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Available online March 23, 2005.
doi:10.1016/j.jaci.2005.01.060

Reply

To the Editor:

We thank Sigsgaard and Heederik¹ for highlighting two issues regarding our Rostrum²: (1) the relevance of other pathogen associated molecular patterns (PAMPs), and (2) the potential for alternative immunological mechanisms underlying the presumed protective effects of PAMPs.

The main hypothesis of our Rostrum is that certain environmental exposures can modify the immune response from an atopic to a nonatopic state at any time in life.² Although we have focused on LPS (lipopolysaccharides) (since most of the evidence points toward LPS), we agree that other PAMPs may be equally (or more) important. As discussed in our Rostrum, there is evidence that exposure to peptidoglycans, CpG containing DNA, and certain viruses may also reduce the risk of atopic disease. Other agents such as mycobacterial lipoglycans (particularly lipoarabinomannan and phosphatidylinositol mannan)³ and even fungal components as suggested in a recent European multicenter study in farmers' children (presented at the 2004 European Respiratory Society Congress) may play a role as well. However, the evidence for these PAMPs is scarce.

In their correspondence, the authors suggest that a protective effect is more likely mediated by other PAMPs on the basis of the potential role of Toll-like receptor (TLR)-2 and their suggestion that "TLR4 polymorphisms have been linked to bronchial hyporesponsiveness only in the farming population." We disagree, because several studies in children (both farming and nonfarming) have shown that genetic variations in TLR4 are also associated with specific IgE and atopic asthma (including one study referenced by the authors).⁴ This, in our view, supports the hypothesis that endotoxin plays at least a partial role. Results regarding TLR4, atopy, and asthma have been mixed, however, hampering a straightforward interpretation.

As noted by Sigsgaard and Heederik,¹ the epidemiological evidence for a downregulation of atopic activity is limited. However, there is additional evidence that LPS and other PAMPs may reverse pre-existing allergy in animals (see our Rostrum²). The converse has also been demonstrated, showing that a loss of protective exposures at some stage in life may result in an upregulation of atopic activity (or a loss of tolerance). For example, a recent longitudinal study in 402 adults in Denmark showed an approximately 3-fold increased risk for new-onset atopy in subjects who migrated from a low-risk rural area to a high-

risk urban area.⁵ Other studies involving subjects migrating from poor to more affluent countries showed a similar effect. This adds to the evidence that atopy appears to be a continuum rather than a fixed immunological state, which can be both upregulated and downregulated at any time of life depending on the level of immunoregulatory exposures (including PAMPs). Taken together with the mainly indirect evidence of the occupational studies (see Rostrum), we believe there is sufficient evidence to warrant future studies to test this hypothesis.

In summary, including other markers of PAMPs (in addition to LPS) in future studies as suggested by Sigsgaard and Heederik¹ is highly relevant. Similarly, a further characterization of the immunological mechanisms is essential in identifying the therapeutic potential of these PAMPs.

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Dr Douwes is supported by a Sir Charles Hercus Research Fellowship from the Health Research Council of New Zealand. The Centre for Public Health Research is supported by a Program Grant from the Health Research Council of New Zealand.

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Available online April 5, 2005.
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Safety of penicillin administration to patients with histories of penicillin allergy

To the Editor:

In the letter by Daulat et al¹ entitled "Safety of cephalosporin administration to patients with histories of penicillin allergy," the authors minimize the cross-reaction

rate of cephalosporins to penicillin because only one reaction occurred when this class of antibiotic was given to patients with a history of penicillin and without testing. I suspect the same patients could have been given penicillin itself with the same safety.

Our experience at The New York Hospital Queens indicates that virtually all such patients can receive penicillin safely. For the last 4 years, we have been evaluating approximately 100 patients per year with a history of penicillin allergy who required a penicillin. All were tested with penicilloyl polylysine and penicillin G until September 30, 2004, when the penicilloyl polylysine became unavailable in this country. We have seen positive skin test responses only once or twice a year, and penicillin was administered to all the patients with negative test responses without any difficulty. In at least one third of the cases, no accurate history was available to evaluate whether the reaction was originally a severe one. Thus rather than showing a very low cross-reaction rate between penicillin and cephalosporins, I suspect that most of these patients were no longer allergic to penicillin.

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Available online April 5, 2005.
doi:10.1016/j.jaci.2005.02.004

Reply

To the Editor:

We appreciate Dr Fine's¹ comments regarding our study.^{1a} We disagree with his assessment that we "minimized" the potential allergic cross-reactivity between penicillin and cephalosporins. The retrospective protocol of evaluating cephalosporin reaction rates in patients with a history of penicillin allergy has inherent limitations, which we clearly outlined in discussing our findings. One limitation was that inpatient pharmacists might have identified some patients with a history of severe penicillin allergy, and these individuals were consequently denied a prescribed cephalosporin (and therefore would not be included in our sample of 606 patients). The other limitation, as Dr Fine correctly points out, is that most of the patients probably lacked penicillin-specific IgE antibodies when they were treated with cephalosporins. However, we disagree with his suggestion that only 1% or 2% of patients with a history of penicillin allergy turn out to have positive penicillin skin test results. Although this might be the experience at his institution, published studies on large groups of patients with a history of penicillin allergy have reported positive

penicillin skin test result rates ranging from 7.1%² to 63%.³ Most large-scale studies have reported positive penicillin skin test result rates of between 10% and 20%.⁴⁻⁶ Therefore if we assume a conservative estimate that 10% of the 606 patients (or 61 patients) in our study had penicillin allergy at the time of treatment with cephalosporins, only 1 of these 61 patients experienced a mild reaction.

We understand that ideally investigation of potential allergic cross-reactivity between penicillin and cephalosporins requires confirmation of patients' type 1 penicillin allergy through penicillin skin testing. One of the authors (RS) has reviewed the published medical literature and found that of 220 patients with positive penicillin skin test results challenged with various cephalosporins, 9 (4.1%) experienced reactions. It was not the objective of our study to perform penicillin skin tests. It must also be recognized that in the real-world practice of clinical medicine, physicians typically do not refer patients with a history of penicillin allergy for skin testing and frequently choose to treat them with cephalosporins.⁷

In summary, our study found a low rate of reactions to cephalosporins in a selected group of inpatients with histories of penicillin allergy. We recognize and stated its limitations, and we look forward to future research to answer once and for all the question of allergic cross-reactivity between penicillin and cephalosporins. We did not minimize the potential cross-reaction rate between penicillin and cephalosporins, and in fact, we concluded our study by stating that "broad administration of cephalosporins to patients with a history of penicillin allergy cannot be recommended at this time."

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