood in a high endemic country and provide clues about immune responses that may be related to protection against Hp infection.

Keywords: *Helicobacter pylori*, adults, children, birth cohort, maternal antibodies, serology, Th17, T cell, B cell, developing country.
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