Experts on Call

Answers to your questions from our medical experts

1. BMT and Sickle Cell Anemia

Can a bone marrow transplant (BMT) be used to cure sickle cell anemia if the patient has a perfect sibling match? How risky is this procedure?

Submitted by: Marichal Binns, MD, Edmonton, Alberta

Allogeneic bone marrow transplantation can be used to cure sickle cell anemia, but the procedure is associated with significant risk. This limits the use of BMT to young (mainly children and young adults), and otherwise healthy, patients with severe debilitating complications of sickle cell disease, such as recurrent episodes of stroke, acute chest syndrome, or painful vaso-occlusive episodes. BMT in this setting is usually only performed from a human leukocyte antigen (HLA) matched sibling donor. The donor must be tested to ensure that they themselves do not have sickle cell disease; although, having sickle cell trait is acceptable.

Treatment with allogeneic BMT in sickle cell disease caries several significant risks, including complications from the conditioning chemotherapy regimen, graft versus host disease, and possible graft rejection. The risk of transplant related mortality is about 7%. Acute graft-versus-host disease (GVHD) occurs in 15 to 20%, chronic GVHD in 15 to 20% of patients, and graft rejection occurs in about 3%. There are also significant long-term risks, including impaired ovarian function and possible infertility, increased risk of secondary malignancies, and risks associated with immunosuppressive drugs, such as prednisone and cyclosporine.

Answered by: Dr. Cyrus Hsia and Dr. Leonard Minuk

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2. Treating Elevated TSH in Asymptomatic Patients

Do you treat an elevated thyroid stimulating hormone (TSH) if the patient is asymptomatic?

Submitted by: Jenny Molson, MD, Kingston, Ontario

Subclinical hypothyroidism occurs relatively often, and many individuals present with a mild to moderate elevation in TSH and normal free T3 and free T4 levels. Because hypothyroidism may occur insidiously over many years, individuals may feel "asymptomatic" with very high levels of TSH. Finally, individuals with subclinical hypothyroidism often worsen over time. Therefore, most clinicians would likely treat these patients with levothyroxine and adjust the dose to achieve a normal TSH level.

Answered by: Dr. Vincent Woo

3. Probability of Nabilone Addiction

Is there any risk of addiction with nabilone in patients with chronic pain, especially if there is a past history of addiction?

Submitted by: Pat Simpson, MD, St. Albert, Alberta

Nabilone is a synthetic cannabinoid with therapeutic use as an antiemetic and as an adjunct analgesic for neuropathic pain. It was approved in 1985 by the U.S. Food and Drug Administration (FDA) for treatment of chemotherapy-induced nausea and vomiting that has not responded to conventional antiemetics. It is also approved for use in treatment of anorexia and weight loss in patients with AIDS. Numerous trials and case studies have demonstrated various benefits for conditions like fibromyalgia.[1]

A clinical trial performed in Canada reviewed the use of nabilone to treat nightmares in individuals suffering from post-traumatic stress disorder.[2] The study found that night time administration of nabilone reduced the frequency and/or intensity of nightmares in 34 out of 47 patients (72%), with 28 reporting complete cessation of nightmares. This study is limited to the extent that there was no placebo control, but it warrants future investigation into the use of cannabinoid therapy in the treatment of post-traumatic stress disorder and other disorders involving recurrent nightmares. The author reported that no tolerance to nabilone was observed among patients who participated in the study.

Resource
1. Skrabek RQ, Galimova L, Ethans K, et al: Nabilone for the Treatment of Pain in Fibromyalgia. J Pain 2008; 9(2):64–173.
2. Fraser, GA. The Use of a Synthetic Cannabinoid in the Management of Treatment-Resistant Nightmares in Posttraumatic Stress Disorder (PTSD). CNS Neurosci Ther 2009; 15(1):84–88.

Answered by: Dr. Hany Bissada

4. Coffee Use in Patients with Ventricular Extrasystoles

Do you advise every patient with ventricular extrasystoles to stop drinking coffee?

Submitted by: Michael Journet, MD, Montreal, Quebec

Caffeine increases the release of norepinephrine from sympathetic nerve endings and increases intracellular calcium. Caffeine acutely increases heart rate and blood pressure. However, despite a widely held belief to the contrary, there is no evidence that caffeine in usual doses causes ventricular or atrial arrhythmias.

Some individuals appear to be more aware of palpitations when they consume beverages containing caffeine (increased inotropic effect of caffeine), and I generally recommend that patients with ventricular extrasystoles avoid excessive caffeine intake (*i.e.* limit caffeine intake to two cups of coffee daily).

Answered by: Dr. Bibiana Cujec

5. Sensorineural Hearing Loss (SSNHL)

Are steroids warranted in the treatment of sudden unilateral hearing loss?

Submitted by: **Jean Clarke, MD,** Vancouver, British Columbia

If administered early, corticosteroids have been shown to be efficacious in limiting or reversing hearing loss in certain circumstances, and it is, thus, crucial that this condition be investigated and treated early. Often hearing loss is not formally diagnosed for weeks, and, after this time, there is no evidence that steroids will provide any advantage. Sudden SSNHL should, therefore, be considered an urgent problem. The incidence is similar for adults of all ages.

Ideopathic SSNHL is the most common cause of this condition, but this is a diagnosis of exclusion and other causes need to be considered. First, conductive hearing loss should be ruled out. This is easily achieved with otoscopy (preferably pneumotoscopy) and tuning fork tests.

Once it is clear that the hearing loss has a sensorineural cause, it is important to obtain an urgent audiogram. Patients with SSNHL usually complain of decreased or absent hearing and aural fullness. Vertigo is usually absent, but tinnitus is almost universally reported. The list of potential causes of SNHL is extensive, so I will only make a few short points. First, drug ototoxicity may result from antibiotics, particularly aminoglycosides, chemotherapeutic agents (usually irreversible hearing loss), or common medications such as aspirin and diuretics (usually reversible hearing loss). Acoustic neuroma is the cause in approximately 1% of SSNHL cases and a (non-urgent) MRI is required to rule out this diagnosis. Dizziness or vertigo is not usual in cases of SSNHL, and this should lead to a different work-up and management.

The mechanism of action by which corticosteroids improve SSNHL is unclear. SSNHL is postulated to be caused by an inflammatory insult to the inner ear that may be infective, autoimmune, vascular, or traumatic in nature, so it is thought that any benefit is likely secondary to modulation of the immune response to this insult.

Mild SSNHL (less than 40 dB) will usually recover spontaneously and usually does not require treatment. Profound SSNHL (> 90 dB) is not likely to recover despite treatment. There is a "steroid responsive range" in between. This represents a degree of SSNHL that has been shown to have improved outcomes when systemic corticosteroids are administered. Wilson's landmark randomized, placebo controlled study showed recovery of at least 50% of the hearing loss in over 78% of those on steroids versus 38% of those on the placebo.[1] Although most otolaryngologists follow a similar approach to that outlined in this paper, the evidence is not concrete; therefore, a discussion with the patient about the potential side-effects of systemic steroids needs to take place. If the patient has a relative contraindication to corticosteroid treatment, it is probably best avoided. A general regimen for SSNHL would be prednisolone at around 50mg (or 1mg per kg) for a week to ten days and then tapered. Intratympanic dexamethasone has been trialled and may be employed by an otolaryngologist if there is no response, or a contraindication to, systemic therapy.

The key point with this condition is to investigate and treat patients early to get the full potential benefit of corticosteroid therapy.

Resource

1. Wilson WR, Byl FM, Laird N: The Efficacy of Steroids in the Treatment of Idiopathic Sudden Hearing Loss. A Double Blind Study. Arch Otolaryngol 1980; 106(12):772–776.

Answered by: **Dr. Benjamin Dixon**

6. Negative Anti-transglutaminase (Anti-tTG)

How long must a person be off wheat (and other gluten grains) to make Anti-tTG negative (in a Celiac patient)?

Submitted by: Bryn Waern, MD, Toronto, Ontario

A patient that is diagnosed with celiac disease often has a positive anti-tTG (tissue transglutaminase) level. It has a high sensitivity and specificity for celiac disease (95% and 94% respectively) and is an excellent test for both the diagnosis and monitoring of celiac disease. Depending on the pretreatment concentration levels, anti-tTG levels will normalize after 3 to 12 months on a strict gluten-free diet.

Caution should be used when using serology tests to monitor response and adherence to therapy. A normal anti-tTG level may not mean normalization of villous atrophy, as mucosa healing is often delayed compared to serology tests. If pretreatment anti-tTG levels are normal, using serology to follow progress is not possible. Serology may not be sensitive enough to measure minor transgressions in the diet, but, if anti-tTG normalize, it often indicates adherence to the gluten-free diet.

Answered by: Dr. Richmond Sy

7. Significance of Endometrial Cells on a Pap Smear

What is the significance of endometrial cells on a Pap?

Submitted by: Maria Yu, MD, Ajax, Ontario

Endometrial cells on a Pap smear in women over 40-years-old may reflect physiologic shedding (especially in the first 12 days of the menstrual cycle) or shedding in response to a pathological process. The cells are reported so the clinician can determine their significance in individual patients.

Large reviews of benign-appearing endometrial cells on cervical cytology in women over 40 have reported that up to 16% can be associated with significant endometrial pathology (hyperplasia or carcinoma). Among women with significant pathology, 79% had abnormal bleeding. Therefore, if symptoms of endometrial cancer are present (abnormal uterine bleeding), the patient should undergo endometrial sampling regardless of menopausal status.

In premenopausal women without abnormal bleeding, benign-appearing endometrial cells are rarely associated with significant pathology, and no further work-up is indicated. However, endometrial sampling can be offered to asymptomatic women with benign-appearing endometrial cells who are at risk for endometrial cancer (personal or family history of breast, colon, or endometrial cancer; tamoxifen use; chronic anovulation; obesity; estrogen therapy; prior endometrial hyperplasia; diabetes). Endometrial sampling is preferable over an ultrasound, as a negative ultrasound does not rule out pathology.

Resource
1. Canfell K, Kang YJ, Clements M, et al: Normal Endometrial Cells in Cervical Cytology: Systematic Seview of Prevalence and Relation to Significant Endometrial Pathology. J Med Screen 2008;15(4):188–198.
2. Beal HN, Stone J, Beckmann MJ, et al: Endometrial Cells Identified in Cervical Cytology in Women > or = 40 Years of Age: Criteria for Appropriate Endometrial Evaluation. Am J Obstet Gynecol 2007; 196(6):568.

Answered by: Dr. Victoria Davis

8. Treatment for Uncontrollable Pruritus

How do you treat uncontrollable pruritus, and why is this reflex present?

Submitted by: Anonymous

Pruritus is defined as an unpleasant sensation that provokes the desire to scratch. The sensation of pruritus is received by free nerve endings in the skin and transmitted through unmyelinated C nerve fibres and Aδ myelinated fibres through the central spinothalamic tracts. Previously, itch was believed to share the same neural pathways as pain, but it has been demonstrated that itch and pain are transmitted by different neural pathways. The reason for the scratch reflex is unknown, but scratching produces a distraction from an annoying itch and replaces it with a positive, more pleasant sensation. PET scanning has shown sensory cerebral cortex activation after an itch stimulus.

Treating uncontrollable pruritus involves trying to make a specific diagnosis of the cause of the pruritus, as treatment will most commonly involve treating the underlying disease. Pruritus can be subdivided into localized or generalized, intermittent or persistent, and can be categorized clinically by whether there are primary lesions seen or all lesions are secondary (*i.e.* excoriations).

Investigation of generalized pruritus, in the absence of primary lesions, should lead to a search for an underlying systemic condition, such as renal failure, cholestasis, endocrine causes, underlying malignancy, and hematologic conditions, including myelodysplastic syndromes.

If a thorough history and physical examination and appropriate laboratory investigations fail to lead to a cause or diagnosis, it may be necessary to treat the patient symptomatically. This would include topical therapy, including moisturizers, cooling agents, such as menthol or camphor, anesthetics such as pramoxzine and systemic therapies, such as sedating oral H1 antihistamines for their soporific effect, as well as a trial of UVB therapy. The patient would need to be carefully monitored, as the cause of the pruritus may only become apparent with continued observation over time.

Answered by: Dr. Richard Haber

9. Use of Sitagliptin and Saxagliptin in Treating Type 2 Diabetes

Can sitagliptin and saxagliptin be used in combination with other oral hypoglycemic agents in type 2 diabetes mellitus?

Submitted by: Anonymous

Sitagliptin and saxagliptin are new antihyperglycemic agents. They are members of the incretin family that belong to the DPP-4 inhibitor class. They act by increasing insulin secretion and decreasing glucagon secretion in a glucose-dependant manner. They are given orally once a day, have virtually no side-effects, and come in only one dose in Canada. They can be used in type 2 diabetes mellitus as an add-on therapy to either metformin or a sulfonylurea, and they can further reduce A1c by about 0.5 to 1.0%, fasting glucose by 1.0 to 1.9 mmol/L, and two-hour postprandial glucose by 1.7 to 3.0 mmol/L based on recent studies. They do not cause hypoglycemia or weight gain. They are not to be used in moderate to severe renal failure. There are no long-term studies in combination with other agents, in triple therapy, or with insulin as of yet, but many are in the pipeline.

Answered by: Dr. Ally Prebtani

10. Implantable Cardioverter-defibrillator (ICD)

Who should get an implantable cardioverter-defibrillator?

Submitted by: Peter Lee, MD, New Glasgow, Nova Scotia

The patients who benefit most from a defibrillator are those who have been resuscitated from ventricular fibrillation (VF) or sustained ventricular tachycardia with good functional recovery. The cause of VF should not be an acute myocardial infarction that has occured within the last 48 hours or any other reversible cause. Most of these patients have underlying structural heart disease. As long as these patients are not in NYHA functional class IV and are expected to live for more than one year, they should be referred to an electrophysiologist for consideration of an ICD.

In terms of primary prevention of sudden cardiac death, patients with ischemic cardiomyopathy and LVEF < 35% (NYHA class I-III) and those with nonischemic cardiomyopathy and LVEF < 35%, who are in functional class II-III, can be considered for ICD as long as they are otherwise in good health and are expected to live for more than one year with good functional status.

Defibrillators can prevent sudden cardiac death, but heart failure progresses over time and discussion regarding eventually turning off the defibrillator should take place at the time implantation is being considered.

Answered by: Dr. Bibianna Cujec

11. Intense Pulsed Light and Rosacea

Does intense pulsed light (IPL) help in the treatment of rosacea?

Submitted by: Heather Cairns, MD, Victoria, British Columbia

Intense pulsed light (IPL) has been shown in several studies to be effective in treating rosacea. It is most useful for treating the erythematotelangiectatic type of rosacea and, therefore, helps to treat facial erythema and telangiectasia. IPL differs from laser light in that the pulsed light source produces wavelengths of light from 500 to 1200 nanometers, and various "cut off" filters are used to produce the desired wavelength range. In contrast, laser light delivers only one wavelength at a time. One advantage of IPL over pulsed dye laser at 585 nm with a 450 µs pulse width (the pulsed dye laser most frequently used to treat rosacea), is the reduction or elimination of unsightly purpura, which can last one to two weeks after the laser treatment. Patients do need to be told that IPL and laser do not offer a cure for rosacea, and maintenance treatments are necessary to reduce the facial erythema. Most frequently, repeat treatments need to be done every four to six months.

Answered by: Dr. Richard Haber

12. Treatment for Essential Tremor

What is the best treatment (if any) for essential tremor?

Submitted by: Anonymous

The treatment of essential tremor can be divided into medical and surgical therapies. The most commonly used medications are propranolol, a beta-blocker, and primidone, a GABA agonist.

Propranolol use for essential tremor was introduced in 1971. Among the different beta-blockers, none is considered to be superior to propranolol. Drugs that are predominantly B1 antagonists are less effective than those that act on B2 receptors as well. Overall, about 25% of patients are able to maintain their initial improvement for about two years. It is a nonselective beta-adrenergic receptor antagonist. Some patients may take propranolol only before social engagements, whereas others may use it on a daily basis. If propranolol is to be taken on a daily basis, the dosage ranges from 60 mg to 260 mg per day. Propranolol is effective in treating essential tremor involving limbs, and many studies have shown that the magnitude of tremor is reduced by at least 50%, as measured by accelerometry and clinical rating scale. Side effects include a drop in blood pressure, fatigue, depression, impotence, and bradycardia.

Primidone, conventionally used as an antiepileptic medication, provides a significant therapeutic benefit for essential tremor. It is a GABA agonist. The initial dose is one quarter of a tablet of 125 mg (31.25 mg), which is increased slowly. The average reduction in tremor is at least 50% when measured by the clinical rating scale and accelerometery. One third of the patients may have a strong feeling of being unwell and experience side-effects of drowsiness, confusion, nausea, and dizziness upon the initiation of this drug. However, these side effects may improve in two to three weeks.

Combined treatment with propranolol and primidone is more effective than monotherapy with either of these agents alone.

Other therapeutic agents include topiramate, gabapentin, benzodiazepines, and especially clonazepam, nimodipine, alprazolam, and botulinum toxin. Surgical treatments include thalamotomy and deep brain thalamic stimulation.

Suggested Reading
1. Rana, AQ: An Introduction to Essential Tremor. iUniverse Publishing, Bloomington, Indiana, 2010.57–66.

Answered by: Dr. Abdul Qayyum Rana

13. Topical NSAIDs

Topical NSAIDs now abound in Canada. How effective are these agents in treating localized arthritis? Are they safe, and, when oral NSAIDs are contraindicated, can they be used if acetominophen isn't helping?

Submitted by: Paul G. Stephan, MD, Scarborough, Ontario

The rationale for developing topical NSAIDs was to treat local musculoskeletal pain without systemic adverse events. The blood concentration of NSAIDs after topical application is typically less than 1/20th of those found in oral NSAIDs. A Cochrane review looking at the efficacy of topical NSAIDs for treatment of acute pain, such as sprains, found that topical NSAIDs are more effective than placebo, and the number-needed-to treat-to-achieve 50% pain relief was 4.5 (3.9 to 5.3).[1] Randomized controlled trials have also shown that topical NSAIDs are more effective than placebo in the treatment of osteoarthritis (OA) of the hands,[2] as well as OA of the knee.[3] The majority of adverse effects were local skin reactions, such as dry skin and dermatitis, which were mild.[4] There were very few systemic side-effects. Therefore, topical NSAIDS can be a reasonable choice for localized pain, particularly when there is a need and indication to avoid systemic therapy.

References
1. Massey T, Derry S, Moore RA, et al: Cochrane Database Syst Rev. 2010; June 16 (6):n.p.
2. Altman RD, Dreiser RL, Fisher L, et al: Dicofenac Sodium Gel in Patients with Primary Hand Osteoarthritis: a Randomized, Double-Blind, Placebo-Controlled Trial. J Rheumatol 2009; 36(9):1991–1999.
3. Niethard FU, Gold MS, Solomon GS, et al: Efficacy of Topical Diclofenas Diethylmine Gel in Osteoarthritis of the Knee. J Rheumatol 2005; 32(12):2384–2392.
4. Shainhouse JZ, Grierson LM, Naseer Z. A Long-term, Open-label Study to Confirm the Safety of Topical Diclofenas Solution Containing Dimethyl Sulfoxide in the Treatment of the Osteoarthritic Knee. Am J Ther. 2010; 17(6):566–76.

Answered by: Dr. Michael Starr and Dr. Fares Kalache

14. Chest X-rays for Pneumonia Patients

In a patient with pneumonia, diagnosed with chest x-ray, how long after treatment should chest x-ray be repeated?

Submitted by: Mark Krieger, MD, Toronto, Ontario

The necessity and timing of performing a follow-up chest radiograph (CXR) in the management of community-acquired pneumonia depends on the clinical context. Patients who fail to respond clinically (*e.g.* no improvement in cough, fever, tachypnea, hypoxemia, or leukocyte count) after 48 to 72 hours of treatment with antimicrobials warrant a follow-up CXR. Among patients that do respond clinically to appropriate treatment of pneumonia, only those who are at increased risk for lung malignancy require follow-up CXR (*e.g.* smoking history, family history of lung cancer, age > 50 years, worrisome features on initial CXR).

The timing of a follow-up CXR, in the setting of a good clinical response to treatment, is influenced by the presence of factors associated with slow radiographic resolution (see Table 1). Most individuals without risk factors for slow resolution of pneumonia will show clearing on CXR after four to six weeks. However, individuals with risk factors may take much longer to clear radiographically — 12 weeks or more.

Table 1
Risk Factors for Slow Radiographic Response in Pneumonia

- Older age
- Underlying chronic lung disease
- Immunosuppression
- Increased severity of pneumonia
- Inadequate antimicrobial therapy
- Features on chest radiograph (e.g. multilobar involvement, cavitary disease, pleural effusion, atelectasis)

Resource
1. Mandell LA, Wunderink RG, Anzueto A, et al: Infectious Disease Society of America/American Thoracic Society Consensus Guidelines on Management of Community-acquired Pneumonia in Adults. Clin Inf Dis 2007; 44(Suppl 2): S27–S72.

Answered by: Dr. Paul Hernandez

15. Starting Pre-diabetics on Metformin

Is it beneficial to start a pre-diabetic (FBS 6.2 to 7.0) HbA1c < 6.0% on metformin? What dose should be used?

Submitted by: David Apramian, MD, Burk's Falls, Ontario

The loss of 5% of initial body weight through intensive and structured lifestyle modification can reduce the risk of progression from impaired glucose tolerance to type 2 diabetes by almost 60%. Progression from prediabetes to type 2 diabetes can also be reduced by pharmacologic therapy with metformin (~30% reduction), acarbose (~30% reduction,) and thiazolidinedione (~60% reduction). A dose of 850 mg b.i.d. was used in the Diabetes Provention Program.

Answered by: Dr. Vincent Woo

16. Hyperprolactinemia Caused by Risperidone

What is the course and outcome of hyperprolactinemia caused by risperidone?

Submitted by: Anonymous

Risperidone significantly increases prolactin levels. Hyperprolactinemia suppresses gonadotropin-releasing hormone (GnRH), which reduces gonadotropin release and can impair gonadal steroidogenesis in men and women. This elevation is sometimes, but not always, associated with inhibited reproductive function and symptoms such as galactorrhea, amenorrhea, gynecomastia, erectile dysfunction, and anorgasmia. Long-term hyperprolactinemia may lead to decreased bone density in both sexes when associated with hypogonadism (although no direct evidence exists that would suggest that risperidone decreases bone density, regardless of prolactin level). Approximately one-third of breast cancers are prolactin dependent. The manufacturer suggests that patients with a history or family history of breast cancer should be monitored for emergent malignancy, especially if they develop hyperprolactinemia while on risperidone.

Resource
1. Marder SR, Hurford IM, van Kammen DR: Second Generation Anti-psychotics. In: Howe (ed.) Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 9th edition, 2009, 3206–3240.

Answered by: Dr. Hany Bissada

17. DDAVP Use in Hereditary Bleeding Disorders

How does DDAVP help prevent bleeding in patients with hereditary bleeding disorders?

Submitted by: Graham White, MD, Parksville, British Columbia

Desmopressin (DDAVP) is a synthetic analogue of vasopressin (antidiuretic hormone). It is indicated in the treatment of bleeding in certain inherited bleeding disorders, including mild haemophilia A, type 1 von Willebrand's Disease (VWD), and in certain platelet function disorders, including storage pool disease and platelet release disorder. DDAVP leads to the release of von Willebrand factor (VWF) and factor VIII from their storage sites, in endothelial cells. This explains the drugs effectiveness in mild haemophilia A and type 1 VWD, but the haemostatic mechanism of action in platelet function disorders is unknown. DDAVP can be administered by either the intravenous, subcutaneous, or intranasal route. Common side-effects include flushing, headache, and nausea. Due to the antidiuretic effect of the drug, patients receiving repeated doses need close monitoring for hyponatremia, and they may require water restriction. The hyponatremia issue, as well as the development of tachyphylaxis, limits the use of DDAVP to brief exposure (*i.e.* 2 to 4 doses), primarily as prophylaxis through surgical procedures or treatment of mild bleeding-episodes. Patients with mild haemophilia A and type 1 VWD require a test infusion of DDAVP prior to any planned use to ensure that they have an adequate increase in VWF and/or factor VIII levels.

Answered by: Dr. Cyrus Hsia and Dr. Leondard Minuk