

CLINICAL REPORT

Guidance for the Clinician in Rendering Pediatric Care

Frank R. Greer, MD; Michael Shannon, MD; the Committee on Nutrition; and the Committee on Environmental Health

Infant Methemoglobinemia: The Role of Dietary Nitrate in Food and Water

ABSTRACT. Infants for whom formula may be prepared with well water remain a high-risk group for nitrate poisoning. This clinical report reinforces the need for testing of well water for nitrate content. There seems to be little or no risk of nitrate poisoning from commercially prepared infant foods in the United States. However, reports of nitrate poisoning from home-prepared vegetable foods for infants continue to occur. Breastfeeding infants are not at risk of methemoglobinemia even when mothers ingest water with very high concentrations of nitrate nitrogen (100 ppm). *Pediatrics* 2005;116:784-786; *methemoglobinemia*.

INTRODUCTION

Nitrate poisoning resulting in methemoglobinemia continues to be a problem in infants in the United States. Most reported cases have been ascribed to the use of contaminated well water for preparation of infant formula.¹⁻³ Fifteen million families in the United States obtain their drinking water from unregulated wells.⁴ In a survey of 5500 private water supplies from 9 Midwestern states, 13% of the wells were found to have nitrate concentrations >10 mg/L or 10 ppm nitrate nitrogen,⁵ the federal maximum contaminant level.⁶ It is estimated that 2 million families drink water from private wells that fail to meet the federal drinking-water standard for nitrate, and 40 000 infants younger than 6 months live in homes that have nitrate-contaminated water supplies.⁴ In urban areas, municipal wastewater-treatment discharges (a source of nutrients) on surrounding farmland aggravate the problem.⁷

There have been occasional cases of nitrate poisoning in infants from ingestion of plant nitrates,⁸⁻¹³ only one of which was reported from the United States.⁹ Nitrates are natural constituents of plant material, and the effect of commercial nitrate-containing fertilizers on the nitrate content of vegetables is inconsistent.¹⁴ Because the intake of naturally occurring nitrates from foods such as green beans, carrots,

squash, spinach, and beets can be as high as or higher than that from well water, these foods should be avoided before 3 months of age, although there is no nutritional indication to add complementary foods to the diet of the healthy term infant before 4 to 6 months of age.^{14,15} Some commercially prepared infant food vegetables are voluntarily monitored for nitrate content by private industry, including spinach, squash, and carrots. A target concentration of nitrate nitrogen for food of <100 ppm is desirable for infants. Because this concentration is frequently exceeded in spinach, this product is often labeled not to be used in infants younger than 3 months.

For breastfed infants, there is no evidence of an increased risk of methemoglobinemia from maternal ingestion of water with nitrate nitrogen concentrations as high as 100 ppm, because these mothers do not produce milk with high nitrate concentrations.¹⁶ Furthermore, the predominant organism in the gastrointestinal tract (*Lactobacillus* species) of the breastfed infant does not reduce nitrate to nitrite (see following section).¹⁴

PATHOPHYSIOLOGY

The potential hazard of nitrate in either food or water is from its conversion to methemoglobin-producing nitrites before and/or after ingestion. The nitrite ion oxidizes ferrous iron in hemoglobin to the ferric state. The resulting compound, methemoglobin, is incapable of binding molecular oxygen and produces a leftward shift in the oxygen-dissociation curve, which results in hypoxemia. Absorbed nitrate that has not been converted to nitrite can be readily excreted in the urine without adverse effects.¹⁴

There are many factors that influence the incidence of methemoglobinemia in infancy.^{14,17} The gastric pH of infants is higher than that in older children and adults, with resultant proliferation of intestinal flora that can reduce the ingested nitrate to nitrite. Fetal hemoglobin, the predominant form in infants up to 3 months of age, is oxidized more readily to methemoglobin by nitrite than is adult hemoglobin. Red blood cells contain methemoglobin reductases that convert methemoglobin back to hemoglobin. Ninety-nine percent of this reduction activity is accounted for by cytochrome-b₅ methemoglobin reductase; the activity of this enzyme is reduced by half in

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

doi:10.1542/peds.2005-1497

PEDIATRICS (ISSN 0031 4005). Copyright © 2005 by the American Academy of Pediatrics.

infants compared with adults.¹⁸ Although these factors explain the higher incidence of methemoglobinemia in infants, there are not enough data to identify a specific level of nitrate intake that is safe for all infants.

CLINICAL MANIFESTATION

Methemoglobinemia generally manifests with few clinical signs other than cyanosis. Methemoglobin represents only 1% of the total hemoglobin of the healthy adult, although it can be slightly higher in preterm and term newborn infants.¹⁹ Obvious cyanosis can occur with methemoglobin concentrations as low as 3% in infants with low hemoglobin concentrations. Symptoms are usually minimal until methemoglobin concentrations exceed 20%.²⁰ The mucous membranes of infants with methemoglobinemia tend to have brown (rather than blue) discoloration. This discoloration increases with the concentration of methemoglobin, as do the manifestations of irritability, tachypnea, and altered mental status.²⁰ In the absence of respiratory symptoms, history of cardiovascular disease, abnormal pulse, or abnormal pulse oximetry, a diagnosis of methemoglobinemia should be considered in a child who becomes acutely cyanotic and fails to respond to oxygen administration. When significant concentrations of methemoglobin (>30%) are present, a pulse oximeter is very misleading and will detect only mild to moderate oxygen desaturations in the 82% to 86% range.²⁰

TREATMENT AND PREVENTION

Health care professionals who suspect that an infant has methemoglobinemia are advised to consult with the local poison control center or a toxicologist to help guide management. An asymptomatic infant with cyanosis who has a methemoglobin concentration of <20% usually requires no treatment other than identifying and eliminating the source of exposure (assuming a normal hematocrit). Anemic children will display toxicity at lower methemoglobin concentrations. More detailed information on diagnosis and treatment has been reviewed elsewhere.²⁰

Clinical diagnosis and treatment for methemoglobinemia is not sufficient. Preventive strategies are needed to identify and eliminate the sources of exposure.²¹ Assessment of potential nitrate exposure includes questions about the family residence, parental occupations, drinking water, foods ingested, topical medications, and folk remedies. Prenatal and newborn care for patients with private wells should include recommendation for testing well water for nitrate contamination. Water with high nitrate concentrations should not be ingested by the infant or used for preparation of infant formulas or infant foods. Use of alternative sources of water should be advised, including deeper wells, public water supplies, or bottled water free of nitrate. Boiling water with nitrate nitrogen concentrations of <10 ppm for 1 minute generally is sufficient to kill microorganisms without over concentrating nitrate.²¹

Effective in-home systems for nitrate removal include ion-exchange resins and reverse osmosis; however, these systems can be expensive. Ordinary water

softeners used in the home do not remove nitrates.²² Water testing for nitrate can be obtained from any reference or public health laboratory using laboratory methods approved by the US Environmental Protection Agency. Most state health departments have listings of these certified laboratories.

There is limited information on the nitrate content of commercial infant foods, although the highest concentrations (>100 ppm of nitrate nitrogen) are found in beets, carrots, spinach, squash, and green beans.^{14,15} Preventive strategy would be not to introduce home preparations of these vegetables to infants before 3 months of age, although there is no nutritional indication to add complementary foods to the diet of the healthy term infant before 4 to 6 months of age.²³ Infants fed commercially prepared infant foods after 3 months of age generally are not at risk of nitrate poisoning, although the containers should be refrigerated after first use and discarded within 24 hours of opening.

SUMMARY

1. The greatest risk of nitrate poisoning (methemoglobinemia) occurs in infants fed well water contaminated with nitrates. All prenatal and well-infant visits should include questions about the home water supply. If the source is a private well, the water should be tested for nitrate. The nitrate nitrogen concentration of the water should be <10 ppm.
2. Infants fed commercially prepared infant foods generally are not at risk of nitrate poisoning. However, home-prepared infant foods from vegetables (eg, spinach, beets, green beans, squash, carrots) should be avoided until infants are 3 months or older, although there is no nutritional indication to add complementary foods to the diet of the healthy term infant before 4 to 6 months of age.
3. Breastfed infants are not at risk of nitrate poisoning from mothers who ingest water with high nitrate content (up to 100 ppm nitrate nitrogen), because nitrate concentration does not increase significantly in the milk.

COMMITTEE ON NUTRITION, 2003–2004
Nancy F. Krebs, MD, MS, Chairperson
Robert D. Baker, Jr, MD, PhD
Jatinder J. S. Bhatia, MD
*Frank R. Greer, MD
Melvin B. Heyman, MD
Fima Lifshitz, MD

LIAISONS
Donna Blum-Kemelor, MS, RD
US Department of Agriculture
Margaret P. Boland, MD
Canadian Paediatric Society
William Dietz, MD, PhD
Centers for Disease Control and Prevention
Capt Van Saxton Hubbard, MD, PhD
National Institutes of Health
Benson M Silverman, MD
US Food and Drug Administration

STAFF

Pamela T. Kanda, MPH

COMMITTEE ON ENVIRONMENTAL HEALTH, 2003–2004

*Michael W. Shannon, MD, MPH,
Chairperson

Dana Best, MD, MPH

Helen J. Binns, MD, MPH

Christine L. Johnson, MD

Janice J. Kim, MD, PhD, MPH

Lynnette J. Mazur, MD, MPH

James R. Roberts, MD, MPH

William B. Weil, Jr, MD

LIAISONS

Elizabeth Blackburn, RN

US Environmental Protection Agency

Robert H. Johnson, MD

Centers for Disease Control and
Prevention/Agency for Toxic Substances
and Disease Registry

Martha Linet, MD

National Cancer Institute

Walter Rogan, MD

National Institute of Environmental Health
Sciences

STAFF

Paul Siple

*Lead Authors

REFERENCES

1. Knobeloch L, Proctor M. Eight blue babies. *WMJ*. 2001;100(8):43–47
2. Herman MI, Chyka PA, Butler AY, Rieger SE. Methylene blue by intraosseous infusion for methemoglobinemia. *Ann Emerg Med*. 1999;33:111–113
3. Johnson CJ, Kross BC. Continuing importance of nitrate contamination of groundwater and wells in rural areas. *Am J Ind Med*. 1990;18:449–456
4. US General Accounting Office. *Information on the Quality of Water Found at Community Water Systems and Private Wells*. Washington, DC: US General Accounting Office; 1997. Publication GAO/RCED-97-123
5. National Center for Environmental Health. A survey of the quality of water drawn from domestic wells in nine Midwest states. Atlanta, GA: Centers for Disease Control and Prevention; 1995. Available at: www.cdc.gov/nceh/emergency/wellwater/WellResults.htm. Accessed July 12, 2005
6. US Environmental Protection Agency. National Primary Drinking Water Regulations: Final Rule, 40. CFR Parts 141–143. *Fed Regist*. 1991; 56(20):3526–3597
7. Nolan BT, Riddy BC, Hitt KJ, Helsel DR. A national look at nitrate contamination in ground water. *Water Cond Purif*. 1998;39:76–79
8. Sanchez-Echaniz J, Benito-Fernandez J, Mintegui-Raso S. Methemoglobinemia and consumption of vegetables in infants. *Pediatrics*. 2001;107:1024–1028
9. Keating JP, Lell ME, Strauss AW, Zarkowsky H, Smith GE. Infantile methemoglobinemia caused by carrot juice. *N Engl J Med*. 1973;288:824–826
10. Hack WW, Douwes AC, Veerman AJ. Spinach: a source of nitrite poisoning in young children [in Dutch]. *Ned Tijdschr Geneesk*. 1983;127:1428–1431
11. Faivre J, Faivre M, Klepping C, Roche L. Methemoglobinemias caused by ingestion of nitrites and nitrates [in French]. *Ann Nutr Aliment*. 1976;30:831–838
12. Ritter R, Schulze U. Methemoglobinemia in an infant following nitrite poisoning by a dinner of kohlrabi [in German]. *Dtsch Krankenpflegez*. 1971;24:233–235
13. Sander C, Jacobi H. Methemoglobin poisoning in a 2-year old boy after eating spinach [in German]. *Z Kinderheilkd*. 1967;98:222–226
14. Phillips WE. Naturally occurring nitrate and nitrite in foods in relation to infant methaemoglobinaemia. *Food Cosmet Toxicol*. 1971;9:219–228
15. Dusdieker LB, Getchell JP, Liarakos TM, Hausler WJ, Dungy CI. Nitrate in baby foods. Adding to the nitrate mosaic. *Arch Pediatr Adolesc Med*. 1994;148:490–494
16. Dusdieker LB, Stumbo PJ, Kross BC, Dungy CI. Does increased nitrate ingestion elevate nitrate levels in human milk? *Arch Pediatr Adolesc Med*. 1996;150:311–314
17. McKnight GM, Duncan CW, Leifert C, Golden MH. Dietary nitrate in man: friend or foe? *Br J Nutr*. 1999;81:349–358
18. Smith RP. Toxic responses of the blood. In: Amdur MO, Doull J, Klaassen CD, eds. *Casarett and Doull's Toxicology: The Basic Science of Poisons*. 4th ed. New York, NY: Pergamon Press; 1991:257–281
19. Kravitz H, Elegant LD, Kaiser KE. Methemoglobin values in premature and mature infants and children. *Am J Dis Child*. 1956;91:1–5
20. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med*. 1999;34:646–656
21. American Academy of Pediatrics, Committee on Environmental Health. Nitrates and nitrites in water. In: Ezel RA, ed. *Pediatric Environmental Health*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:301–309
22. Reynolds KA. The prevalence of nitrate contamination in the United States. *Water Cond Purif Mag*. Available at: www.wcponline.com/ArchiveNewsView.cfm?pkArticleID=1330&AT=T. Accessed July 26, 2005
23. American Academy of Pediatrics. Complementary feeding. In: Kleinman RE, ed. *Pediatric Nutrition Handbook*. 5th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2004:103–115

All policy statements from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

Infant Methemoglobinemia: The Role of Dietary Nitrate in Food and Water

Frank R. Greer and Michael Shannon

Pediatrics 2005;116;784

DOI: 10.1542/peds.2005-1497

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/116/3/784>

References

This article cites 15 articles, 1 of which you can access for free at:
<http://pediatrics.aappublications.org/content/116/3/784#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

Current Policy

http://www.aappublications.org/cgi/collection/current_policy

Committee on Nutrition

http://www.aappublications.org/cgi/collection/committee_on_nutrition

Council on Environmental Health

http://www.aappublications.org/cgi/collection/council_on_environmental_health

Metabolic Disorders

http://www.aappublications.org/cgi/collection/metabolic_disorders_sub

Environmental Health

http://www.aappublications.org/cgi/collection/environmental_health_sub

Nutrition

http://www.aappublications.org/cgi/collection/nutrition_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:

<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Infant Methemoglobinemia: The Role of Dietary Nitrate in Food and Water

Frank R. Greer and Michael Shannon

Pediatrics 2005;116:784

DOI: 10.1542/peds.2005-1497

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/116/3/784>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2005 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

