1. Efficiency of Phosphodiesterase Type 5 Inhibitors

Sildenafil or tadalafil? Which is more effective and safer to use?

Submitted by: Raymond Zatzman, MD, Thornhill, Ontario

There is no head-to-head study comparing the efficiency of phosphodiesterase Type 5 (PDE5) inhibitors. So, it is fair to say that PDE5 inhibitors have similar efficiency. The Patient RespOnse with VardENafil in sildenafil non-responders (PROVEN) trial examined the success rates of patients with erectile dysfunction who previously failed with sildenafil citrate. This study showed that men were three times more likely to complete sexual intercourse successfully on vardenafil than on placebo.

The safety profile of PDE5 inhibitors is also comparable. PDE5 inhibitors are contraindicated in those taking nitrate medication. They are also contraindicated in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors.

Answered by: Dr. Hugues Widmer

2. Adjusting Long-Acting Insulins

How can we adjust new long-acting insulins like glargine and detemir?

Submitted by: Julie Grenier, MD, St-Charles-Boromée, Quebec

Extended, long-acting glargine and detemir are used as basal insulins for individuals with Type 1 and Type 2 diabetes.

In Type 1 diabetics, these insulins are usually used as part of a multi-dose insulin regime with rapid-acting insulins for meals. Basal insulins are often used once daily at night; however, both can be used twice daily, or insulin glargine can be given once daily in the morning. The insulins are usually adjusted to achieve target morning glycemic control without overnight hypoglycemia. These insulins also provide a basal insulin level between meals, especially when the meal intervals are long and the rapid-acting insulin wears off.

For Type 2 diabetics, extended long-acting insulins are often initiated when oral agents no longer provide adequate control. There are a number of "treat-to-target" studies that initiate insulin as monotherapy, usually at bedtime. The starting dose is 5 units to 10 units added to oral agents. The oral agents should be reduced if daytime hypoglycemia occurs. Insulin should be titrated to achieve fasting glucose goals without overnight hypoglycemia. Titration can be performed by the patient and/or the healthcare provider. Self-monitoring of blood glucose is essential as is hypoglycemia teaching. Titration should not happen if overnight hypoglycemia occurs until the cause is elucidated; and a reduction of the dose should also be strongly considered.

Answered by: Dr. Vincent Woo

3. Side-Effects of Vincristine

What percentage of patients develop permanent paresthesias from vincristine? Are there any good treatments?

Submitted by: Maury O'Neil, MD, Collinwood, Ontario

Vincristine is a naturally-occurring vinca alkaloid which acts as an antimicrotubule agent that blocks mitosis by metaphase arrest. Peripheral neuropathy is the most common type of neuropathy and develops in almost all patients. It is the primary and dose-limiting toxicity of vincristine. Paresthesias with vincristine are dose-related and *often* reversible, but in some patients, neurotoxicity can persist for months after the discontinuation of this therapy. Permanent neuropathy is believed to be rare (< 2% to 3%); however, this clearly depends upon multiple factors, including cumulative dose and duration of use, grade of neuropathy, comorbidities and age. The elderly are particularly prone.

Other than the discontinuation of vincristine, there is no proven therapy to treat vincristine-induced paresthesias. Data regarding the use of folinic acid, vitamin B12, pyridoxine, thiamine and oral glutamate have been conflicting.

For the treatment of neuropathic pain, tricyclic antidepressants or gabapentin may be of symptomatic benefit.

Answered by: Dr. Sharlene Gill

4. Bypassing an Egg Allergy to Administer a Vaccine

How can you get around a severe egg allergy in a child to be able to administer the measles, mumps and rubella (MMR) vaccine?

Submitted by: Adam Kayumi, MD, Mississauga, Ontario

Historically, the concern regarding the MMR vaccine and children with an egg allergy is that the vaccine is grown using cultured chick embryo fibroblasts as a substrate. In fact, this material does not contain significant amounts of egg protein (ovalbumin). This issue was addressed several years ago in a large study that showed egg-allergic children were no more likely to react to the MMR vaccine than non-allergic children.[1] Well-designed studies of > 1,200 children with severe allergic reactions to eggs have clearly shown that these children can safely receive the MMR vaccine. Current recommendations state that egg-allergic children can be vaccinated and simply observed in the office setting for 30 minutes following injection. On a side note, those with an allergy to chicken or feathers also have never been shown to be at an increased risk for reaction to the vaccine.

Reference
1. James JM, Burks AW, Roberson PK, et al: Safe Administration of the Measles Vaccine to Children Allergic to Eggs. N Engl J Med 1995; 332(19):1262-6.

Answered by: Dr. Tom Gerstner

5. Melatonin Suppression

Is there any research on the side-effects of melatonin suppression (*e.g.*, using a seasonal affective disorder [SAD] lamp)?

Submitted by: Carol Lavallée, MD, North Bay, Ontario

The hormone melatonin is the primary controller of circadian (day/night) bio-rhythms. Most of the melatonin in the human body is secreted by the pineal gland, a small pinecone-shaped gland located near the center of the brain. The pineal gland receives information from the optic nerve about the ambient light level and adjusts its melatonin output accordingly.

Bright light suppresses the output of melatonin. Ordinary indoor lighting does not. After sunset, the pineal gland responds to the decreased light levels by greatly increasing its output of melatonin. After a few hours, blood melatonin levels reach a point where sleep is induced. Melatonin levels usually peak two to four hours after the onset of sleep and decrease gradually during the remaining sleep period. Daylight inhibits the production of melatonin and levels of melatonin usually reach a minimum sometime during the afternoon.

Irregularities in melatonin production can cause sleep problems, lethargy and mood disorders. Some animal studies have shown that melatonin reverses stress-related suppression of the immune system. A number of animal studies have shown that melatonin reduces the incidence of some types of cancer, especially estrogen-mediated cancers (*e.g.*, breast cancer). Experiments to confirm these effects in humans have not yet been completed. However, some researchers suspect that melatonin suppression, due to artificial lighting during this century, may be a contributor to the rise in breast cancer rates since sufficiently bright artificial light will suppress melatonin production. This does not mean that one should avoid artificial lighting. It is just as important to have several waking hours with low melatonin levels as it is to have several hours in the period just before and during sleep with high melatonin levels.

Resource

1. Reiter RJ, Robinson J: *Melatonin: Your Body's Natural Wonder Drug.* Bantam, New York, 1995. http://www.teleport.com/~jor/.

Answered by: Dr. Hany Bissada

Some researchers suspect that melatonin suppression, due to artificial lighting during this century, may be a contributor to the rise in breast cancer rates.

6. Can We Test for an Allergy to Cigarette Smoke?

Can we test for an allergy to cigarette smoke?

Submitted by: Jonathan Murray, MD, Kentville, Nova Scotia

In short, no. Skin and radioallergosorbent testing measures specific IgE antibodies produced against a particular antigen. Antigens (or allergens, in the case of specific IgE), are usually protein, or glycoprotein structures whose epitope interacts with T and B cells during the induction of an antibody response. Smoke is an irritant with no consistent structure, *per se*. The literature does suggest that exposure to environmental tobacco smoke may enhance an IgE response to other allergens (*i.e.*, act as a catalyst), but on its own, it is not an allergen.

Exposure to smoke in allergic individuals enhances the inflammatory airway response by way of irritation of the respiratory mucosa, making it difficult to control inflammation and symptoms of the upper and lower airway in allergic and non-allergic patients.

Answered by: Dr. Tom Gerstner

7. Adequate Lithium Levels in Geriatric Patients

What is an adequate lithium level in geriatric patients during the maintenance treatment of mood disorders?

Submitted by: Janice Van Kampen, MD, Toronto, Ontario

With appropriate monitoring, lithium use in the elderly can be both safe and effective. However, the use of lithium in the elderly is complicated by factors that include associated medical illnesses and medications, special diets, age-related reduction in glomerular filtration rate and increased sensitivity to adverse effects. For that reason, a serum level between 0.6 mEq/L and 0.8 mEq/L is recommended in the geriatric population.

In general, the elderly should be started on lower-than-usual dosages, with dosage changes occurring less frequently than in younger patients. The elimination half-life of lithium increases with age and the time required to reach a steady state is much longer in the elderly. If lithium is stopped, serum levels fall more slowly and the resolution of adverse effects and toxicity may be prolonged.

The elderly should be started on lower-than-usual dosages of lithium.

Elderly patients with renal failure and those with hypertension or other medical illnesses that require thiazide diuretics (causing sodium depletion) are at a higher risk of decreasing renal clearance of lithium and potentiating its toxicity. These patients should probably be switched to another mood stabilizer. However, if the two drugs must be used together, lithium dosage should be decreased by 50% with close monitoring of lithium concentration, serum electrolytes and fluid intake.

Answered by: Dr. Hany Bissada

8. Testing for Acetylsalicylic Acid Resistance

How frequently should we be testing for acetylsalicylic acid (ASA) resistance?

Submitted by: David Hepburn, MD, Victoria, British Columbia

The short answer is never. One cause of ASA nonresponse (*i.e.*, the failure of ASA to prevent an acute vascular thrombotic event) is ASA resistance which is the laboratory observation of failure of ASA to inhibit arachidonic acid-induced platelet aggregation. There are no standardized *in vitro* laboratory tests for ASA activity that have shown a correlation with clinical outcomes. The difficulty is that clinical events depend not only on platelet aggregation *in vitro*, but also on endothelial function and interactions with other blood cells. Technical and clinical factors such as posture, time of day, smoking and exercise affect laboratory measured platelet aggregability.

Other causes of vascular events in patients on ASA are:

- non-compliance,
- treatment failure (ASA prevents 25% of vascular events, not 100%),
- more intense platelet activation in some patients,
- drug interactions (such as with ibuprofen) and
- poor absorption of ASA.

The 2005 Working Group on Aspirin Resistance does not recommend laboratory testing of patients for ASA resistance or use of alternative antiplatelet drugs, such as clopidogrel, based on results of *in vitro* assays.[1]

Reference

1. Michelson AD, Cattaneo M, Eikelboom JW, et al: Aspirin Resistance: Position Paper of the Working Group on Aspirin Resistance. J Thromb Haemost 2005; 3(6):1309-11.

Answered by: Dr. Bibiana Cujec

9. Proton Pump Inhibitors and Vitamin B12 Deficiency

Please comment on the use of proton pump inhibitors (PPIs) and the risk of vitamin B12 deficiency.

Submitted by: S. Scala, MD, Toronto, Ontario

Vitamin B12 deficiency is relatively common among older adults. There are multiple causes, including pernicious anemia, atrophic gastritis, *etc.* There is a theoretical concern that chronic acid suppression by PPIs may increase the risk of B12 deficiency. Normally, vitamin B12 is liberated from food in the stomach by the low pH of gastric acid and PPIs may prevent this from occurring. However, despite the current widespread use of PPIs, this theoretical concern has not been definitively shown.

Answered by: Dr. Robert Bailey; and Dr. Justin Cheung

10. Pharmacotherapy for Panic Disorder

How long do you continue pharmacotherapy for panic disorder? Patients frequently experience a relapse of symptoms when they taper the dose (often done on their own). Are they having withdrawal syndrome or are they still suffering from their disorder? How do we distinguish one from the other?

Submitted by: Stuart Glaser, MD, Mount Royal, Quebec

The duration of pharmacotherapy for panic disorder varies from patient to patient and depends on whether the panic disorder was triggered by a traumatic event (*e.g.*, a car accident), or due to a genetic predisposition.

If the disorder was triggered by a traumatic event, the duration of pharmacotherapy would be limited to somewhere between six months to one year, provided the patient gets the appropriate supportive counselling.

If the disorder is due to a genetic predisposition, there is usually a positive family history for anxiety disorders and the patient developed the panic disorder sometime in adolescence or early adulthood without any triggering traumatic events. In this situation, the pharmacotherapy would be long-term, maybe even years long. Of course, each case should be evaluated individually.

Withdrawal symptoms usually occur when the medication is stopped abruptly, triggering acute physical symptoms, such as:

- palpitations,
- excessive sweating,
- shakiness,
- occasional GI symptoms, in addition to
- the experience of anxiety and panic.

Patients usually describe these symptoms as different from their regular panic attacks. On the other hand, when the medication dosage is gradually reduced, the patient may experience a gradual resurgence of the initial panic attack symptoms for which they were prescribed the medication in the first place. In this case, the symptoms reappear gradually and get worse with further reduction of the medication dosage. It is unusual that a gradual reduction of the medication dosage would cause true withdrawal symptoms.

Answered by: Dr. Hany Bissada

11. Testosterone for the Aging Male

Can testosterone preparations help to prevent muscle loss in an aging, but still physically active, male?

Submitted by: S. Sullivan, MD, Victoria, British Columbia

Testoterone administration has a positive effect on muscle mass and can help to prevent muscle loss in the aging male. Testosterone supplementation should not be administered to a man if his measured bio-available testoterone is normal. It should only be considered if his bio-available testoterone is low or borderline low.

Answered by: Dr. Hugues Widmer

12. Lower-Dose Estrogen vs. a Standard Dose

What is known about the safety of lower-dose estrogen (*e.g.*, 0.3 mg) compared to a standard dose?

Submitted by: Barbara Campbell, MD, Kingston, Ontario

OC pills consist of ethinyl estradiol and a range of gestagenic compounds. When OC pills were introduced, they contained up to 150 µg of either ethinyl estradiol or mestranol. The latter is no longer used and doses of ethinyl estradiol have declined so that 20 µg to 35 µg doses are the norm; infrequently is 50 µg used.

Fortunately, significant complications of the OC pill are rare, making rates of comparison of life-threatening complications difficult. Complication rates also depend on the nature and dose of gestagen in the pill (*e.g.*, some third-generation gestagens have been reported to increase the risk of thromboembolism compared with earlier preparations). Obviously, some OC pills would be considered unsafe in any dose in women with a genetic predisposition to thromboembolism.

In general, there does not appear to be evidence that decreasing the estrogen dose to < 35 µg results in a significantly lower risk of complications. It is not clear if OC pills containing > 20 µg of ethinyl estradiol provide more effective contraception than lower dose pills, but there does seem to be an increased frequency of menstrual disruption with lower dose pills. It makes good medical sense to at least consider their use as first-line for contraception.

For resources, please contact **diagnosis@sta.ca.**

Answered by: Dr. David Cumming

13. Merits of Parathyroid Hormone Analgesics

In a patient with well-established osteoporosis, where no clinical response has been seen with bisphosphonates, what are the merits of parathyroid hormone (PTH) analgesics?

Submitted by: M. I. Ravalia, MD, Twillingate, Newfoundland

Compared to placebo, PTH has been shown to improve BMD and reduce fracture rate.[1] The mechanism of action is "anabolic," stimulating bone formation and activating bone remodelling, in contrast to bisphosphonates which are antiresorptive agents. Despite these different mechanisms of action, combination therapy has not been shown to be as effective as PTH alone, with bisphosphonates blunting the powerful anabolic effect of PTH.[2] This different mechanism may benefit the population of patients refractory to bisphosphonates. Therefore, it may be reasonable to consider PTH for those patients with worsening bone density despite bisphosphonate use, particularly those with new fractures.

For references, please contact **diagnosis@sta.ca.**

Answered by: Dr. Sabrina Fallavollita; and Dr. Michael Starr

14. Looking at Inhaled Corticosteroids

What are considered to be a safe dose of inhaled corticosteroids?

Submitted by: Laith Barsoom, MD, Winnipeg, Manitoba

Inhaled corticosteroids (ICs) are used in the treatment of a number of chronic respiratory conditions, particularly asthma and chronic obstructive pulmonary disorder (COPD). ICs are well known to cause local adverse effects (*e.g.*, dysphonia, candidiasis) due to the deposition of medication in the oropharynx. These effects can be minimized by the use of a spacer device with pressurized metered dose inhalers and mouth washing after the inhalation of any ICs. Of greater concern is the risk of systemic adverse effects, such as:

- easy bruising,
- osteoporosis,
- increased fracture rates,
- adrenal suppression and
- cataracts.

Systemic effects differ among ICs based on:

- dose,
- relative potency,
- delivery device,
- bioavailability,
- gut absorption and
- first-pass metabolism in the liver.[1]

Recent long-term studies in COPD patients have not demonstrated convincing evidence of increased rates of serious systemic adverse effects when ICs are prescribed at currently recommended doses (*e.g.*, 250 mcg to 500 mcg of fluticasone propionate or equivalent b.i.d.).[2,3] There is conflicting data on the effect of long-term IC use on growth and final height attained in children with asthma; however, doses of < 400 mcg of budesonide or equivalent seem to be safe.[1]

Recent long-term studies in COPD patients have not demonstrated convincing evidence of increased rates of serious systemic adverse effects when ICs are prescribed at currently recommended doses.

Ultimately, decisions are made in individual patients based on an assessment of the potential benefits of treatment with ICs balanced against the possible risks of local and systemic adverse effects.

References
1. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma. November 2006. www.ginasthma.org
2. O'Donnell DE, Aaron S, Bourbeau J, et al: State of the Art Compendium: CTS Recommendations for the Management of COPD. Can Respir J 2004; 11 (Suppl B):7B-59B.
3. Calverley PM, Anderson JA, Celli B, et al: Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease. NEJM 2007; 356(8):775-89.

Answered by: Dr. Paul Hernandez

15. What is Prolotherapy?

What is prolotherapy? Is there any evidence for its use?

Submitted by: G. Davies, MD, Devon, Alberta

Prolotherapy is an injection-based alternative treatment for chronic pain. It involves repeatedly injecting ligaments with irritant compounds, such as dextrose. The theory is that this restarts the body's natural healing process by causing controlled acute inflammation (swelling) in the areas injected. Proponents of prolotherapy believe this leads to stronger ligaments that can better support the affected area. Injections are often combined with other treatments, such as:

- spinal manipulation,
- exercises and
- corticosteroid injections into tender muscles to maximize its effect.

With regards to evidence supporting its use, there are numerous case reports documenting its efficacy in the literature; however, there is little in the way of randomized clinical trials. A review of the literature published in 2005 found six randomized trials using prolotherapy with conflicting results. Two studies in knee osteoarthritis reported the following after prolotherapy:

- decreased pain,
- increased range of motion and
- increased patellofemoral cartilage thickness.

Yet, two studies on low back pain reported significant improvements in pain and disability compared with control subjects, whereas two other studies did not. All studies were small and had significant methodological limitations and used additional therapies in addition to prolotherapy. A recently published Cochrane review, in the setting of lower back pain, had similar findings.

In summary, there is conflicting evidence regarding the efficacy of prolotherapy injections for patients and larger, well designed trials are needed prior to its introduction into mainstream medicine.

Resources

1. Dagenais, Yelland MJ, Del Mar C, et al: Prolotherapy Injections for Chronic Low-Back Pain. Cochrane Database Syst Rev 2007; (2):CD004059.
2. Rabago D, Best TM, Beamsley M, et al: A Systematic Review of Prolotherapy for Chronic Musculoskeletal Pain. Clin J Sport Med 2005; 15(5):376-80.

Answered by: Dr. Sabrina Fallavollita; and Dr. Michael Starr

Prolotherapy is an injection-based alternative treatment for chronic pain. It involves repeatedly injecting ligaments with irritant compounds.

16. Severe Mastalgia: What Treatment is Effective?

Is there anything proven effective for severe mastalgia? (Not necessarily just premenstrual pain). The patient already uses a good sports bra and limits her caffeine intake.

Submitted by: Julia Bihun, MD, Ottawa, Ontario

Breast pain is the most common benign breast complaint. It is important to recognize cancer fears and exclude malignant disease. Recent reviews have advocated the use of a good support bra but have suggested that the common practice of restricting caffeine has no benefit. Other commonly used approaches, without proven benefit, include evening primrose oil and vitamin E.

The need for and the dose of any current estrogenic hormonal medication should be re-evaluated. Reasonable first-line treatments include a low-fat, high-carbohydrate diet, flaxseed and topical NSAID gel (2% diclofenac in pluronic lecithin organogel, applied every eight hours). Hormonal agents, such as bromocriptine (2.5 mg q.d.), tamoxifen (10 mg q.d.) and danazol (200 mg q.d.), have all demonstrated efficacy in the treatment of mastalgia, particularly in cyclic mastalgia, but their usefulness is limited by side-effects. Treatment courses of three to six months should be employed and recurrence (up to 60%) can be expected. Noncyclic mastalgia responds less well to treatment but resolves spontaneously in up to 50% of cases over six to 12 months.

For resources, please contact **diagnosis@sta.ca**

Answered by: Dr. David Cumming

17. Best Medicine for Atrial Fibrillation

What is the best medicine for atrial fibrillation?

Submitted by: **Melvin De Levie, MD,** Vancouver, British Columbia

There are two strategies for the medical management of atrial fibrillation. The first strategy involves effective heart rate control with a ß-blocker, non-dihydropyridine calcium channel blocker (diltiazem or verapamil) and digoxin used alone or in various combinations as required. The target heart rate should be 60 bpm to 70 bpm at rest and < 110 bpm with moderate exertion for most patients. ß-blockers are usually selected initially and digoxin is reserved as a second or third-line adjunct, particularly in older and more sedentary patients.

Both medical treatment strategies of atrial fibrillation require that the patient be treated with warfarin anticoagulation to a target INR of between 2.0 and 3.0, unless they are at a very low risk of cardiac emboli.

The second strategy involves both heart rate and heart rhythm control with the use of a rate-lowering and antiarrhythmic agent, such as sotalol or amiodarone, with intermittent electrical cardioversion of periodic atrial fibrillation recurrences to maintain normal sinus rhythm. This strategy is generally preferred for younger patients with paroxysmal atrial fibrillation or in anyone who remains symptomatic on a rate-control strategy alone.

Both medical treatment strategies of atrial fibrillation have similar rates of intermediate term morbidity and mortality, with the latter actually trending to be lower with the rate control strategy in recent studies. Importantly, both medical treatment strategies of atrial fibrillation require that the patient be treated with warfarin anticoagulation to a target INR of between 2.0 and 3.0, unless they are at a very low risk of cardiac emboli, which is classified as:

- < 65-years-of-age,
- lone atrial fibrillation,
- no hypertension,
- no diabetes and
- no previous transient ischemic attack or cerebrovascular accident.

Patients with atrial fibrillation in whom warfarin anticoagulation is contraindicated are currently offered 80 mg to 325 mg of acetylsalicylic acid (ASA) q.d., but this preventive treatment is only about half as effective at reducing the risk of cerebral or systemic cardioemboli. Whether combining clopidogrel with ASA is more effective prevention than ASA alone is currently not known and is the subject of the ongoing Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) study.

Answered by: **Dr. George N. Honos**

18. The Use of Aromatase Inhibitors in Breast Cancer

If a breast cancer patient was on tamoxifen for five years and is now "disease free," is there any role for anastrozole?

Submitted by: Ilona Grymonpre, MD, Nelson, British Columbia

For women with post-menopausal, hormone-receptor positive breast cancer, multiple strategies for the incorporation of aromatase inhibitors (AIs) into adjuvant hormonal therapy have been and are currently being studied. The American Society of Clinical Oncology Expert Panel on Technology has published a review of the subject, indicating that an AI should be considered as part of the standard adjuvant hormone therapy of newly-diagnosed post-menopausal women with breast cancer. The optimal strategy or duration has not yet been determined:

- upfront use of an AI for five years vs.
- two to three years of tamoxifen followed by an AI for three to two years vs.
- five years of tamoxifen followed by three to five years of an AI.

No studies have yet determined the optimal duration of an AI, nor have they established whether one AI is superior to another (anastrazole, letrozole, exemestane). In a woman who has completed five years of tamoxifen therapy, there may be a role for further therapy with an AI, particularly if she had high-risk disease.

A review with the patient's treating oncologist is essential to understand the potential additional benefits with an AI and the associated short- and long-term side-effects.

For resources, please contact **diagnosis@sta.ca.**

Answered by: Dr. Sharlene Gill

19. Testing for Wilson's Disease

What is the most specific and sensitive test for Wilson's disease?

Submitted by: Craig Render, MD, Kelowna, British Columbia

There is no one single test that is diagnostic of Wilson's disease. Its clinical manifestations often involve multiple organ systems (liver, neurologic, renal and blood) and its diagnosis is made based on the clinical manifestations, physical exam and laboratory findings and, in some cases, may require a liver biopsy.

A patient's presentation may vary depending on their age, but the majority of individuals present before the age of 50 with liver or neuropsychiatric abnormalities. Screening for a low ceruloplasmin is often the first step in this group and is followed-up with a 24-hour urine copper collection (elevated) and ophthalmologic exam for the presence of Keyser-Fleischer rings or sunflower cataracts, if clinical suspicion is high. More specialized testing, such as copper quantification on liver biopsy, penicillamine challenge or genetic screening for family members of affected patients, requires referral to a hepatologist or gastroenterologist.

For resources, please contact **diagnosis@sta.ca.**

Answered by: Dr. Phil Wong; and Dr. Min Soo Song

20. Antiendomysial Antibody Testing for Celiac Disease

How sensitive and specific is an antiendomysial antibody test (given a normal IgA level)? If positive, how necessary is a confirmatory small bowel biopsy before initiating a gluten-free diet?

Submitted by: Martin Davies, MD, Calgary, Alberta

Antiendomysial antibody (EMA) testing for celiac disease is performed by indirect immunofluorescence, whereby monkey esophagus (ME) or human umbilical (HU) cord tissue is used as a substrate against the test subject's serum. The subject's antibodies (if present) bind to the tissue substrate and then are detected by a fluorescein-tagged anti-human antibody. This process is viewed under fluorescence microscopy.[1] In a recent review of literature, the pooled sensitivity of EMA testing was 97.4% and 90.2% using ME or HU cord tissue substrate, respectively.[2] Specificity was 99.6% with either tissue substrate. However, sensitivity of this test is closely associated with the histologic grade of the disease on small bowel biopsy and is high only for subjects demonstrating total villous atrophy (Marsh classification Grade III or IV). Sensitivity decreases with less severe histology and is < 50% in the setting of Marsh Grade I or II lesions.[2,3]

The pooled sensitivity of EMA testing was 97.4% and 90.2% using ME or HU cord tissue substrate, respectively. Specificity was 99.6% with either tissue substrate.

Given the implications of the celiac disease diagnosis (*i.e.*, lifelong gluten-free diet and monitoring for associated complications) it is necessary to confirm a positive serologic test. Certainly, this is true of high-grade histologic changes in the setting of a positive serologic test. These changes include the presence of:

- intraepithelial cell lymphocyte infiltrates,
- intestinal villous atrophy and
- crypt hyperplasia.

Currently, small bowel intestinal biopsy is the gold standard to diagnose celiac disease.[3] Small bowel biopsies may not always clearly diagnose celiac disease, as mucosal changes tend to be patchy and the histologic changes are not unique to this process. Yet, given the variability in presenting symptoms and the variable sensitivity of the available serologic tests, information provided by small bowel biopsy is essential in establishing the diagnosis of celiac disease, initiating appropriate management and in monitoring the improvement of the disease by noting subsequent histologic normalization of small intestinal mucosa. Dx

References
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2. Rostom A, Dubé C, Cranney A, et al: Celiac Disease. Evid Rep Technol Assess (Summ) 2004; (104):1-6.
3. Rostom A, Murray J, Kagnoff M: American Gastroenterological Association (AGA) Institute Technical Review on the Diagnosis and Management of Celiac Disease. Gastroenterology 2006; 131(6):1981-2002.

Answered by: Dr. Robert Bailey; and Mr. Philip J. B. Davis