

Mayo Clinic and the Thyroid Cancer Guidelines From the American Thyroid Association

The American Thyroid Association (ATA) recently published guidelines to help endocrinologists, surgeons, and others manage thyroid cancer.* “The purpose of these guidelines,” says Bryan McIver, MBChB, PhD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, and a coauthor of the document, “was to define ‘best practice’ in the treatment of thyroid cancer.”

Dr McIver goes on to say: “What surprised me most, as this group of 10 experts met, was how much consensus exists in a field that is infamous for its infighting and disagreements.”

The initial assessment of a thyroid nodule should include an ultrasound (US) and fine-needle aspiration (FNA) biopsy. Hossein Gharib, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, says: “US-guided FNA biopsy provides the most accurate and most cost-effective means to assess a thyroid nodule. The US-guided FNA result is typically available on the same day the patient is seen at our center.” Amy C. Clayton, MD, of the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, states: “Our goal is to provide an accurate cytological diagnosis to the physician within 4 hours of receipt of the specimen.”

Initial surgical management of a thyroid cancer involves a near-total or total thyroidectomy. “If the diagnosis is definitive before the surgery, we perform a near-total or total thyroidectomy and exploration of the central compartment of the neck,” says Melanie L. Richards, MD, of the Department of Surgery at Mayo Clinic in Rochester. Dr Richards adds: “Surgical experience is the key to safely operating in this part of the neck. The high volume of thyroid cancer surgery we perform allows us to



Hossein Gharib, MD, Amy C. Clayton, MD, and Bryan McIver, MBChB, PhD

maintain those skills, resulting in some of the best outcomes and among the lowest complication rates in the country.” For nodules with malignant potential but for which the final diagnosis is in doubt before surgery, Dr Clayton notes: “Intraoperative frozen section provides a definitive diagnosis in most cases, allowing our surgeons to offer the safest, most appropriate surgery to our patients.”

The ATA guidelines support the use of postoperative staging in all cases of thyroid cancer. Dr McIver explains: “The use of prognostic scoring systems (eg, the metastases, age, completeness of resection, invasion, size [MACIS] scoring system) allows accurate survival prediction for a patient with thyroid cancer and should inform every aspect of that patient’s future care. The ATA has endorsed the use of MACIS or other similar scoring systems, several of which were developed here at Mayo Clinic.”

The use of postoperative radioactive iodine remains one of the most contentious issues in the management of thyroid cancer, and that controversy was clearly in evidence when the guidelines were written. Ian D. Hay, MD, PhD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, cau-

* Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM; The American Thyroid Association Guidelines Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2006;16(2):109-42.

Inside This Issue

**DHEA Supplementation:
Does It Delay the Age-
Related Decline in
Physical Function? 2**

**New and Emerging
Treatments for
Osteoporosis 4**

**Diabetes Complicating
Pregnancy: An Update
for the Clinician 6**



Ian D. Hay, MD, and Keith C. Bible, MD

tions: “The current guidelines err by recommending excessive use of radioactive iodine for the majority of patients we know to be at extremely low risk of mortality from their thyroid cancer. It is imperative that we do not overtreat this low-risk group with a treatment that could actually prove to be harmful.” Dr McIver echoes Dr Hay’s concerns, pointing out that the guidelines “agree with the principle that radioactive iodine should be used selectively, particularly in low-risk patients.”

According to both Mayo Clinic and the ATA, monitoring for thyroid cancer recurrence requires measurement of serum thyroglobulin and the use of neck US. Dr Hay adds: “US represents the best tool to identify the source of an elevated or rising thyroglobulin, which in most cases reflects the growth of thyroid cancer within cervical lymph nodes. If the cancer does recur, repeat surgery is often the treatment of choice—

although alternatives exist, including the use of percutaneous US-guided ethanol ablation.”

The management of metastatic disease remains a serious problem. Dr McIver explains: “While radioactive iodine has been the mainstay of treatment for metastatic thyroid cancer for the past 40 years, older patients or those with more aggressive variants often fail to concentrate radioactive iodine within the tumor. For these patients, we need something more, so we have been working with the Mayo Clinic Comprehensive Cancer Center to develop clinical trials of new agents that show promise in the management of thyroid cancer.”

Keith C. Bible, MD, PhD, of the Department of Medical Oncology at Mayo Clinic in Rochester and director of the Endocrine Malignancies Group within the Mayo Comprehensive Cancer Center, says: “The development of clinical trials in thyroid cancer is realistic now, because basic science has revealed some of the mechanisms by which thyroid cancer grows and spreads. These clinical trials are an important priority for the Cancer Center, and we already have access to several promising agents.”

Rebecca S. Bahn, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, and president of the ATA summarizes: “I am pleased, both as a Mayo Clinic clinician and as president of the ATA, that the ATA guidelines so closely match how thyroid cancer is managed here. Mayo Clinic and the ATA are striving for the same goal: the best possible treatment for patients with thyroid cancer.”



Melanie L. Richards, MD, and Rebecca S. Bahn, MD

DHEA Supplementation: Does It Delay the Age-Related Decline in Physical Function?

Dehydroepiandrosterone (DHEA) is often touted as an “antiaging” drug. K. Sreekumaran Nair, MD, PhD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, explains: “The reason for this notion is largely derived from the observation that the levels of DHEA and its sulfated form (DHEA-S) steadily decline from the age of 30 years onward, and the decline in these levels parallels the decline in many bodily functions. Also, observational studies indicate close associations between low DHEA levels

and many degenerative diseases. Moreover, in humans and in nonhuman primates, longevity is associated with higher blood DHEA-S levels. Studies in rodents have shown that DHEA therapy resulted in many beneficial effects, including improvement in immunity and reduction in cancer, diabetes mellitus, obesity, and cardiovascular disease. These laboratory animal studies—in association with the results from early short-term human studies—offered promise for DHEA therapy to delay aging in humans. However, the rodent stud-



K. Sreekumaran Nair, MD, PhD

ies had major limitations:

- Rodents have very low baseline DHEA levels.
- Supraphysiologic doses of DHEA were used.
- DHEA was administered to growing rodents, whereas in humans growth ceases before DHEA levels start to fall.

Recently, several long-term studies in humans were conducted to determine whether there is a role for DHEA supplementation in the aging population. A 2-year randomized, placebo-controlled, double-blind study conducted at Mayo Clinic in Rochester compared the effects of exogenous administration of DHEA in elderly (at least 60 years of age) men ($n = 62$) and women ($n = 57$). Dr Nair explains: "In this study, we administered DHEA (75 mg per day) to elderly men who had low DHEA-S and bioavailable testosterone levels and a lower dose (50 mg per day) of DHEA to elderly women who had low blood concentrations of DHEA-S. Treatment with DHEA resulted in blood DHEA-S concentrations in both elderly men and women to the levels that are commonly observed in people 20 to 30 years of age. DHEA administration significantly increased testosterone and estradiol levels in women and estradiol levels in men. However, no statistically significant effects of DHEA treatment were observed on body composition (weight, body mass index, fat free mass, percent body fat, visceral fat, or thigh muscle area) in either elderly men or women. However, treatment with DHEA did modestly improve bone mineral density of ultradistal radius in elderly women and femoral neck in men; no significant effects on other bones such as the lumbar spine or hip were noted. DHEA treatment also had no effect on physical performance (maximal oxygen consumption, seated chest press, isometric knee extension, and double leg press) or quality of life (mental and physical component scores). In a more recent study, we observed that treatment with DHEA (50 mg per day) for 3 months in postmenopausal women had no added benefits to the exercise-induced improvements in physical performance or body composition. Treatment with DHEA significantly reduced HDL cholesterol in elderly women, and a similar trend was noted in elderly men. DHEA has been reported to modestly

improve insulin sensitivity in elderly people when the supplement was administered for 6 months; however, this effect is not sustained with 2 years of DHEA administration.

Although no adverse effects from DHEA treatment (50 to 75 mg per day) for approximately 2 years were found, we studied a healthy elderly population:

- Men in the study had undergone a prostate evaluation, and only those with normal PSA and normal prostate size with no nodules were included in the study.
- Excluded were subjects with a history of any malignancy, active coronary artery disease, diabetes mellitus, and any other active illness.

It is therefore not possible to exclude adverse effects of DHEA if any of these preexisting conditions are present.

On the basis of all current evidence, long-term treatment of elderly people with DHEA—at doses of 50 to 75 mg daily—offers no clinically useful benefits except for a modest improvement of bone mineral density. Because there are more effective therapies to improve bone mineral density, there is no case for DHEA administration for this purpose. Additional concerns include the lowering of the HDL cholesterol concentration and the potential adverse effects of DHEA when administered to an unselected general population.

DHEA Replacement in Hypoadrenal Women

Although DHEA and DHEA-S are the most abundant plasma steroid hormones, their physiologic role remains uncertain. DHEA and DHEA-S levels are very low or undetectable in people who have primary autoimmune adrenal failure or have undergone bilateral adrenalectomy. Although both glucocorticoids and mineralocorticoids are replaced in hypoadrenal people, DHEA is not routinely replaced.

DHEA is peripherally converted to androgens and estrogen. Both testosterone and DHEA are converted to the more active dihydrotestosterone in target tissues. Since many studies have reported that quality of life is diminished in hypoadrenal women treated with replacement doses of glucocorticoid and mineralocorticoid, a case has been made to replace DHEA as well.

A recent study demonstrated that 3 months of DHEA replacement modestly but significantly increased insulin sensitivity in hypoadrenal women. In addition, DHEA replacement also significantly reduced total cholesterol, triglycerides, and LDL and HDL cholesterol levels. The effect of

DHEA on insulin sensitivity—based on hyperinsulinemic euglycemic glucose clamp—is minimal, and currently it is unclear whether this modest effect has any potential impact on preventing diabetes or impaired glucose tolerance in hypoadrenal women. The effect of DHEA replacement on lipid metabolism is also modest and includes a decline in HDL cholesterol, which is unlikely to be helpful. Future long-term studies are needed to determine whether these effects are sustained and will result in any clinically significant beneficial effects.

DHEA replacement has no beneficial effect on body composition and physical performance in hypoadrenal women. There are some inconsistent data on beneficial effects on some subjective outcomes such as energy, motivation, and perception of

fatigue. However, no long-term studies have shown beneficial effects on cognitive or sexual function.

Conclusions

Dr Nair concludes: “DHEA tablets—available in retail stores as health food supplements—are used extensively as an antiaging therapy by the public. However, there is no evidence to support DHEA therapy in elderly people to prevent or delay aging-related decline in physical and mental functions. There are modest metabolic changes that occur with DHEA replacement in hypoadrenal women, but it remains to be determined whether these changes in metabolic parameters will be translated into clinically relevant outcomes on long-term use.”

New and Emerging Treatments for Osteoporosis



Bart L. Clarke, MD, and Sundeep Khosla, MD

Most US Food and Drug Administration (FDA)–approved osteoporosis therapies have focused almost exclusively on inhibition of osteoclast recruitment and activation. Bart L. Clarke, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, explains: “These therapies have proven successful in reducing bone loss and preventing fractures in postmenopausal women and men. The only therapy approved by the FDA to date that stimulates osteoblast activity is teriparatide (recombinant human

parathyroid hormone 1-34). This drug is effective at increasing bone density and preventing fractures when given once a day by subcutaneous injection for up to 2 years. New and emerging treatments for osteoporosis represent improvements in the potency or formulation of previously available drugs or agents directed at new therapeutic targets.”

Zoledronic Acid

Intravenously administered zoledronic acid was previously approved by the FDA for treatment of hypercalcemia of malignancy, multiple myeloma, and skeletal metastatic prostate and breast cancer. The recently published pivotal fracture prevention trial—7,765 postmenopausal women with or with-

out fractures were randomly assigned to receive 5 mg of zoledronic acid intravenously over 15 minutes once a year or placebo for 3 years—showed 70% reduction in morphometric vertebral compression fractures, 77% reduction in clinical vertebral fractures, 41% reduction in hip fractures, and 25% reduction in nonvertebral fractures compared with placebo. Serious atrial fibrillation was more common in the treatment group in this study, but there were no differences in cardiovascular or renal function outcomes.

Another recently published study—2,127 hip fracture patients were randomly assigned to receive 5 mg of zoledronic acid intravenously over 15 minutes once a year or placebo starting within 90 days of their hip fracture—showed that, when compared with placebo, zoledronic acid reduced expected deaths after hip fracture by 28% and reduced new clinical fractures by 35%. Serious atrial fibrillation was not more common in the treatment group in this study, and there were no differences in cardiovascular or renal function outcomes. Sundeep Khosla, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester notes: “This was the first demonstration that an osteoporosis treatment drug was able to reduce the expected increase in mortality after hip fracture.”

Ibandronate

Daily orally administered ibandronate—initially approved by the FDA for prevention and treatment

of osteoporosis at a dose of 2.5 mg a day—was never marketed because 2 once-weekly oral bisphosphonates had already been approved. Subsequently, a once-monthly 150-mg oral dosage of ibandronate was approved by the FDA and marketed. In 2006, the FDA approved intravenously administered ibandronate for treatment of osteoporosis at a dose of 3 mg over 15 to 30 seconds every 3 months.

Risedronate

Orally administered risedronate—initially approved by the FDA for prevention and treatment of osteoporosis at 5 mg a day in 1998—was approved for the same indication at 35 mg once weekly in 2002, and more recently at 75 mg a day for 2 days each month, and now at 150 mg once a month.

Denosumab

Denosumab is a fully humanized mouse monoclonal antibody directed against receptor-activated nuclear factor- κ B (RANK) ligand. The RANK ligand is expressed by osteoblasts and osteoblast precursors and stimulates recruitment and differentiation of osteoclast precursors. Dr Clarke explains: “Osteoprotegerin is a decoy receptor produced and secreted by osteoblasts and osteoblast precursors that inhibits the effect of secreted RANK ligand. Denosumab functions like osteoprotegerin to limit RANK ligand activity and thereby reduce osteoclast numbers and activity. Phase 2 clinical trials have shown efficacy in treatment of osteoporosis and phase 3 clinical trials—in patients with postmenopausal osteoporosis, male osteoporosis, glucocorticoid-induced osteoporosis, rheumatoid arthritis, and cancer—are rapidly concluding. Denosumab is given once every 6 months by subcutaneous injection and appears to be as effective as oral bisphosphonates.”

Sclerostin Antibody

Sclerostin is a protein produced by the *SOST* gene almost exclusively in osteocytes. Dr Khosla says: “This protein normally inhibits bone formation by preventing interactions of Wnt proteins with the LRP-5/6 receptor on the plasma membrane of osteoblasts and osteoblast precursors on bone surfaces, thereby decreasing osteoblast recruitment and activation. A new monoclonal antibody to sclerostin inhibits sclerostin activity, thereby upregulating Wnt signaling pathways and activating osteoblast recruitment and activity. Increased osteoblast activity leads to increased bone formation similar to what is seen with the anabolic agent teriparatide. Phase 1 and 2 studies are begin-

ning with this monoclonal antibody.”

Cathepsin K Inhibitors

Cathepsin K is a serine protease released by activated osteoclasts into the bone resorption compartment beneath osteoclasts during bone remodeling. Dr Clarke comments: “This protease is the major protease that helps degrade type 1 collagen and other proteins in bone matrix during bone resorption. Type 1 collagen represents about 90% of the total protein in bone, so inhibition of type 1 collagen degradation should limit bone resorption by activated osteoclasts. Several phase 2 trials with cathepsin K inhibitors have been completed, demonstrating mild to moderate antiresorptive effect.”

Strontium Ranelate

Strontium ranelate is a strontium salt that has unique effects on bone. This oral agent has been approved in Europe and other countries for treatment of postmenopausal osteoporosis at a dose of 2 g per day, but it has not yet been approved for use in the United States. Dr Khosla highlights: “Strontium is incorporated into the skeleton, replacing calcium ions in the hydroxyapatite crystal lattice over time, and increases bone density at least partly because it has a higher atomic weight than calcium. However, strontium has unique dual functions on bone cells that make it unlike all other currently available osteoporosis drugs. Strontium stimulates bone formation by osteoblasts, while it simultaneously inhibits bone resorption by osteoclasts. These effects make strontium ranelate potentially an ideal treatment for osteoporosis—although overall, the effects of strontium on bone metabolism are fairly modest. Phase 3 clinical trials published over the last several years have shown clinically significant fracture reduction and increased bone density. The main adverse effect of strontium ranelate is gastrointestinal upset in about 30% of patients. Rare severe allergic reactions have recently been reported.”

Other Agents

Other compounds are undergoing evaluation for potential use in prevention and treatment of osteoporosis, including c-Src inhibitors, integrin inhibitors, and chloride channel inhibitors.

Conclusion

Dr Clarke concludes: “The new classes of drugs for osteoporosis treatment will expand the available therapeutic armamentarium and allow clinicians to individualize patient treatment.”

Diabetes Complicating Pregnancy: An Update for the Clinician

Gestational Diabetes Mellitus

It is generally accepted practice to screen for gestational diabetes in all pregnancies. Although risk factors such as advanced maternal age, family history of diabetes, and obesity may increase the incidence of this complication, diabetes may occur in 1% of those with no risk factors. Roger L. Nelson, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at the Mayo Clinic in Rochester, says: “We screen patients at 24 to 28 weeks’ gestation, with a 50-g oral glucose test and measure of serum glucose 1 hour later. In patients with risk factors (eg, gestational diabetes in a prior pregnancy, body mass index more than 30 kg/m²), we screen earlier in gestation and repeat the screen later in pregnancy if the initial test result is negative. Unfortunately, there are 2 criteria for an abnormal 1-hour glucose challenge test result—more than 130 mg/dL and more than 140 mg/dL—with no evidence to determine which cutoff is optimal. If the 1-hour glucose challenge test result is abnormal, a 3-hour oral glucose tolerance test is indicated. To diagnose gestational diabetes, we use the Carpenter-Coustan criteria of plasma glucose thresholds of 95 mg/dL fasting, 180 mg/dL at 1 hour, 155 mg/dL at 2 hours, and 140 mg/dL at 3 hours. If 2 blood glucose values exceed these cutoffs, the diagnosis of gestational diabetes mellitus is confirmed. If the 1-hour glucose challenge test blood glucose value exceeds 200 mg/dL, a 3-hour diagnostic oral glucose tolerance test can be omitted, because the chance of a positive test is near 100%.”

Dietary therapy is the initial treatment and may take up to 2 weeks to be fully effective. The goals of dietary therapy are fasting plasma glucose lower than 90 mg/dL and 2-hour postprandial plasma glucose less than 120 mg/dL. If more than 20% of the blood glucose values exceed these targets, then pharmacologic therapy is indicated—options include insulin or glyburide. William J. Watson, MD, of the Department of Obstetrics and Gynecology at Mayo Clinic in Rochester, notes: “Glyburide does not appear to cross the placenta and is effective clinically. We begin glyburide at 2.5 mg daily and increase gradually up to 10 mg twice daily if needed. Approximately 20% of patients will need to be converted to insulin. No other oral



Roger L. Nelson, MD, and William J. Watson, MD

agents, except metformin, have been adequately studied during pregnancy.”

In pregnancy complicated by gestational diabetes, there is no increase in congenital anomalies. Dr Watson outlines: “If control is good, we begin antepartum testing at 38 weeks in diet-controlled patients and at 32 to 34 weeks in those on glyburide or insulin. After delivery, usually no therapy is needed. These patients have up to a 50% risk of developing type 2 diabetes later in life, and continued lifestyle modification is important. We do not usually do postpartum diagnostic testing for diabetes, unless risk factors are present.”

Pregnancy With Preexisting Diabetes

Since the introduction of insulin therapy some 8 decades ago, it has become increasingly clear that perinatal outcome in pregnancy complicated by maternal diabetes is directly related to the level of maternal glycemic control. Optimal glycemic control decreases the risk of fetal congenital malformations. Dr Watson summarizes: “Many reports have documented a 3- to 5-fold increase in major congenital malformations in the infants of mothers with type 1 diabetes, which correlates with the first trimester hemoglobin A_{1c} level. The most common fetal malformations seen are cardiovascular, central nervous system, and genitourinary. In later pregnancy,

sudden stillbirth is increased, and this complication is more commonly seen in pregnant patients with vascular disease, poor glycemic control, and polyhydramnios.”

Dr Nelson suggests: “Optimally, the clinician should see the patient in a preconception visit. Increasingly, more of these women have type 2 diabetes mellitus. Counseling these women to time pregnancy and optimize glycemic control is the single most important intervention to reduce spontaneous abortion and birth defects. During this time, an assessment can be made for evidence of vascular disease. Testing includes an ophthalmologic examination, an electrocardiogram, 24-hour urine collection for creatinine clearance and proteinuria, and blood testing for hemoglobin A_{1c} and thyroid-stimulating hormone. A therapeutic goal for hemoglobin A_{1c} is less than 6%. Folic acid, 1 mg per day, or prenatal vitamins should be advised.

Aggressive treatment with insulin during pregnancy is indicated to reduce pregnancy complications of embryopathy, macrosomia, and traumatic birth. Insulin requirements generally increase during pregnancy, and therapeutic goals are the same as those for gestational diabetes. Administration of rapid-acting insulin before meals prevents glucose elevation after meals; longer-acting insulins are used to control

glucose in the fasting state. The newer short-acting insulin analogs are safe to use during pregnancy, as is insulin pump therapy. Neutral protamine Hagedorn (NPH) insulin has been the standard for longer-acting insulins, but a growing body of evidence suggests that glargine is safe and effective as well.”

Obstetric Considerations

Dr Watson says: “For obstetric care, we do a high-detail ultrasound at 18 to 20 weeks, with an emphasis on careful evaluation of the fetal heart. Antepartum testing is begun at 32 weeks in those with good glycemic control, but earlier in those with vasculopathy or poor glycemic control. We do twice-weekly testing with non-stress test/amniotic fluid index or biophysical profile (consists of the nonstress test combined with 4 observations made by ultrasonography) after 32 weeks’ gestation. Early delivery is considered in those with vasculopathy or poor obstetric history, and most patients are delivered before the estimated due date. We offer primary cesarean to those with estimated fetal weight in excess of 4,500 g. There is no evidence that induction of labor for suspected macrosomia improves maternal or fetal outcome, and it appears to increase the rate of cesarean delivery.”



2008 Graduating Clinical Endocrinology Fellows

Left to right (and their upcoming appointments): Teck K. Khoo, MD (Mercy Medical Center, Des Moines, Iowa); Brian A. Swiglo, MD (Allina Medical Clinic-United Medical Specialties, St. Paul, Minnesota); Gunjan Y. Gandhi, MD (Mayo Clinic, Jacksonville, Florida); and John T. C. Chow, MD (Endocrinology Clinic of Minneapolis, Edina, Minnesota).

Education Opportunities

Mayo Clinic Nutrition in Health and Disease, October 11-12, 2008, Chicago, Illinois. This course, designed for physicians, dietitians, nurses, and pharmacists, will provide a full-spectrum, in-depth overview of challenging nutritional issues that clinicians encounter in the ambulatory and hospital settings. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html.

12th Mayo Clinic Endocrine Course

March 16-20, 2009, on the Big Island of Hawaii. This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders. The 5-day course (7:30 AM to 12:30 PM daily) will span the full spectrum of endocrinology. For more information about this course, please visit <http://endo.course.mayo.edu>.

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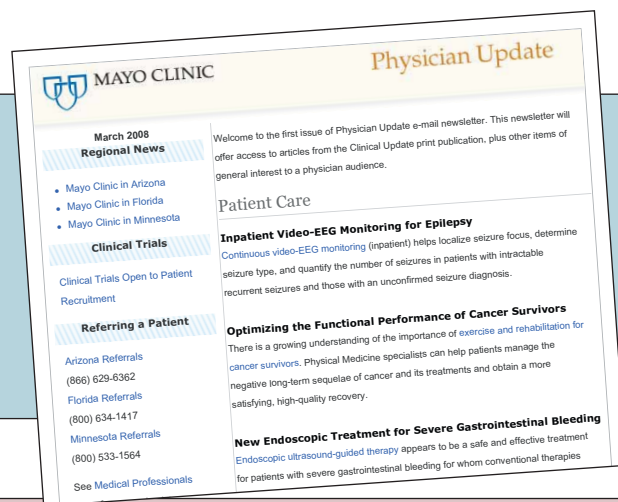
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