

# Vitamin A Treatment of Measles

Committee on Infectious Diseases

In spite of the availability of effective vaccines, measles continues to be a public health problem throughout the world. In 1990, the Centers for Disease Control received more than 27 672 reports of measles in the United States. Complications were reported in one third of infected children younger than 5 years of age.<sup>1</sup> Of the 89 measles-related deaths in 1990, 55% occurred in children younger than 5 years old.

Several recent investigations have indicated that vitamin A treatment of children with measles in developing countries has been associated with reductions in morbidity and mortality. The World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) issued a joint statement recommending that vitamin A be administered to all children diagnosed with measles in communities where vitamin A deficiency (serum vitamin A <10 µg/dL) is a recognized problem and where mortality related to measles is ≥1%. The recommended regimen is 100 000 IU by mouth at the time of diagnosis for infants younger than 12 months of age, and 200 000 IU for older children. In the presence of ophthalmologic signs of vitamin A deficiency, such as night blindness, Bitot's spots (grayish white deposits on the bulbar conjunctiva adjacent to the cornea) or xerophthalmia, the WHO recommends the dose be repeated in 24 hours and again 4 weeks later.<sup>2</sup> Vitamin A is available in low-cost liquid formulations and is supplemented in infant formulas (2000 µ/L).

## RATIONALE FOR VITAMIN A

Vitamin A is a necessary substrate for preserving epithelial cell integrity and in addition plays a role in immune modulation.<sup>1-3</sup> Acute vitamin A deficiency often develops in marginally nourished children. Although the exact cause is unclear, these patients apparently have little or no hepatic reserves of vitamin A when they are infected with measles.<sup>4</sup> This may be secondary to an acute decline in the level of proteins (prealbumin and retinol-binding protein) necessary to mobilize vitamin A from the liver. This decline has been observed in children with measles and other acute illnesses. Deficiency results in low serum retinol levels and impaired regeneration of epithelial surfaces.

The exact mechanism of vitamin A immune modulation has not yet been defined.<sup>5</sup> Recently, low vi-

itamin A levels were documented in 22% of 89 measles-infected New York children younger than 2 years of age. This correlated with lower measles-specific antibody levels and increased morbidity.<sup>6</sup> A similar investigation in South Africa linked vitamin A immunopotentiality to decreased morbidity and mortality.<sup>7</sup>

Markowitz et al<sup>8</sup> observed that vitamin A deficiency was associated with increased mortality in Zairian children younger than 24 months of age hospitalized with measles, pneumonia, and lymphopenia. Formal nutritional evaluation was not done, but 25 of 283 patients were considered to have muscle wasting. The overall case mortality rate in this cohort was 26%.<sup>8</sup>

The potential benefit of vitamin A therapy for measles was first reported in 1932.<sup>9</sup> Recently, a randomized, double-blind, placebo-controlled study in South African children, who were younger than 13 years old and without obvious clinical signs of malnutrition, resulted in significantly lower complication rates and mortality among children who had received large doses of vitamin A (400 000 IU) at the time of hospitalization.<sup>10</sup> The differences in morbidity and mortality were more striking in infants younger than 2 years of age. Additional studies have confirmed the reduction of measles morbidity by vitamin A supplementation.<sup>7,11</sup>

Vitamin A deficiency is not recognized as a significant problem in the United States. The children in the study by Hussey and Klein<sup>10</sup> were substantially different in growth parameters from the average child in the United States. Recently, however, Frieden et al<sup>6</sup> in New York and Butler et al<sup>12</sup> in Milwaukee reported that indigent children with measles had low serum levels of vitamin A that correlated with more severe disease. Arrieta et al<sup>13</sup> also found low vitamin A levels in 10 of 20 well-nourished patients hospitalized with measles in California.

## SAFETY OF VITAMIN A

Acute vitamin A toxicity is uncommon and usually associated with high intake (cumulative doses frequently greater than 1 000 000 IU) over 2 to 3 weeks.<sup>14,15</sup> A transient bulging fontanel and vomiting are the main clinical features in infants; nausea, vomiting, headache, and pseudotumor cerebri (increased intracranial pressure) are reported in children and adults.<sup>15,16</sup> Abnormal liver function tests and cortical hyperostosis may also occur with excessive doses of vitamin A. Vitamin A is teratogenic at therapeutic dosages and should not be prescribed

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for pregnant subjects.<sup>17</sup> There are no reports to date related to acute vitamin A toxicity in children with measles with use of the dose recommended by the WHO in 1987. It is important to recognize that the doses recommended for the therapy of measles are 100 to 200 times the recommended dietary allowance for this vitamin.<sup>18</sup> The American Academy of Pediatrics considers the data on efficacy and safety of vitamin A in US children with measles to be limited and, therefore, cautions practitioners to select patients for treatment carefully, as described below, and to monitor clinically for side effects (eg, bulging fontanel, headache, and vomiting). Pharmacies can be instructed to dispense vitamin A as an age-appropriate unit dose as a precaution against continued administration and potential toxicity.

### RECOMMENDATIONS

Although the available data are incomplete and insufficient to determine the appropriate use of vitamin A for all children with measles, the American Academy of Pediatrics recommends that vitamin A supplementation should be considered in selected circumstances:

1. Patients 6 months to 2 years of age hospitalized with measles and its complications (eg, croup, pneumonia, diarrhea) (Limited data are available regarding the safety and need for vitamin A supplementation for infants younger than 6 months of age.<sup>10</sup>)
2. Patients older than 6 months of age with measles who have any of the following risk factors and who are not already receiving vitamin A:
  - Immunodeficiency (eg, acquired immunodeficiency syndrome, congenital immunodeficiencies, immunosuppressive therapy)
  - Ophthalmologic evidence of vitamin A deficiency including night blindness, Bitot's spots, or evidence of xerophthalmia
  - Impaired intestinal absorption (eg, biliary obstruction, short bowel syndrome, cystic fibrosis)
  - Moderate to severe malnutrition, including that associated with eating disorders
  - Recent immigrants from areas where high mortality rates from measles have been observed

### Available Formulation

Vitamin A solution, 50 000 IU/mL for oral administration, is available in the United States.

### Recommended Dose

The dosage should be similar to that recommended by the WHO and UNICEF<sup>2</sup>:

- Single dose of 200 000 IU by mouth for children 1 year of age and older (100 000 IU for children 6 months to 1 year of age). The higher dose may be associated with vomiting and headache for a few hours.
- The dose should be repeated the next day and at 4 weeks for children with ophthalmologic evidence of vitamin A deficiency.

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