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Folate Levels in the Evalution of Macrocytosis or Anemia

Source: Robinson AR, Mladenovic J. *Am J Med*. 2001;110:88-90.

Evaluation of red blood cell (RBC) macrocytosis typically includes measurement of serum folate. Serum folate, however, is an inconsistent reflection of actual body stores, since depleted plasma levels are rapidly replenished by minimal folate intake. Even though RBC folate levels better represent body stores, this measurement may remain unaltered early in deficiency states. Robinson and Mladenovic examined the clinical use of folate measurements by retrospectively reviewing all folate levels (n = 2998) ordered in 3 teaching hospitals over a 12-month period.

Only 2.3% of folate measurements were too low. Chart review indicated that only half of subnormal folate levels were so-indicated in the hospital progress notes (possibly indicating that some results returned to the record after patient discharge). Similarly, only half of those with low folate noted by clinicians actually received folic acid replacement therapy.

Almost $90,000 was spent to perform the 1247 folate tests. Only 9 patients had any clinical intervention as a result of the testing. Given that folic acid replacement is of minimal cost (< $5/3 months supply), Robinson and Mladenovic note that empiric folate treatment would have incurred a cost savings of almost $83,000 in this study group.

In the evaluation of macrocytosis, vitamin B-12 assessment is necessary, lest folate replacement mask progressive neurologic consequences of B-12 deficiency. Robinson and Mladenovic suggest that empiric folic acid replacement in this circumstance (0.4-1 mg/d folic acid) be tried, with folate measurement reserved for macrocytosis unresponsive to this intervention. ■

Compounded Testosterone Gel in Hypogonadal Men

Source: Cutter CB. *J Am Board Fam Pract*. 2001;14:22-32.

Testosterone replacement in hypogonadal men currently depends primarily on either intramuscular injection or transcutaneous patches; neither of these methods is fully satisfactory to all patients. Recently, a gel formulation of testosterone intended for transcutaneous use has been available to clinicians. Cutter used a personally compounded testosterone gel applied to 10 men who had been previously managed with either depot testosterone injections or transdermal testosterone (Androderm patch).

Testosterone gel was compounded by mixing micronized testosterone and lecithin in a Pluronic F-127 vehicle. Patients applied 1-3 mL of compounded testosterone gel (0.5-10% concentrations) daily. Doses were increased by monitoring testosterone levels weekly until a therapeutic level was achieved (attained in 9/10 patients by 4 weeks).

Treatment was associated with statistically significant improvements in erectile capacity, memory, depression, and energy levels. Respondents indicated satisfaction with treatment and desire to continue to use this method of treatment. Cutter reports that subsequent to this report, he has empirically arrived at a dose of 6% gel, 2.5 mL, applied daily to a nonhairy body area near the axilla, as efficacious for most subjects. A proprietary formulation of testosterone gel 1% (Androgel™) is currently available for clinicians wishing to consider this method of testosterone replacement. Caution must be observed that areas of cutaneous application not contact intimate partners, as transfer of hormone may thus unintendidly occur. Testosterone gel offers another therapeutic tool for androgen replacement. ■

Effectiveness of Oseltamivir

Source: Welliver R, et al. *JAMA*. 2001;285:748-754.

The rapid spread of influenza to family contacts is a prominent source of community virus dissemination. There is some information that first-generation influenza antivirals (amantadine, rimantadine) reduce contact infection. Since the second-generation influenza agent oseltamivir (OSV) is efficacious for both influenza A and B, the therapeutic role of more selective therapies such as amantadine and rimantadine has greatly diminished. This study evaluated the efficacy of OSV in preventing spread of influenza virus from infected persons to household contacts.

Index case subjects were initially identified by clinical profile, consisting of fever, respiratory symptoms, and constitutional symptoms. Influenza virus infection was

subsequently confirmed in almost half of clinically diagnosed cases. Within 48 hours of symptom onset in the index case, OSV 75 mg QD (or placebo) orally for 7 days was administered to all household contacts older than age 12.

Use of OSV reduced the incidence of laboratory-confirmed influenza by almost 90% in contacts of an index case. There were no serious adverse effects. When administered within 48 hours of contact with an index case, clinicians can anticipate a high protective success rate for OSV treatment of asymptomatic household contacts. ■

Estrogen Replacement Therapy and Ovarian Cancer Mortality in U.S. Women

Source: Rodriguez C, et al. *JAMA*. 2001;285:1460-1465.

The preponderance of epidemiologic data associates both endometrial and breast cancer with postmenopausal estrogen replacement therapy (ERT). The relationship of ovarian cancer to ERT is less clear. Recent case-control studies have suggested an increased risk with ERT, especially of long duration. Rodriguez and colleagues investigated the association between ERT and ovarian cancer mortality in a large population of female participants in the Cancer Prevention Study II (n = 676,526). Data were accrued over 14 years of observation, and include almost 1000 ovarian cancer deaths.

Even users of ERT had a slightly increased rate of ovarian cancer mortality (rate ratio = 1.23). This positive association increased in strength with duration of ERT use, so that persons using ERT for more than 10 years had an approximately 2-fold increase in relative risk. When coupled with the earlier case-control studies, this current report strengthens the concerns that ERT, especially of long duration, increases the risk of ovarian cancer mortality. Nonetheless, since total lifetime risk of ovarian cancer mortality is relatively small (< 2%), other potential favorable effects of ERT in other tissue compartments must be taken into account in the risk-benefit analysis. Additionally, the effect of concomitant progestational treatment has not been comprehensively addressed. ■

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Effects of A Low-Molecular Weight Heparin on Thrombus Regression and Recurrent Thromboembolism in Patients with Deep-Vein Thrombosis

Source: Breddin HK, et al. *N Engl J Med*. 2001;344:626-631.

Low molecular weight heparin (LMWH) has been found to be as useful as traditional unfractionated heparin (HEP) for early management of deep vein thrombosis (DVT) or pulmonary embolism (PE), but offers the advantage that monitoring activated partial thromboplastin (APPT) is not necessary. Meta-analysis of earlier trials has suggested that LMWH affords a greater likelihood of thrombus regression, as well as a reduced rate of clinical recurrence. The current trial (n = 1137) was developed to explore the relative efficacy of LMWH and HEP in reference to thromboembolic recurrence and thrombus regression, assessed by venography.

LMWH, whether administered once or twice daily, demonstrated statistically significantly greater likelihood of thrombus regression (relative likelihood = 1.3 compared to HEP). LMWH was also significantly less likely to be associated with recurrent thromboembolic events.

Breddin and colleagues conclude that LMWH is more effective than unfractionated heparin in reduction of thrombus size, recurrent DVT, and new pulmonary embolism. ■

Effects of Vitamin E on Lipid Peroxidation in Healthy Persons

Source: Meagher EA, et al. *JAMA*. 2001;285:1178-1182.

There is much debate about the perceived potential benefit of antioxidant therapies, including vitamin E, upon cardiovascular, oncologic, and neurologic end points. Oxidized LDL has been particularly associated with progressive atherosclerotic vascular damage. It has been postulated that vitamin E might reduce the ability of lipids to become oxidized, yet a model for quantification of such an oxidation protective effect has been lacking until recently. Meagher and colleagues used 2 newly developed quantitative markers of lipid peroxidation status: isoprostanes and 4-hydroxynonenenal (4-HNE). Subjects received doses of vitamin E ranging from 200-2000 IU daily for 8 weeks (n = 30).

Irrespective of dose used, there was no demonstrable effect of vitamin E supplementation on markers of lipid peroxidation. Recent large data sets, such as the HOPE trial, also failed to demonstrate a beneficial effect of vitamin E supplementation on cardiovascular end points. Meagher et al question the potential benefit of supplemental vitamin E consumption. ■