differing nationalities of the two groups (nationality was a strong determinant of *H. pylori* infection in our population). This was described in our Results section. Therefore, the method used by Luzza and Pallone to compare the two crude prevalence figures is misleading because it does not take into account the differences in nationality and other relevant determinants. In our study, we provided only the estimates of the multivariable analysis that were controlled for the main determinants of the *H. pylori* infection status of the children, among them nationality. This method makes a careful comparison of the two odds ratios for *H. pylori* infection of children according to current infection status of mother or father less problematic. Also, we pointed out in the Discussion that the children accompanied by mothers differed somewhat from the group accompanied by fathers, an issue that was taken into account when we formulated our conclusions.

Third, as we noted and as correctly rephrased by Luzza and Pallone, the father’s infection status may be related to the mother’s infection status, and therefore further studies, including simultaneous measurement of both maternal and paternal infection, are needed to further clarify the role of parental infection status. However, epidemiologic theory allows the assessment of the consequences of the possible association between maternal and paternal infection. The implications of this eventual association are (as outlined in the second to the last paragraph of our Discussion section) that the described association between infection of parents and children may be confounded by the mother’s infection status, resulting in an overestimation of the role of paternal *H. pylori* infection status or vice versa. These issues were clearly discussed and taken into consideration when we formulated our conclusions.

Nevertheless, although the association of the weaker of two predictor variables (in our case, paternal *H. pylori* infection) with a dependent variable (in our case, the child’s *H. pylori* infection status) may, in theory, be due entirely to confounding by the stronger predictor variable (in our case, maternal *H. pylori* infection), the opposite scenario is not possible. Furthermore, the key role of the mother in transmitting *H. pylori* to the child seems quite plausible, because in our society she usually has the closest contact with the child.

Fourth, in Germany most children attend kindergarten (e.g., 97% of our study population did so). In kindergarten, children are together regardless of parental infection status. It would be extremely unlikely that the strong associations observed between infection status of children and parents would persist if considerable transmission of infection occurred outside the family. Attendance of day care facilities by children below kindergarten age was less common but was not associated with *H. pylori* infection in our study population. The same was true for other potential sources of infection, including siblings or pets.

In summary, this and our earlier studies [3–6], which Luzza and Pallone seem not to have taken into consideration, strongly suggest that *H. pylori* infection may be acquired early in life—before kindergarten age—and that parent-child transmission, in particular mother-child transmission, plays a key role.

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**Modulation of the Pro- and Antiinflammatory Cytokines by Amphotericin B**

To the Editor—We read with great interest the article by Rogers et al. [1] reporting the activation by amphotericin B of human genes encoding for the proinflammatory cytokines tumor necrosis factor (TNF) and interleukin (IL)–1β and for the antiinflammatory cytokine IL-1 receptor antagonist (IL-1Ra). Amphotericin B is still a major component of antifungal therapy, but its use is limited by severe adverse effects such as fever, chills, and hypotension. It has been hypothesized that these adverse effects of amphotericin B treatment are mediated through induction of pyrogenic proinflammatory cytokines [2–5]. The increase of the mRNA expression of these genes reported by Rogers et al. represents a strong argument that amphotericin B induces production of cytokines through transcriptional mechanisms, and this information may prove valuable in finding strategies to combat this deleterious side effect of the drug.
Recently, we also reported that amphotericin B increases the production of proinflammatory cytokines by human mononuclear cells, and this induction is mediated through activation of transcription of TNF and IL-1β genes [6], sustaining the results of Rogers et al. Our data not only corroborate the results of Rogers et al. that amphotericin B alone can induce TNF and IL-1β mRNA expression, but we extended these observations with data showing that amphotericin B potentiates lipopolysaccharide (LPS)–induced TNF and IL-1 mRNA expression. However, Candida albicans and Staphylococcus aureus–stimulated expression of cytokine genes were not influenced by amphotericin B [6], suggesting that induction of proinflammatory cytokines by different microbial stimuli is mediated through divergent pathways that are differentially modulated by amphotericin B.

Rogers et al. [1] also reported that the production of the antiinflammatory cytokine IL-1Ra, as well as the expression of IL-1Ra mRNA, are significantly stimulated by amphotericin B [1]. As IL-1Ra can block the IL-1 receptors and antagonize the proinflammatory action of IL-1, they hypothesized that this may represent a counterregulatory mechanism involved in the attenuation of the amphotericin B–related adverse effects. In contrast with the data of Rogers et al. obtained in a human monocytic cell line, we showed that amphotericin B under similar conditions causes a significant reduction of the spontaneous release of IL-1Ra by freshly isolated peripheral blood mononuclear cells (PBMC) of healthy volunteers [6]. Moreover, LPS- and S. aureus–induced IL-1Ra production was also down-regulated by amphotericin B [6]. This inhibition results in a shift toward proinflammatory cytokine production, as indicated by a significantly decreased IL-1Ra/IL-1β ratio. This balance was recently found to play a key role in type I diabetes, chronic inflammatory bowel diseases, rheumatoid arthritis, and Lyme arthritis, and we propose that it also represents an important pathophysiologic mechanism mediating such adverse effects as fever and chills caused by amphotericin B treatment.

The cause of the differences in IL-1Ra induction between our study and those of Rogers et al. remains speculative. The cell types used in the experiments constitute the major difference between the two studies. In our study, we used freshly isolated PBMC, whereas Rogers et al. used the human mononuclear cell line THP-1, on which the effects of amphotericin B may be divergent. It may be hypothesized that the effects of amphotericin B on PBMC of human volunteers may closely mimic those in human subjects.

The importance of the cell type used in this type of experiments is also underlined by the contradictory data in the literature regarding the capacity of amphotericin B to stimulate the production of cytokines. Several investigators have reported increased cytokine production upon amphotericin B stimulation of mononuclear cells in vitro [2, 4, 7], whereas others have been unable to find such an effect [8–10]. An explanation that may account for these differences is the source of the cells used; some studies have been done with human PBMC [5, 8–10], and others have used murine macrophages [2, 4, 7]. It is also important to underline that even in the studies reporting induction of cytokines by amphotericin B, the stimulation was much lower than that obtained with a strong stimulus such as LPS [2–5]. Given the strong potency of amphotericin B to induce chills and fever in vivo, one may wonder whether the in vitro findings regarding cytokines explain these side effects.

References


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