Revaccinating with Recombinant HPV Quadrivalent Vaccine

1. Should doctors revaccinate females that received recombinant human papillomavirus quadrivalent vaccine in 2007, knowing that anibodies decrease at five years?

Question submitted by:
Dr. Gilda Frent
Halifax, Nova Scotia

It is still too early to answer this question. Indeed, antibody levels will certainly fall with time, as they do for pretty much every vaccine. However, large follow-up studies show that, at seven years or so, the titres have held-up remarkably well. The real question, however, is how long will protection against cervical neoplasia persist, and the antibody titres are only an uncertain surrogate for this endpoint. The ideal situation would be to have a vaccine like that against hepatitis B, which protects against clinical disease long after detectable antibodies have faded away. In addition, for such an expensive vaccine, the question arises as to how much deterioration of protection is allowable before it is cost-effective to revaccinate. Also, if we vaccinate adolescents and protect them up to an age where many tend to be in monogamous relationships, the cost-effectiveness of vaccination changes again. Finally, we don't really know much about the natural history of this disease in a cohort where the age at first infection may be pushed back decades. Nor do we know what the serologic or clinical efficacy of booster doses at various ages and schedules might be. In effect, only time will tell.

Answered by:
Dr. Michael Libman

Bisphosphonates for Osteopenia

2.

How do you treat a young female between the age of 25 and 35, who has been diagnosed with osteopenia on bone density testing? Would you recommend starting bisphosphonates?

Question submitted by:
Dr. Michelle Sue
Toronto, Ontario

Treatment decisions for fracture prevention need to take into consideration the absolute fracture risk of patients and not just the BMD results. A 49-year-old, healthy woman with a T-score of -2.6 has a lower 10 year risk of a fragility fracture than a 74-year-old woman who has had a previous wrist fracture and has a T-score of -1.8. Thus, pharmacotherapy may not be indicated in the 49-year-old, but the 74-year-old will benefit from treatment. I would like to know what prompted the physician to order a bone density test on a young female. Are there other risk factors? Is the patient on long-term glucocorticoids? Is there a history of fractures, malabsorption, hyperparathyroidism, *etc*? In the absence of other risk factors, the risk of an otherwise young female sustaining a fragility fracture is very low. In general, bisphosphonates should not be used in women of child-bearing age, unless the risk of fracture outweighs the risks associated with the long-term use of these agents. I would suggest consulting the Canadian Osteoporosis Society Guidelines for further reference. It can be accessed at: www.osteoporosis.ca.

Answered by:
Dr. Hasnain Khandwala

Treatment for Seizures of Acute Onset in Children

3.

Manufacturers of rectal valium state that it is contraindicated for children < six-months-of-age. In the ER, what is the treatment of choice for a seizure?

Question submitted by:
Dr. Maury O'Neil
Collingwood, Ontario

The first line of drug therapy for seizures of acute onset in children — following stabilization and ensuring that airway, breathing and circulation have been assessed — are benzodiazepines. Historically, diazepam has been the most commonly used drug, although more recently lorazepam and midazolam have become more commonly used. Studies have demonstrated that lorazepam is more effective than diazepam and has a lower rate of respiratory depression. In addition to being given intravenously, lorazepam can be given by the rectal or intranasal route. Midazolam has been shown to be effective, but it has a shorter half life. Midazolam can be administered in a number of ways, including intramuscular, intravenous, intranasal, oral, buccal, or rectal administration. The treatment that I prefer using is lorazepam, ideally intravenously, but by the rectal or nasal route if intravenous access is problematic.

Answered by:
Dr. Michael Rieder

Differentiating Between Corns and Warts

4.

On physical exam, how would warts and corns be differentiated?

Question submitted by:
Dr. Bill Taylor
Medicine Hat, Alberta

The accurate diagnosis of warts vs. corns for the implementation effective therapy is different for each patient. Corns tend to occur on pressure areas, have preserved skin markings, and are tender to direct pressure. Warts may occur in both pressure and non-pressure areas, interrupt skin lines, and are often tender on deep pressure (as in squeezing from the side). Also, warts usually have thrombosed blood vessels, giving them the appearance of black seeds. Corns have a smooth, glassy centre. Paring the surface of the wart or corn may reveal these differences.

Answered by:
Dr. Scott Murray

Identifying Remission after Depression

5.

What qualifies as a remission from depression, and when is it appropriate to stop antidepressants?

Question submitted by:
Dr. Bhooma Bhayand
London, Ontario

Major Depressive Disorder (MDD) is a common condition that affects approximately one in five adults at some point in their life.[1] People with MDD often present with key emotional and physical symptoms, such as sadness, anhedonia, and disturbed sleep. They also demonstrate impaired psychosocial functioning.[1] Treatment of these symptoms is important, because their persistence and impact on a person's life can further increase the risk of relapse and future episodes of depression.[1] With each recurrence, it becomes that much more difficult to successfully treat depression, as the size of the hippocampus shrinks with each major depressive episode (MDE). A study out of Hamilton, Ontario, in 2003 demonstrated that after five MDEs, the hippocampal size decreased to such an extent that the likelihood of successful prolonged outcomes was less than 1%.[2]

Therefore, the primary goal of treatment in patients with MDE is complete remission with an aim to achieving functionality.[1] Although there is no universally agreed upon definition of remission, the most commonly used definition of remission is a score of ≤ 7 on the 17–item Hamilton Depression Rating Scale (HAM-D-17).[3] Studies in the literature have demonstrated that approximately 40% of patients with MDD will achieve full remission after receiving first- or second-line treatment.[1] In those patients who achieve complete remission, the long-term outcomes are significantly better than those who only report symptomatic improvement as a result of treatment.[1] In my experience, the patient's return to normal functionality is critical to long-term success.

Once patients have achieved remission, they should continue taking their antidepressant therapy for an additional 6 to 12 months to prevent an MDE recurrence. My general rule is to continue to treat with the antidepressant for one year multiplied by the number of MDEs experienced in the patient's lifetime. For example, if a patient has experienced three MDEs in his or her life, continue the antidepressant for a minimum of three years. If the patient has experienced five or more MDEs, lifelong antidepressant therapy should be considered.[4]

References
1. Weihs K, Wert JM: A Primary Care Focus on the Treatment of Patients with Major Depressive Disorder. Am J Med Sci 2011; 342(4):324–330.
2. Macqueen G, Campbell S, McEwen B, *et al*: Course of Illness, Hippocampal Function, and Hippocampal Volume in Major Depression. PNAS 2003; 100(3):1387–1392.
3. McIntyre RS, Fallu A, Konarski JZ: Measurable Outcomes in Psychiatric Disorders: Remission as a Marker of Wellness. Clin Ther 2006; 28(11):1882–1891.
4. Lamoure J, Stovel J: Depression: A Deeper Shade of Blue. Pharmacy Practice, 2009; 25(1):38–42.

Answered by:
Dr. Joel Lamoure

Referring to an Infertility Specialist

6. How should a family doctor work-up a couple prior to referring to an infertility specialist?

Question submitted by:
Dr. I. D'Souza
Toronto, Ontario

A thorough history and physical should be done to evaluate for potential causes of infertility, such as ovulatory defects, pelvic inflammatory disease, or endometriosis in the female, or testicular problems, or a history of mumps in the male. It is important that the couple understand the concept of fertile periods and the need for frequent enough attempts at intercourse to get pregnant. Prior to referral, a semen analysis should be completed in the male and a test for tubal patency with a hysterosalpingogram should be done in the female. Evaluation for ovulatory cycles with menstrual history should also be documented. Usually, after one year of being unable to conceive, or immediately if there is an identified cause, a referral would be appropriate. As couples delay child bearing, referrals can be made sooner: after six months of unprotected intercourse at age 35 or immediately at 40. Infertility investigations and treatments are very stressful for couples, and it is important that the family physician work with the specialist to support the couple through this emotionally charged process.

Answered by:
Dr. Cathy Popadiuk

Treating ADHD Adult Patients

7. How do you treat ADHD in an adult?

Question submitted by:
Dr. Nguyen Myvan
Verdun, Québec

Attention deficit hyperactivity disorder (ADHD) in adults is a highly debated diagnosis. Under the DSM-IV-TR, there is no set diagnostic criterion for adult ADHD. In fact, accodring to the pending DSM-V criteria a diagnosis of ADHD occurs before the age of seven.[1] It is anticipated that the diagnostic age in the DSM-V will be raised to 13-years-of-age, which still is not helpful for diagnosing the adult population.

ADHD exists on a spectrum with a classic triad of symptoms that includes impulsivity, hyperactivity, and inattentiveness. It is important for clinicians to be aware that not all of the items in the clinical triad need to be present for a diagnosis of ADHD.[1] According to the National Comorbidity Study, 4% of adults have had ADHD since childhood.[2]

There is a high psychiatric comorbidity with ADHD. Over 80% of children, adolescents, and adults with ADHD have other comorbid disorders. There is a lot of overlap in mood disorders and ADHD, and more than half of adults with ADHD have been found to have either anxiety disorders, mood disorders, or both. Substance abuse also runs very high, depending on the literature, up to four times above the general population, depending on the citation.

Root cause analysis should be carried out to examine the differential diagnosis regarding behaviours indicative of ADHD. Problems at work, addictive behaviours, or mood disturbances may present. Treatment modalities are basically the same. Beyond the standard NRIs and stimulants, antidepressants may offer some benefit and may be coupled with an atypical antipsychotic, such as quetiapine, which also has mood stabilizing properties. One of the metabolites of quetiapine is structurally similar to methadone, which makes quetiapine susceptible to being abused.[3]

As with any area in psychiatry, nonpharmacological interventions may be beneficial. Regular routine, diet, exercise, sleep, hygiene, and support groups may be as effective as pharmacotherapy or, at the very least, may augment it. In fact, exercise has been compared to low dose methylphenidate (5 mg immediate release), as it releases the catecholamines dopamine and serotonin. This combination has been linked to an increase in motor performance.[4]

References
1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th edition, Text Revision. Washington, DC: American Psychiatric Association 2000.
2. Kessler RC, Adler L, Barkley R, *et al*: Am J Psychiatry 2006; 163:716–723.
3. Lamoure J, Stovel J: Does Quetiapine Produce False-Positive Methadone Tests? Medscape ATE January 2008 http://www.medscape.com/viewarticle/568245. Accessed August 4, 2011.
4. Gualtieri M, Hicks RE, Levitt J, *et al*: Methylphenidate and Exercise: Additive Effects on Motor Performance, Variable Effects on the Neuroendocrine Response. Neuropsychobiology 1986;15(2):84–88.

Answered by:
Dr. Joel Lamoure

Usage of Infliximab for Crohn's and Ulcerative Colitis Treatment

8.

What is the success rate of infliximab in refractory Crohn's and ulcerative colitis (refractory to all other therapies, such as mesalamine, azathioprine, *etc*.)?

Question submitted by:
Dr. P. Hung
Vancouver, British Columbia

A recent systematic review evaluated the efficacy of anti-TNF therapy in Crohn's disease (CD) and ulcerative colitis (UC). In outpatients with moderate to severe UC, infliximab was found to be more effective than placebo, with 59% of patients achieving remission (NNT= 4; 95% CI: 3 to 10). Efficacy in hospitalized UC patients demonstrated a nonstatistically significant trend of superiority of infliximab treatment in comparison to placebo (NNT= 6; 95% CI). There are insufficient data with respect to the efficacy of infliximab and maintenance of remission in UC. In patients with active CD, disease remission was achieved in 28% of refractory patients randomized to receive anti-TNF therapy (including studies evaluating infliximab, adalimumab, and certolizumab) at 4 to 12 weeks of treatment, compared with 19% of placebo patients (NNT= 8; 95% CI: 6 to 17), with statistically significant heterogeneity of the data related to predominant efficacy of infliximab and adalimumab. Furthermore, 56% of the patients randomized to anti-TNF treatment relapsed at 26 to 56 weeks in comparison to 78% of those randomized to receive placebo (NNT= 4; 95% CI: 3 to 5). Subgroup analysis of anti-TNF trials has suggested efficacy in the treatment of fistulizing CD, although only a single trial was designed with fistula healing as a primary outcome. This study demonstrated that infliximab was significantly better at healing fistulizing CD (NNT= 3; 95% CI: 2 to 6) when compared to placebo.

Resource
1. Talley NJ, Abreu MT, Achkar JP, *et al*: American College of Gastroenterology IBD Task Force. An Evidence-based Systematic Review on Medical Therapies for Inflammatory Bowel Disease. Am J Gastroenterol 2011; 106(Suppl1):S2–S25.

Answered by:
Dr. Theodore Xenodemetropoulos

Premature Ovarian Failure Treatment

9.

What is the appropriate dosage of estrogen and progesterone replacement for a woman with premature ovarian failure? What dose and what available prescription?

Question submitted by:
Dr. Bernadette Yuan
Richmond,
British Columbia

Premature ovarian failure (POF) may occur spontaneously or as a result of therapeutic treatments, such as a surgical oophorectomy, chemotherapy, or directed radiation. Estrogen is required to minimize the risk of developing osteoporosis and cardiac disease and to relieve symptoms of hot flashes, night sweats, and vaginal atrophy. If the uterus is still in place, then progesterone must be part of the regimen for hormone replacement therapy (HRT) to protect the endometrial lining from hyperplasia or cancer.

There is no one best regimen for HRT in POF. Treatment depends upon patient preference, side effects, cost, and physician familiarity with the regimens. In a young woman with a uterus, low-dose oral contraceptive pill (OCP) with ethinyl estradiol (EE) and progesterone taken continuously may be satisfactory and easy, and prevent pregnancy. With idiopathic POF, unpredictable return of ovarian function may occur resulting in spontaneous pregnancies in 5 to 10% of affected women. Patients with POF tend to need a higher dose of estrogen compared to older post menopausal women to achieve serum estradiol levels equivalent to pre-menopausal mid-follicular levels. The minimum daily dose of estrogen effective for maintenance of bone health is 0.625 mg of conjugated estrogen (CE), 0.5 mg of micronized U7 β-estradiol, 50 µg of transdermal estradiol, or 5 µg EE (one-quarter the estrogen dose in a low-dose OCP). Progesterone can be given continuously or cyclically and is available in various oral and transdermal preparations. The minimum dose of progesterone to protect the endometrium is 2.5 mg medroxy-progesterone acetate daily or 10 mg medroxyprogesterone acetate cyclically. Micronized progesterone prometrium, can also be used: 100 to 200 µg daily or 200 to 300 µg cyclically. If the patient is experiencing menopausal symptoms, the dose of estrogen can be increased. The transdermal route of estrogen avoids first-pass hepatic metabolism that can minimize the effects on clotting factors and triglycerides and allows a more physiologic continuous infusion of estrogen. If a patch causes local irritation or falls off, estrogen gel, applied daily, is an alternative. Of the vaginal products, menopausal-dose estrogen preparations are not used for systemic HRT but for local symptoms. The combined contraceptive vaginal ring acts systemically and is another newer option for POF.

Ultimately, the treatment must be tailored to each individual patient and is usually discontinued when natural menopause is reached at the age of 50 or 51. In the postmenopausal period, estrogen replacement is associated with increased risk of CVD and breast cancer. Please see Table 1 for a breakdown of product formulations, supplied dosage recommendations, and the equivalent or usual administered dose.

Resources
1. Regier L: Postmenopausal Pharmacotherapy Comparison Chart. www.Rxfiles.ca. Accessed April 10, 2012.
2. SOGC Hormone Therapy Products Available in Canada for Treatment of Menopausal Symptoms. 2nd ed. Physician Desk Reference. menopauseandu.ca/documents/HTbooklet11.pdf. Accessed April 15, 2012.

Answered by:
Dr. Cathy Popadiuk and
Suzy Stever, BSc. Pharmacy

Table 1 Product Formulations	Dosage Supplied	Equivalent or Usual Dose
Estrogen		
Conjugated Equine Estrogen (CEE) *Premarin*	0.3, 0.625, and 1.25 mg tablets	0.625 mg p.o. q.d.
Conjugated Estrogen Sulfate (CES)	0.3, 0.625, and 0.9 mg tablets	0.625 mg p.o. q.d.
Micronized 17β–estradiol *Estrace*	0.5, 1, and 2 mg scored tablets	1 mg p.o. q.d.*
Progesterone		
Medroxy Progesterone Acetate (MPA) *Provera*	2.5, 5, and 10 mg tablets	2.5 mg p.o. q.d. or 5–10 mg p.o. q.d. for 12–14 days per month for uterine protection
Micronized Progesterone *Prometrium*	100 and 200 mg capsules	100–200 mg p.o. q.h.s. or 200–300 mg p.o. q.d. for 10–14 days for uterine protection
Estrogen and Progesterone Combination		
Ethinyl Estradiol and Norethindrone Acetate (NE) *FemHRT*	2.5 µg/0.5 mg and **5 µg**/1 mg	5 µg/1 mg tablet p.o. q.d.
Estradiol/NE *Activelle*	1 mg Estradiol (as hemihydrate) and 0.5 mg NE	1 tablet p.o. q.d.
Activelle Low Dose	0.5 mg Estradiol (as hemihydrate) and 0.1 mg NE	N/A
Estradiol/Drospirenone *Angeliq*	0.5 mg estradiol (E2)/0.25 mg Drosperinone	1 tablet p.o. q.d.
TRANSDERMAL/TOPICAL PREPARATIONS		
Estradiol-17β Patch	25 µg and 100 µg q.d.	25 µg twice a week
Estraderm	25, 37.5, 50, 75, 100 µg q.d.	50 µg twice a week
Estradot (oestradiol)	50, 75, and 100 µg q.d.	50 µg twice a week
Oesclim	25, 50 µg q.d. matrix	50 µg twice a week
Climara	25, 50, 75, 100 µg q.d. matrix	50 µg once a week
Estradiol-17β Topical Gel *Estrogel*	0.75 mg/1.25 g gel	2.5 g gel for 1.5 mg Estradiol, applied to each arm q.d.
Estrogen/Progesterone Combination Patch		
Estradiol–17β/Norethindrone *Estalis*	Estradiol 50 µg a day and NE 140 µg or 250 µg q.d. matrix	Apply twice a week continuously
Estradiol–17β/Levonorgestrel *Climara Pro*	Estradiol 45 µg/day and Levonorgestrel 15 µg q.d.	Worn continuously for one week
Low-dose Oral Contraceptive Pill Comparison		
Alesse	**20 µg** Ethinyl Estradiol and 100 µg Levonorgestrol	**FemHRT has one quarter the Ethinyl Estradiol of Alesse**
Contraceptive Vaginal Ring *NuvaRing*	15 µg Estradiol and 120 µg Etongestrel (active form of Desogestrel Progesterone) per day release	Change every three weeks

* 0.625 mg Premarin = 0.625 mg CES = 1 mg Estrace for equivalents

Surgically Treating a Mucous Retention Cyst

10.

When should a mucous retention cyst of a sinus be treated surgically?

Question submitted by:
Dr. David Hawkins
Kelowna, British Columbia

Mucosal or mucous retention cysts in the maxillary sinuses are common findings on computed tomography (CT) scans. The nature of these cysts and the associated risk factors are not well understood. The incidence is higher in females than in males. They are most commonly located unilaterally as solitary cysts. Smoking is regarded as a single important risk factor. No significant association has been found between nasal and/or respiratory symptoms and the presence of the cysts. Obstruction of the maxillary sinus ostium occurs if the cyst is large and subsequent sinusitis may occur. In these cases, endoscopic surgery is the main course of treatment. On the other hand, if the patient is undergoing nasal surgery for other reasons, such as polyps or deviated nasal septum, the surgeon may elect to excise a retention cyst from the maxillary sinus at the same sitting.

Another type of cyst that could occur in the same location is the radicular cyst, and it should be differentiated from the mucosal variety. Radicular cysts are the most common inflammatory jaw cystic lesions that result from infected and necrotic teeth pulps. They account for over 50% of all odontogenic cysts. Radicular cysts cause slowly progressive, painless swelling. They do not cause any symptoms until they become large. Antibiotherapy should be prescribed and enucleating the radicular cyst is recommended.

The differentiated diagnosis should also include polyps within the sinus cavity, mucoceles, and benign or malignant tumours.

Answered by:
Dr. Ted Tewfik

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