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<http://jama.ama-assn.org/cgi/content/short/302/15/1685>

CLINICIAN'S CORNER

**Rethinking Screening for Breast Cancer and Prostate Cancer**

Laura Esserman, MD, MBA; Yiwey Shieh, AB; Ian Thompson, MD

JAMA. 2009;302(15):1685-1692.

## ESSENCE OF ARTICLE IS WHOLE ARTICLE

After 20 years of screening for breast and prostate cancer, several observations can be made. First, the incidence of these cancers increased after the introduction of screening but has never returned to prescreening levels. Second, the increase in the relative fraction of early stage cancers has increased. Third, the incidence of regional cancers has not decreased at a commensurate rate. One possible explanation is that screening may be increasing the burden of low-risk cancers without significantly reducing the burden of more aggressively growing cancers and therefore not resulting in the anticipated reduction in cancer mortality. To reduce morbidity and mortality from prostate cancer and breast cancer, new approaches for screening, early detection, and prevention for both diseases should be considered.

Author Affiliations: Department of Surgery and Radiology (Dr Esserman) and School of Medicine (Mr Shieh), University of California, San Francisco, and Department of Urology, University of Texas Health Science Center, San Antonio (Dr Thompson).

## THIS ARTICLE HAS BEEN CITED BY OTHER ARTICLES

Screening for Breast and Prostate Cancers -- Not Living Up to Its Reputation?

JWatch Women's Health 2009;2009:1-1.

FULL TEXT

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Screening for Prostate and Breast Cancers

JWatch General 2009;2009:1-1.

FULL TEXT

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<http://womens-health.jwatch.org/cgi/content/full/2009/1029/1>

## **Screening for Breast and Prostate Cancers — Not Living Up to Its Reputation?**

### ESSENCE OF ARTICLE

“The ACS plans to modify its message in early 2010 to indicate that prostate and breast screening benefits might have been overstated, possibly leading to overtreatment of patients with small cancers (New York Times Oct 10 2009”

### ARTICLE

Diagnosis of early breast and prostate cancer has risen with screening, but the number of advanced cancers has not fallen.

Breast and prostate cancer account for more than a quarter of all cancers in the U.S., and the American Cancer Society (ACS) has supported extensive screening programs for both. A new analysis suggests that we rethink screening for breast and prostate cancer. During the last 20 years, after screening was introduced, incidence of breast and prostate cancer rose and never returned to prescreening levels; also, more cases were early cancers. However, the absolute number of advanced breast and prostate cancers that were diagnosed during this period has not fallen as

predicted. Thus, whereas colon and cervical cancer screening detects precancerous, treatable conditions (e.g., polyps, cervical intraepithelial neoplasia), prostate and breast cancer screening promotes detection of early cancers, some of which might not be destined to progress or to be lethal. The ACS plans to modify its message in early 2010 to indicate that prostate and breast screening benefits might have been overstated, possibly leading to overtreatment of patients with small cancers (New York Times Oct 10 2009).

Comment: Explaining "small" cancers to patients is difficult, as simply uttering the word "cancer" can invoke intense anxiety. The authors suggest that minimal-risk lesions should not be called "cancer," but rather a term such as "indolent lesions of epithelial origin (IDLE)." Patients who are aware that mortality associated with breast and prostate cancers has fallen during the last 2 decades might attribute the decrease to screening instead of to better treatments. The authors also point out the importance of developing different means (e.g., biomarkers) to determine whether tumors are likely to progress without treatment; in addition, they emphasize the need to put a damper on treatment for minimal-risk disease, to focus on prevention in high-risk patients, and to develop tools for shared decision making in breast and prostate screening. The ACS's planned modification to its previous screening stance is certain to provoke controversy.

— Wendy S. Biggs, MD

Published in Journal Watch Women's Health October 29, 2009

Citation(s):

Esserman L et al. Rethinking screening for breast cancer and prostate cancer. JAMA 2009 Oct 21; 302:1685.

- Original article (Subscription may be required)
- Medline abstract (Free)

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<http://www.ingentaconnect.com/content/mksg/pto/2009/00000105/00000002/art00004>

### **Effect of N-Acetyl Cysteine against Aluminium-induced Cognitive Dysfunction and Oxidative Damage in Rats**

Authors: Prakash, Atish; Kumar, Anil

Source: Basic & Clinical Pharmacology & Toxicology, Volume 105, Number 2, August 2009 , pp. 98-104(7)

#### ESSENCE OF ARTICLE

“Chronic administration of N-acetyl cysteine significantly improved memory retention in tasks, attenuated oxidative damage and acetylcholinesterase activity in aluminium-treated rats. The study suggests a neuroprotective effect of N-acetyl cysteine against aluminium-induced cognitive dysfunction and oxidative damage.”

#### ARTICLE

Abstract:

Aluminium is a potent neurotoxin involved in the initiation and progression of various cognitive disorders like Alzheimer's disease. Chronic aluminium exposure induces oxidative stress and increases amyloid beta levels in vivo. The role of oxidative stress has been well-suggested in these cognitive problems. Therefore, the present study was designed to explore the possible role of N-acetyl cysteine against aluminium mediating cognitive dysfunction and

oxidative stress in rats. Aluminium chloride (100 mg/kg, p.o.) was given to rats daily for 6 weeks. N-acetyl cysteine (per se; 50 and 100 mg/kg, i.p.) pre-treatment was given 30 min. before aluminium daily for 6 weeks. On the third (21st day) and sixth week (42nd day) of the study, various behavioural tests (Morris water maze and elevated plus maze task paradigms) and locomotion (photoactometer) were done to evaluate cognitive tasks. The rats were killed on the 43rd day following the last behavioural test, and various biochemical tests were performed to assess the extent of oxidative damage. Chronic aluminium chloride administration resulted in poor retention of memory in Morris water maze, elevated plus maze task paradigms and caused marked oxidative damage. It also caused a significant increase in the acetylcholinesterase activity. Chronic administration of N-acetyl cysteine significantly improved memory retention in tasks, attenuated oxidative damage and acetylcholinesterase activity in aluminium-treated rats. The study suggests a neuroprotective effect of N-acetyl cysteine against aluminium-induced cognitive dysfunction and oxidative damage.

Document Type: Research article

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Medscape Medical News CME

### **IDF Releases New Guidelines on Diabetes Management CME**

<http://cme.medscape.com/viewarticle/711266?src=cmemp&uac=65163MT>

News Author: Alison Palkhivala

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Authors and Disclosures

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Disclosure: Désirée Lie, MD, MSED, has disclosed no relevant financial relationships.

Sarah Fleischman

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Disclosure: Sarah Fleischman has disclosed that she has no relevant financial relationships.

Learning Objectives

Upon completion of this activity, participants will be able to:

- Inform clinicians of the latest medical information about the new guidelines for screening and management of diabetes in pregnant women, as presented at the International Diabetes Federation at the 20th World Diabetes Congress 2009.

- Inform clinicians of the latest medical information on self-monitoring of blood glucose in patients with type 2 diabetes.

October 26, 2009 — The International Diabetes Federation (IDF) announced the release of several new guidelines related to diabetes management here at the IDF 20th World Diabetes Congress. These include the first-ever international guidelines on the management of diabetes in pregnancy and guidelines on the use of self-monitoring of blood glucose (SMBG) among type 2 diabetic patients not being treated with insulin.

#### Pregnancy and Diabetes Guidelines Call for Universal Screening

Lois Jovanovič, MD, CEO and chief scientific officer of Sansum Diabetes Research Institute in Santa Barbara, California, and clinical professor of medicine at the University of Southern California-Los Angeles Medical Center, is one of the authors of the IDF Global Guideline on Pregnancy and Diabetes. "The guidelines were created with evidence-based medicine. Then we asked an international group [of experts] to give us their opinion," she told Medscape Diabetes & Endocrinology.

"There was no international standard [for the diagnosis and management of gestational diabetes], said Dr. Jovanovič. "There was no consensus, there was a lot of confusion, women were suffering, and their pregnancy outcome was affected by having no standard by which to judge whether their diabetes was worth treating or not. This is the first time there is a worldwide consensus."

A key message of the new guidelines, according to Dr. Jovanovič, is the importance of universal screening. "Look for hyperglycemia in pregnancy," she said. "Preconceptional counseling [also] has to be universal. . . . For a [primary care] physician who has a [patient] in child-bearing years, the first question should be: Are you interested in getting pregnant again?"

#### Self-Monitoring of Blood Glucose in Noninsulin-Treated Type 2 Diabetes

The IDF Guideline on Self-Monitoring of Blood Glucose in Non-Insulin Treated Type 2 Diabetes was developed in a manner similar to the IDF pregnancy guidelines. Their highlights include the following:

- SMBG should be considered at the time of diagnosis but should only be used when patients, their caregivers, and/or their healthcare providers have the knowledge and willingness to incorporate findings into the diabetes management plan.
- SMBG should be considered a part of ongoing diabetes self-management education.
- SMBG protocols should be individualized.
- Patients and their healthcare providers should agree on how to use SMBG data.
- Tools used to measure SMBG must be easy to use and accurate.

#### Unique Features of Guidelines

Both sets of guidelines have key features that differentiate them from guidelines on the same topics put out by other diabetes associations, such as the American Diabetes Association (ADA), said Dr. Jovanovič.

"The ADA hopefully will change soon, but right now they don't subscribe to the philosophy of universal screening [in pregnancy]. They talk about selective screening. Our guidelines not only talk about universal screening but almost assume that every woman has diabetes [and] doing the testing is to reassure her that she doesn't. So, it's a paradigm shift. The second major difference is the [IDF] recommendation that it be a 1-step [oral glucose tolerance]

test, not a 2-step test [as currently recommended by the ADA]. The ADA also have the criteria for diagnosis [of gestational diabetes] very high to minimize the number of women identified. The strategies in the [IDF] guidelines actually increase the number of women that would be identified and therefore offer treatment worldwide with 1 standard of care."

According to a coauthor of the SMBG guidelines, David Owens, MD, from the Cardiff University Diabetes Research Unit in the United Kingdom, a unique feature of the IDF SMBG guidelines is that they clarify the role of SMBG in diabetic patients who are not receiving insulin therapy. "For the noninsulin-treated individuals, [other guidelines] say that it's a good idea to incorporate SMBG, . . . but there is no real clarity as to what to do about it. That's where we've tried to extend the story more toward what the patient can do about it in their circumstances. . . . There are [other] guidelines that suggest that maybe there's no reason to monitor blood glucose in the noninsulin-treated, and they say that . . . you need to look at the current evidence and see its limitations. Many of those publications are really not designed to ask [that] question."

Dr. Jovanović has disclosed no relevant financial relationships. Dr. Owens reports being paid for lecturing by Roche Diagnostics, Sanofi-Aventis, Novo Nordisk, Merck Sharpe & Dohme, LifeScan, and Pfizer; being on advisory boards for Roche Diagnostics, Sanofi-Aventis, Novo Nordisk, Merck Sharpe & Dohme, LifeScan, and Pfizer; and receiving research funding from Sanofi-Aventis and Novo Nordisk.

International Diabetes Federation (IDF) 20th World Diabetes Congress: Abstracts 0498 and 0499. Presented October 22, 2009.

#### Study Highlights

- Pregnancy and diabetes
- A 1-stage oral glucose tolerance test at 26 to 28 weeks' gestation is recommended to screen all pregnant women for gestational diabetes vs the ADA recommendation for selective screening in at-risk women only.
- For women at high risk for diabetes because of previous gestational diabetes, screening should be performed as soon as practical and should be repeated at 26 to 28 weeks' gestation.
- For women with preexisting diabetes, glycemic control should be optimized before planned pregnancy.
- Angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers should be stopped and substituted with appropriate medications in pregnant women.
- Statins, fibrates, and niacin should be stopped in pregnancy.
- In women with existing diabetes or gestational diabetes, risks for glucose-lowering agents should be discussed, and use of insulin and the type of insulin should be assessed and discussed.
- A hemoglobin A1c target of 6.0% or lower is desired in pregnant women with diabetes.
- If possible, SMBG should be done frequently in pregnant women with diabetes.
- Doses of glucose-lowering agents should be adjusted according to self-monitoring results, hemoglobin A1c level, and experience of hypoglycemia.
- Eyes should be examined at the first prenatal visit and at each trimester.
- Breast-feeding should be encouraged.

- SMBG
- SMBG should be performed to attain agreed-on treatment goals, and results should be acted on.
- Protocols (intensity and frequency) for SMBG should be individualized to specific behavioral and clinical requirements and meet the needs of therapeutic decision making.
- SMBG should be performed in patients with type 2 diabetes in conjunction with self-management and education of patients.
- An easy procedure should be available to patients who perform SMBG to monitor the performance and accuracy of their glucose meter.

#### Clinical Implications

- The IDF recommends screening all pregnant women for diabetes using a 1-stage testing process.
- SMBG should be performed to attain specific treatment goals.

We conducted five database searches of MedLine, Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment, and National Institute for Health and Clinical Excellence from 2000 to September 2006, supplemented by a search for screening prior to 24 weeks gestation from 1966-99 (Appendix A Table 2). Articles were also obtained from outside experts and through reviewing bibliographies of other relevant articles and systematic reviews. We also considered all articles cited in the 2003 Evidence Synthesis<sup>5</sup> for inclusion. Two investigators reviewed the 2003 USPSTF report's reference list, relevant abstracts, and full articles (168 total), to ensure we were reviewing all prior literature using the updated criteria. Two investigators reviewed 1403 abstracts and 277 articles against inclusion and exclusion criteria for each key question. Discrepancies were resolved by consensus.

We included only randomized trials that used the currently accepted one-step and two-step diagnostic criteria to evaluate GDM screening and treatment for assessing potential benefit of GDM screening and treatment. We considered prospective cohort studies if RCT evidence was not available. Any study design was considered for potential harms, and inclusion criteria were less stringent for study harms. For example, articles that used standard methods, but not standard cut-off criteria, were accepted. The actual glucose levels used to define GDM were considered less important in assessing the harms of screening than the process used for GDM screening and the receipt of a diagnosis. Details for inclusion and exclusion criteria are provided in Appendix A Table 3. Ninety of the potentially included articles were excluded for study design and 12 for poor quality.

We found no RCTs of screening for KQ1 or studies for KQ2 that reported sensitivity, specificity, and yield rates using one of the three acceptable screening methods (Table 1) for specified health outcomes (Figure 1 ). We included the following articles that met final inclusion and quality-rating criteria: seven RCTs reported in eight publications that test interventions that alter glycemic control and reported specified health outcomes in women diagnosed at 24 weeks gestation or later for KQ3a; one prospective study addressing treatment of women diagnosed with GDM prior to 24 weeks gestation for KQ3b; three studies reporting harms of screening for GDM were found for KQ4; one additional article, along with six of the eight articles included in KQ3, reported adverse effects of treatment for KQ5. Tables of excluded articles and reason for exclusion are provided in Appendix D. Using the USPSTF's study design-specific criteria (Appendix B), two investigators critically appraised and rated the quality of all included articles as well as those articles excluded for quality reasons only.

#### USPSTF Involvement

The authors worked with four USPSTF members at key points throughout the review process to develop and refine the analytic framework and key questions and resolve issues involving the scope, treatment modalities, and health outcomes. This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. AHRQ staff provided oversight for the project and reviewed and assisted with the external review of the draft evidence synthesis.

Table 1. Screening strategies

Three screening tests with generally accepted criteria are frequently used for the diagnosis of GDM with a one- or two-step method. These are typically performed between 24 and 28 weeks' gestation and are defined as follows:

- 1

50 g Initial Screening Test: A two-step method using an initial 1-hr 50 g oral glucose challenge test (GCT) and followed by a diagnostic 75 or 100 g oral glucose tolerance test (OGTT) if the GCT is positive. The GCT has two criteria accepted as a positive result, depending on the level of sensitivity desired: 1,2

- o  $\geq 130$  mg/dL (identifies 90 percent of women with GDM)<sup>1</sup>
- o  $\geq 140$  mg/dL (identifies 80 percent of women with GDM)<sup>1</sup>

- 2

100 g Diagnostic Test: A one-step or a two-step method using a 3-hour 100 g diagnostic OGTT. This test is defined as positive if two or more of the hourly plasma glucose levels meet or exceed the following values:

Criteria for Abnormal Result on 100 g, Three-Hour Oral Glucose Tolerance Tests in Pregnant Women<sup>1,30</sup>

Blood sample	National Diabetes Data Group Criteria	Carpenter and Coustan Criteria
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Fasting	105 mg/dL (5.8 mmol/L)	95 mg/dL (5.3 mmol/L)
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1-hour	190 mg/dL (10.5 mmol/L)	180 mg/dL (10.0 mmol/L)
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2-hour	165 mg/dL (9.2 mmol/L)	155 mg/dL (8.6 mmol/L)
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3-hour	145 mg/dL (8.0 mmol/L)	140 mg/dL (7.8 mmol/L)
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- 3

75 g Diagnostic Test: A one-step or two-step method using a 75 g diagnostic oral glucose tolerance test (OGTT). This test is defined as positive if two or more of the hourly plasma glucose levels meet or exceed the following values (different criteria apply based upon WHO or ADA recommendations):

Criteria for Abnormal Result on 75-g Oral Glucose Tolerance Test in Pregnant Women<sup>1,2</sup>

Blood Sample	ADA mg/dL	ADA mmol/l	WHO* mmol/l
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Fasting 95 5.3 7.0

1-hour 180 10.0

2-hour 155 8.6 7.8

\*

Note 7.0 mmol/l=126 mg/dl and 7.8 mmol/L=140 mg/dl)

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<http://www.ncbi.nlm.nih.gov/pubmed/19838927>

Nutr Cancer. 2009;61(4):544-53.

### **Curcumin synergizes with resveratrol to inhibit colon cancer.**

Majumdar AP, Banerjee S, Nautiyal J, Patel BB, Patel V, Du J, Yu Y, Elliott AA, Levi E, Sarkar FH.

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#### ESSENCE OF ARTICLE

“Our current data suggest that the combination of curcumin and resveratrol could be an effective preventive/therapeutic strategy for colon cancer.”

#### ARTICLE

Development and progression of many malignancies, including colorectal cancer, are associated with activation of multiple signaling pathways. Therefore, inhibition of these signaling pathways with noncytotoxic natural products represents a logical preventive and/or therapeutic approach for colon cancer. Curcumin and resveratrol, both of which inhibit the growth of transformed cells and colon carcinogenesis, were selected to examine whether combining them would be an effective preventive and/or therapeutic strategy for colon cancer. Indeed, the combination of curcumin and resveratrol was found to be more effective in inhibiting growth of p53-positive (wt) and p53-negative colon cancer HCT-116 cells in vitro and in vivo in SCID xenografts of colon cancer HCT-116 (wt) cells than either agent alone. Analysis by CalcuSyn software showed synergism between curcumin and resveratrol. The inhibition of tumors in response to curcumin and/or resveratrol was associated with the reduction in proliferation and stimulation of apoptosis accompanied by attenuation of NF-kappaB activity. In vitro studies have further demonstrated that the combinatorial treatment caused a greater inhibition of constitutive activation of EGFR and its family members as well as IGF-1R. Our current data suggest that the combination of curcumin and resveratrol could be an effective preventive/therapeutic strategy for colon cancer.

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<http://www.winrho.com/treatment/antid.html>

### **Anti-D Immunoglobulin**

WinRho® SDF is the first Anti-D Immunoglobulin approved for use in ITP. It is derived from human plasma (the liquid portion of blood) and is specially prepared to have high levels of a specific antibody, Anti-D. Currently it is thought that this antibody prevents the destruction of platelets in the spleen.

Anti-D immunoglobulin (WinRho® SDF) is given by a 3-5 minute infusion into a vein.

Anti-D may help raise the platelet level for 1-3 months after each infusion<sup>1</sup>. Periodic infusions of Anti-D may allow patients to achieve stable platelet counts.<sup>2</sup>

Side effects sometimes occur and may include:

Mild anemia

Headache

Fever

Chills

Other possible side effects may include back pain, shaking chills, dark colored or discolored urine, decreased urine production, swelling or shortness of breath.<sup>3</sup> Please contact your physician promptly if you experience these symptoms.

Anti-D Immunoglobulin is only effective in Rh-positive patients and in patients whose spleen has not been removed.

Because Anti-D Immunoglobulin is made from human plasma, special processes are used in the preparation of WinRho® SDF to help safeguard against known viruses that may be found in human blood. However, the potential to transmit infectious agents cannot be totally eliminated.

Please see the Important Risk Information for WinRho® SDF for more detailed risk information and the Prescribing Information for full prescribing details.

1. Data on file. Cangene Corporation. Baxter Healthcare Corporation.
2. Sandler S.G. and Tutuncuoglu S.O. Immune Thrombocytopenic Purpura -- current management practices. *Expert Opin Pharmacother.* 2004; 5(12): 2515-2527.
3. WinRho® SDF. [Rho(D) Immune Globulin Intravenous (Human)] package insert, Cangene Corporation, Winnipeg, Canada, Baxter Healthcare Corporation, Westlake Village, CA, USA, April 2006.

<http://www.itppeople.com/winrho.htm>

Anti-D antibody is a blood product used to achieve a temporary and occasionally long-term elevation of the platelet counts. It is marketed under several trade names including WinRho SDF and Rhophylac. According to one study, it has 79-90% efficacy, depending on the type of ITP.

It is a sterile freeze dried gamma globulin fraction containing antibodies to Rh (D). Within a few minutes of an intravenous infusion, anti-D coats the recipient's (normal) red cells with purified IgG, which resembles the coating of platelets by the (abnormal autoimmune) ITP immunoglobulin. After D(Rh)-positive red cells are coated with anti-D, they compete with the recipient's IgG(ITP)-coated platelets for phagocytosis (destruction) by macrophages in the spleen. Usually, IgG(WinRho)-coated red cells succeed in blocking the spleen's destruction of IgG (ITP)-coated platelets, thus increasing platelet counts. Significant increases in platelet counts occur within 1-3 days with peak counts observed 8 days after infusion. The effects last approximately one month.

Anti-D is made from human plasma derived from a limited list of donors in a special program. It undergoes a viral inactivation and micro filtration process using solvent/detergent. Donors are stimulated to produce Ig with especially high levels of specific antibodies so a smaller amount of the product is required. This reduces the cost per infusion by about half of what IVIg would cost. Also, because anti-D has been treated to inactivate any viral contamination, it is safer to use than IVIg. However, because anti-D antibodies and action are so specific, it is only effective for people who are Rh positive (85% of population) and have a spleen. It may not be suitable for some pregnant women.

#### Dosage

Suggested dosing is 50 mcg/kg of bodyweight although some clinical studies report greater success at a 75 mcg/kg dose. The infusions take about three to five minutes for the IV push and about 30 minutes for the IV drip. Anti-D can be given as a single dose or as two divided doses given on separate days. The dose and frequency of administration are determined from the patient's clinical response.

#### Side Effects

Side effects developed following 4% of the infusions, and included headaches, chills, fever and body aches. Pain and swelling at the injection site have occurred in a few cases. A remote risk of anaphylaxis (shock response) exists for patients with hypersensitivity to blood products. Because of the specific antibodies that the product uses, anemia caused by hemolysis (destruction of red blood cells) can also be a problem. RBC levels should be monitored, especially in people with low hemoglobin.

#### News

1] Continued postmarketing safety surveillance has shown rare, but severe and sometimes fatal, intravascular hemolysis and potentially serious complications, including disseminated intravascular coagulation in patients with ITP. Physicians should discuss the risks and benefits of WinRho SDF, alert patients who are being treated for ITP about the signs and symptoms associated with intravascular hemolysis (back pain, shaking chills, fever, discolored urine, decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath) and advise patients to report any symptoms immediately to their physicians.

2] Maltose in IVIG products, such as the liquid formulation of WinRho SDF, has been shown to give falsely high blood glucose levels in certain types of blood glucose testing systems. Due to the potential for falsely elevated glucose readings, only testing systems that are glucose-specific should be used to test or monitor blood glucose levels in patients receiving this product.

From [www.medwatch.gov](http://www.medwatch.gov)

## Help

1-800-4WINRHO (1-800-494-6746)

[winrho@baxter.com](mailto:winrho@baxter.com)

Baxter Healthcare Corporation

One Baxter Parkway

Deerfield, IL 60015

Baxter has a Patient Assistance Program for individuals who meet certain criteria.

## Related Web Sites

<http://www.winrho.com>

<http://www.rhophylac.com>

<http://www.projinf.org/pub/17/itp.html>

<http://www.fda.gov/medwatch/safety/2000/winrho.html>