

# Ethylene oxide allergy in children with spina bifida

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**Background:** Allergic reactions to ethylene oxide (EtO)-treated products have occurred in several children with myelomeningoceles.

**Objective:** The object of this study was to define the prevalence and significance of EtO-specific IgE among the children in our myelomeningocele clinic.

**Methods:** The study population comprised three groups: children with myelomeningoceles, chronically ill controls (defined as children who had undergone at least three major operations), and well-child controls. Serum specimens were collected from each child, and a commercially available ELISA designed to identify IgE directed against both EtO and latex was performed on the specimens.

**Results:** Seventeen of 75 (23%) children with myelomeningoceles had antibodies directed against EtO, as did 1 of 26 (4%) chronically ill controls. None of the 25 well controls had detectable levels of anti-EtO IgE. Children with antibodies directed against EtO were more likely to be atopic ( $p = 0.007$ ) and to have a shunt ( $p = 0.021$ ) and were markedly more likely to have antibodies directed against latex ( $p < 0.001$ ). On average they had undergone more shunt revisions and other operations than had children without anti-EtO antibodies.

**Conclusion:** During the period of study no child had anaphylaxis thought to have been due to EtO exposure. (*J ALLERGY CLIN IMMUNOL* 1995;96:486-8.)

**Key words:** Ethylene oxide, latex, myelomeningocele, allergy

Allergic reactions to ethylene oxide (EtO), a commonly used medical sterilant, are not infrequent. Most of the clinical problems associated with these reactions have occurred in patients undergoing hemodialysis.<sup>1-6</sup> Recent reports have suggested, however, that sensitivity to EtO may develop in other people with either long-term or repeated exposure to EtO.<sup>7,8</sup>

Systemic reactions thought to have been due to EtO allergy have occurred in several children with myelomeningoceles.<sup>8</sup> The children appear to be at increased risk for the development of EtO allergy because almost all of them have had multiple operations and many have long-term implants. The significance of these reported cases and the impli-

## Abbreviation used

EtO: Ethylene oxide

cations for those providing care to these children are difficult to define because of a lack of basic epidemiologic data. Consequently, we tried to determine the prevalence and clinical importance of anti-EtO antibodies in the children with myelomeningoceles cared for at Cardinal Glennon Children's Hospital.

## METHODS

The study population comprised three groups: children with myelomeningoceles, chronically ill controls, and well-child controls. The chronically ill controls were children who had undergone at least three major operations but in whom there was no evidence of immunosuppression or cancer. These children were drawn from the neurosurgery, genitourinary, general surgery, and orthopedic surgery services, as well as from the neonatal follow-up clinic. The well-child group was composed of children who had undergone at most one minor procedure and had no recognized chronic illness or other

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reason for frequent medical contact. They were recruited from the orthopedic and general surgery services and the ear, nose, and throat clinics.

A questionnaire was filled out by, or for, each of the children with a myelomeningocele and each of the chronically ill controls. The information requested included diagnosis, demographic data, and a detailed history of allergic diseases. In addition, there were specific questions concerning exposure to catheters, implanted devices, and the number and type of previous surgical procedures.

Serum specimens were collected from each child. A commercially available ELISA (CAP System Pharmacia Diagnostics, Piscataway, N.J.) designed to identify IgE directed against both EtO and latex was performed on the specimens.

Finally the charts of the children with myelomeningoceles were reviewed. The operative reports and anesthesia records were examined. Specific attention was paid to perioperative episodes of hypotension, bronchospasm, and urticaria. Records of nonsurgical admission were checked for any indication of significant allergic reactions. In addition, relatively detailed information about ventriculoperitoneal shunt function was gathered. The experimental design was reviewed and approved by the Institutional Review Board at St. Louis University.

## RESULTS

There were 126 children in the study: 75 with myelomeningoceles, 26 chronically ill controls, and 25 well-child controls.

The children with myelomeningoceles ranged in age from 1 to 18 years (median, 8). They had undergone an average of 7.9 operations (S.D., 6.38; median, 6; range, 1 to 30), of which 2.71 (S.D., 2.02; median, 2; range, 1 to 10) were shunt related. Fifty-nine (79%) were, or had been, on an intermittent catheterization program, but all were using vinyl catheters at the time of the study. Twenty-one (28%) were atopic by history. Seventeen of the 75 children (23%) had IgE directed against EtO, and 44 (59%) of them, including 15 of the 17 (89%) with anti-EtO antibodies, had antibodies directed against latex.

The chronically ill control group ranged in age from 1 to 18 years (median, 11). Each had undergone an average of 6.08 operations (S.D., 3.87; median, 5; range, 3 to 20). Seven (28%) of the children had ventriculoperitoneal shunts; they had undergone an average of 7.14 operations (S.D., 3.13; median, 7; range, 3 to 12) of which 2.72 (S.D., 2.14; median, 2; range, 1 to 7) were shunt related. Two (8%) of the children were on an intermittent catheterization program, and four (16%) gave a history of allergies. One of the 26 (4%) children in the group had anti-EtO antibodies, and three,

including the child with anti-EtO antibodies, had antibodies directed against latex.

The children in the well-child control group were between 2 and 15 years old (median, 5.5). They had undergone an average of 0.15 operations. None had a shunt; none had been on an intermittent catheterization program. Four (15%) of the children had a history of allergies. None had detectable levels of IgE directed against either EtO or latex.

Children with myelomeningoceles were significantly more likely to possess anti-EtO antibodies than were either the chronically ill controls (Fisher's exact test,  $p < 0.001$ ) or the well-child controls (Fisher's exact test,  $p = 0.005$ ). There was no significant difference demonstrable in the rates of anti-EtO antibodies between the two control groups. Similarly, children with myelomeningoceles were significantly more likely to have antibodies directed against latex than were children in either of the other two groups (Fisher's exact test,  $p < 0.001$ ,  $p < 0.001$ ); the difference in prevalence between the two control groups was not significant.

Children in any group with antibodies directed against EtO were more likely to be atopic (Pearson's chi-square,  $p = 0.007$ ) and to have a shunt (Pearson's chi-square,  $p = 0.021$ ) and were markedly more likely to have antibodies against latex (Pearson's chi-square,  $p < 0.001$ ). On average they had undergone more shunt revisions and other operations than had children without anti-EtO antibodies. These differences were significant in the chronically ill controls (Pearson's chi-square,  $p = 0.003$ ), but they did not attain statistical significance in the myelomeningocele group. No significant relationship between having been on an intermittent catheterization program and the presence of anti-EtO antibodies was recognized.

During the period of study no child had anaphylaxis that was thought to have been due to EtO exposure. Two children, whose cases have been previously reported, had serial sterile shunt malfunctions that were thought to have been caused by an immunologically mediated response to EtO.<sup>9</sup>

## DISCUSSION

EtO is a highly active alkylating agent commonly used to sterilize biomedical products. It is extremely irritating in high concentrations and even in low concentrations is capable of altering native protein and potentially creating allergenic antigens.<sup>10</sup> Since Poothullil et al.<sup>5</sup> first reported in 1975 anaphylaxis from EtO, many others have described systemic IgE-mediated hypersensitivity reactions

to EtO-protein conjugates, most commonly during hemodialysis.<sup>1-4, 6</sup> The reactions have included urticaria, angioedema, bronchospasm, hypotension, and cardiovascular collapse. In addition, local reactions have been reported in patients who had undergone reconstructive knee surgery during which freeze-dried EtO-sterilized bone grafts were used.<sup>11</sup>

Immunologically mediated reactions directed against EtO have also been described in children with myelomeningoceles. A few of the children have had anaphylaxis when they were exposed to gas-sterilized products; those children had detectable levels of anti-EtO IgE.<sup>8</sup> Local reactions have also been seen. The histories of two children who had repeated sterile shunt malfunctions thought to have been due to an immunologic response to EtO were recently published.<sup>9</sup>

Although few problems among children with myelomeningoceles have been attributed to EtO allergy, antibodies directed against EtO are common in the population. Twenty-three percent of the children we tested had detectable levels of anti-EtO IgE. As might be expected, the antibody rate was highest among those with the greatest exposure: children who had undergone more operations and those who had a shunt, especially a shunt that had been revised several times. The rates were also high among those with other environmental allergies. These are the type of children—and in many instances the same children—who have antibodies directed against latex.

It is possible that the high incidence of latex allergy among patients with myelomeningoceles has made it difficult to recognize what are likely to be the less dramatic effects of EtO allergy in this group. Some reactions to EtO are likely to have been thought due to latex; others may have been ameliorated or prevented by premedication or some other precautions used to avoid latex exposure. Still others, such as an increased incidence of shunt malfunctions, may not have been recognized as being immunologically mediated. It may also be that the principal importance of allergy to EtO in this population is that it alters or augments the reactions of some patients to latex products. Perhaps patients with antibodies to both latex and EtO are at particular risk for systemic reactions; a

recent report suggests that this is unlikely,<sup>12</sup> but our data are not sufficient for us to draw any conclusion about this question.

It is difficult to define the clinical importance of EtO allergy in children with myelomeningoceles. Given the widespread use of EtO and its known capacity as an allergen, it seems unreasonable to think that it would have no effects among these children. Experience would suggest that the problem is small, but that it likely exists.

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