Experts on Call

Answers to your questions from our medical experts

1. Metformin Use in Pregnancy

What are the dangers of metformin in pregnancy?

Submitted by: **Wanda Lints, MD,** Red Sucker Lake, Manitoba

There is no evidence to suggest that metformin, when used in early pregnancy or throughout pregnancy, causes any fetal, neonatal or maternal complications. Indeed, a recent study demonstrated that in women with polycystic ovarian syndrome who used metformin continuously during pregnancy there was a reduction in the rate of miscarriage, gestational diabetes requiring insulin and fetal growth restriction.

Resources

1. Koren G, Gilbert C, Valois M: Metformin Use During the First Trimester of Pregnancy—Is It Safe? Available at: www.motherrisk.org.
2. Nawaz FH, Khalid R, Naru T, et al: Does the Continuous Use of Metformin Throughout Pregnancy Improve Pregnancy Outcomes in Women with Polycystic Ovarian Syndrome? J Obstet Gynaecol Res 2008; 34(5):832-7.

Answered by: **Dr. Victoria Davis**

2. Migraine Therapy for Those with Increased Cardiac Risk

For patients with migraine who are at increased risk for cardiac events (*i.e.*, hypertension, diabetes, previous MI), what is the best anti-migraine therapy? Are triptans contraindicated?

Submitted by: **Atma Persad, MD,** Creston, British Columbia

The most effective medications for treating moderate to severe migraine pain are the triptans. Unfortunately, the triptans are contraindicated if the patient has:

- Known cerebrovascular, cardiovascular, or peripheral vascular disease
- Uncontrolled hypertension
- Known previous hypersensitivity

In addition, it is recommended that if the patient has two or more risk factors for atherosclerotic disease, then they should have a work-up, specifically for cardiac disease. This work-up should include a history, physical, blood work and an EKG. If there is still a question of safety, you can refer your patient to an appropriate specialist for an opinion.

If the patient is unable to take triptans, then migraine treatment should include both optimal prophylaxis, as well as acute treatment. Options for acute treatment are limited, as ergots (including dihydroergotamine) are contraindicated in the same populations as triptans. For this population, opiates are the mainstay of treatment (*e.g.*, codeine). They are often given with anti-nauseants (*e.g.*, dimenhydrinate, metoclopramide). Another option is 975 mg of effervescent ASA in water with 10 mg of metoclopramide. In one study, this was found to give equivalent relief to sumatriptan and this regimen is not contraindicated in patients with cardiac disease.

Resource

1. Papademetriou, V: Cardiovascular Risk Assessment and Triptans. Headache 2004; 44 Suppl 1:S31-9.

Answered by: **Dr. Inge Loy-English**

3. At What Age Can Isotretinoin be Started?

What is the youngest age at which isotretinoin can be used if severe acne is present?

Submitted by: Dennis Glubish, MD, St. Albert, Alberta

Isotretinoin is an oral retinoid approved for treating severe acne. It is dosed according to weight, started low, 0.5 mg/kg q.d., and increased to 1 mg/kg q.d. for up to six months, achieving a cumulative dose of up to 150 mg/kg, to decrease likelihood of relapse. It often produces dramatic improvement after a period of four to eight weeks where there may be a temporary flare.

Isotretinoin has numerous, relatively common, minor side-effects including dry skin, dry eyes, mucous membranes, telogen effluvium and headaches. More importantly, it has potential to cause serious side-effects that require careful prevention and monitoring. Some of these include teratogenicity (including a period after taking the medication), lipid abnormalities, transaminase elevations, decreased night vision, pseudotumor cerebri and depression with suicidal ideation. A rare but relevant complication when treating younger patients includes bone effects such as premature epiphyseal closure. It generally occurs at higher doses and limits long-term therapy. It is important to monitor a child's height before and during therapy with systemic retinoids.

Although there is no definitive answer to this question, a physician experienced with isotretinoin must carefully weigh all the risks of isotretinoin with potential benefits.

Answered by: Dr. Charles Lynde; and Dr. John Kraft

4. Elevation of Creatine Kinase While on a Statin

If a patient develops an asymptomatic but high (> 800) absorption of creatine kinase (CK) on a statin, should it be decreased, continued but monitired? Is it safe to try a different statin?

Submitted by: Warron D. Murschell, MD, Vancouver, British Columbia

Elevation of CK may occur in patients receiving statin therapy and may be associated with symptoms of myositis. When significant elevations of CK (> 10 times normal) occur in the absence of symptoms, one can usually stop therapy and start an alternative therapy such as non-statin cholesterol medication. If the elevation is three to 10 times normal, then one can continue therapy and monitor for symptoms of myositis or more severe elevations of CK. Careful monitoring of the CK levels should be considered when there are factors that may increase the risk of myopathy, such as advanced age, small body size and frailty, in addition to a number of medications/toxins (such as fibrates, macrolides antibiotics, alcohol and even large quantities [> 1 qt.] of grapefruit juice).

Answered by: Dr. Richard Sheppard

5. The Difference Between IBS and IBD

Please elaborate on the difference between irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) and how to diagnose between the two?

Submitted by: Anonymous

IBS is a functional disorder involving abdominal pain or discomfort associated with defecation or a change in bowel habit. The Rome III criteria for the diagnosis of IBS requires recurrent abdominal pain or discomfort at least three days per month in the last three months associated with at least two of the following:

1. Improvement with defecation
2. Onset associated with change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

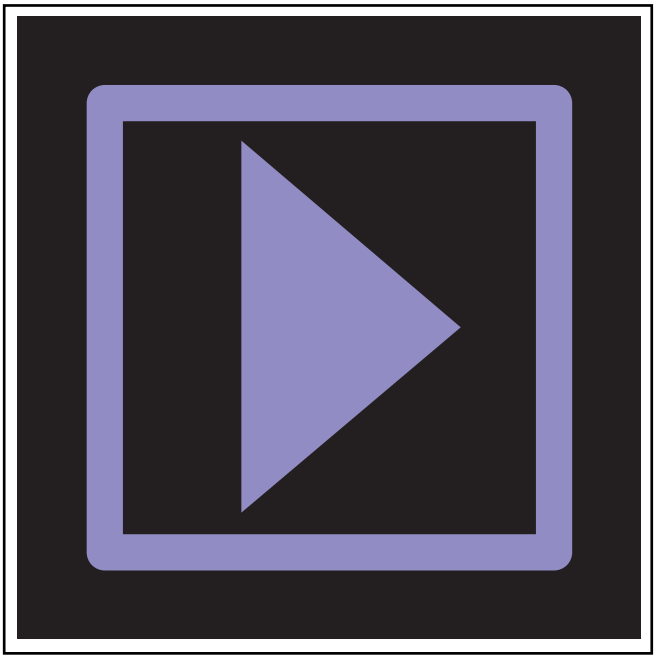
Criteria need to be fulfilled for the last three months with symptom onset at least six months prior to diagnosis. Endoscopy and biopsies of the colonic and small bowel mucosa are normal. Management of IBS is targeted towards dominant symptom control of either diarrhea or constipation. Therapies include loperamide or cholestyramine resin for diarrhea and psyllium husk, lactulose, or magnesium for constipation dominant symptoms.

IBD can be divided into Crohn's disease and ulcerative colitis (UC). Crohn's affects the full thickness of the intestinal wall, most commonly the ileum and colon and can extend from the mouth to the anus. The disease is often patchy with intervening areas of normal mucosa. There may be rectal sparing. UC affects only the colonic mucosa. Inflammation may be present from the anal verge in an uninterrupted pattern to involve all or part of the colon. Both Crohn's and UC have a potential for extraluminal inflammation. Therapy for IBD (*i.e.*, UC) ranges from 5-ASA products and steroids to biologic therapies such as infliximab and adalimumab.

Resources

1. Longstreth GF, Thompson WG, Chey WD, et al: Functional Bowel Disorders. Gastroenterology 2006; 130(5):1480-91.
2. Loftus EV Jr: Clinical Epidemiology of Inflammatory Bowel Disease: Incidence, Prevalence, and Environmental Influences. Gastroenterology 2004; 126(6):1504-17.
3. Podolsky DK: Inflammatory Bowel Disease. N Engl J Med 2002; 347(6):417-29.

Answered by: Dr. Robert J. Bailey; and Dr. Naseem Hoque



6. Practical Work-Up for Chronic Cough or Sore Throats

What is the practical work-up for chronic cough or sore throats?

Submitted by: Mark D. Poulin, MD, Côte-des-Neiges, Quebec

Chronic cough or chronic sore throat often presents as a diagnostic challenge for the clinician. Typically, "chronic" implies persistent symptoms for longer than eight weeks. In both situations, it is imperative to rule out malignancy within the oral cavity, pharynx, larynx or tracheobronchial tree. Alarm bells should sound if either symptom is associated with weight loss, dysphagia, hoarseness or a history of smoking or excessive alcohol intake. A thorough ENT history and examination, with the aid of a chest radiograph if suspicion warrants, should help exclude neoplasia. Chest CT scan, bronchoscopy, needle biopsy and sputum studies may be required if a pulmonary lesion is found.

The most common cause of a chronic sore throat is chronic pharyngitis. This is non-infective and may be triggered by smoking, postnasal drip/chronic sinusitis and acid reflux. History and laryngopharyngeal examination should come together to suggest these diagnoses. With respect to suspected laryngopharyngeal reflux, if flexible nasopharyngoscopy reveals the characteristic laryngeal edema and erythema, laryngeal pseudosulcus, posterior commissure hypertrophy or pachydermia, a trial of PPI should be considered. In some instances, oropharyngeal examination may reveal cryptic tonsils harbouring specks of white debris; chronic infective tonsillitis may be at play here. Rarely HIV infection can indirectly produce a chronic sore throat through secondary infection with oropharyngeal *Candida* or cytomegalovirus. In such situations, serology for HIV should be considered.

The etiologies of chronic cough are numerous. Obvious causes such as smoking and ACE inhibitor use can be easily ascertained through the history. Prospective studies have shown that three conditions account for chronic cough in 92% to 100% of immunocompetent, non-smoking patients with normal chest radiographs. In order of frequency, they are upper airway cough syndrome (UACS), previously referred to as postnasal drip syndrome, asthma and gastroesophageal reflux disease (GERD). Once again, a thorough history and examination are paramount. From both theoretical and cost effectiveness standpoints, empiric treatment of the three most common causes of cough is favoured over extensive testing at the outset. For UACS, this would comprise an oral antihistamine and nasal decongestant with allergy testing for allergic rhinitis or a sinus CT scan for sinusitis, as indicated. Suspected asthma may be evaluated with spirometry and empirically treated with oral leukotriene inhibitors and corticosteroids. The evaluation of GERD has been previously alluded to.

Only when management of the most common causes has failed to resolve symptoms, should a more extensive work-up begin. This can include induced sputum testing for acid fast *Bacillus* and non-allergic eosinophilic bronchitis, a high resolution CT scan of the chest and bronchoscopy.

Answered by: Dr. Jonathan Irish; and Dr. Sanjay Verma

7. Mindfulness Therapy

Please review all indications for "mindfulness" therapy.

Submitted by: J. Molson, MD, Kingston, Ontario

Mindfulness-based stress reduction (MBSR) has been taught and researched in clinical settings in the US for > 20 years and has proved to be of considerable benefit to patients suffering from chronic pain, hypertension, psoriasis, GI disorders and cancer, as well as for psychological problems such as generalized anxiety disorder. Mindfulness training enables patients to access their own resources for responding in positive ways to chronic illness and has been shown to result in both subjective and objective improvements in health status. MBSR is now considered to be one of the mainstream psychosocial treatments in the US and has entered the curriculum of some medical schools.

Mindfulness-based cognitive therapy is an adaptation of MBSR. It combines the ideas of cognitive therapy with meditative practices and attitudes based on the cultivation of mindfulness. It is designed to be used to prevent relapse and recurrence of depression in those who are in recovery, especially for people who had suffered repeated bouts of depression in their lives.

Answered by: Dr. Hany Bissada

8. Annual Limit of Prostatic Biopsies

Is there any limitation on the number of prostatic biopsies a patient can have per year?

Submitted by: John M. Dawson, MD, Richmond Hill, Ontario

There is no limit to the amount of biopsies per year, although there are not many indications for doing multiple series of biopsies in one year. These biopsies are generally very well tolerated especially when proper local analgesia is given. Side-effects include hematuria, hemospermia, blood in the stools and infections that can sometimes lead to sepsis. Clinical judgement and the patient's non-willingness to undergo a second or third series of biopsies per year will often dictate the number of biopsies.

Answered by: Dr. Hugues Widmer

9. How to Approach Significant LDL-C Levels

What approach would you use with significant LDL-C levels and intolerance to all statins and nicotinic acid (positive family history elevated C-reactive protein [CRP])?

Submitted by: Edward W. Papp, MD, Edmonton, Alberta

The first issue is to assess the patient's risk of coronary artery disease (CAD). This can be done with the Framingham risk score which incorporates the patient's age, sex, hypertension, smoking and cholesterol levels. If the patient has a 10-year risk of developing CAD that is > 20%, has known CAD or diabetes for several years, then the target LDL-C is < 2.0 mmol/L.[1] The Reynolds risk score includes a history of parental infarction at < 60-years-of-age and the patient's high-sensitivity CRP to further define the risk categories.[2,3] Target LDL-C is < 3.5 mmol/L if the patient is at intermediate risk of CAD (10-year risk of coronary event 10% to 20%) and < 5.0 mmol/L in the low risk category (10-year risk of coronary event < 10%).

Once the target LDL-C is defined for the patient, antilipemic therapy that is tolerated and effective must be found. Statins are by far the most effective drugs to decrease LDL-C and decrease MIs and strokes. If the patient cannot tolerate a statin or nicotinic acid, then they should be tried on a bile acid resin (cholestyramine resin, colestipol) and/or ezetimibe. Patients at high risk of CAD should be referred to a specialty lipid clinic. Sometimes LDL-C apheresis is required in patients with drug resistant familial hypercholesterolemia and CAD.

References
1. McPherson R, Frohlich J, Fodor G, et al: Canadian Cardiovascular Society Position Statement-Recommendations for the Diagnosis and Treatment of Dyslipidemia and Prevention Of Cardiovascular Disease. Can J Cardiol 2006; 22(11):913-27.
2. Ridker PM, Buring JE, Rifai N, et al: Development and Validation of Improved Algorithms for the Assessment of Global Cardiovascular Risk in Women: The Reynolds Risk Score. JAMA 2007; 297(6):611-9.
3. Reynolds Risk Score: http://www.reynoldsriskscore.org/. Accessed: February 26, 2009.

Answered by: Dr. Bibiana Cujec

10. Best Treatment for Hypercholesterolemia

What is the best treatment for hypercholesterolemia in a patient with intrinsic liver disease (*e.g.*, mild high liver function tests due to hemochromatosis, chronic Hepatitis C, alcohol liver disease)?

Submitted by: Christina Tong, MD, Montreal, Quebec

The statins are the standard of care for treatment of hypercholesterolemia. The safety of using statins in patients with intrinsic liver disease is not well established with robust, prospective clinical trials. Furthermore, there are no head-to-head comparisons among the statins that address this issue. In studies of statins for hypercholesterolemia, there does not seem to be increased risk of adverse events in the subpopulation of patients with liver disease. I would first determine if the patient warrants treatment with a hypercholesterol lowering agent and if they do, then any statin is acceptable with monitoring of their liver enzymes.

Resource
1. Onofrei MD, Butler KL, Fuke DC, et al: Safety Of Statin Therapy In Patients With Preexisting Liver Disease. Pharmacotherapy 2008; 28(4):522-9.

Answered by: Dr. Richmond Sy

11. Neurocardiogenic Syncope vs. Postural Hypotension

How can you distinguish neurocardiogenic syncope from postural hypotension?

Submitted by: Anton Nel, MD, Meadow Lake, Saskatchewan

Neurocardiogenic syncope is transient loss of consciousness precipitated by a stressor, such as standing for a prolonged period, fear or other strong emotion. A catecholamine surge in response to the stressor initially increases the heart rate and contractility. Secondary stimulation of baroreceptors in the ventricles and aorta results in a vagal response with profound bradycardia and withdrawal of peripheral adrenergic tone with hypotension. Neurocardiogenic syncope can be reproduced by a tilt table test in which the patient is strapped to a table that is tilted to 70°. There is venous pooling because of the lack of muscle contraction in the legs to enhance venous return. The decrease in preload precipitates the neurally mediated bradycardia and hypotension.

Postural hypotension is a drop in BP when the patient stands up (> 15 mmHg drop in systolic pressure or > 10 mmHg drop in diastolic pressure). The patient complains of lightheadedness with change in position. Causes include hypovolemia, vasodilator drugs and autonomic neuropathy. Unlike neurocardiogenic syncope, there is usually a compensatory increase in heart rate.

Resource
1. Hendel RC, Patel MR, Kramer CM, et al: Accf/Acr/Scct/Scmr/Asnc/Nasci/Scai/Sir 2006 Appropriateness Criteria For Cardiac Computed Tomography And Cardiac Magnetic Resonance Imaging: A Report Of The American College Of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College Of Radiology, Society Of Cardiovascular Computed Tomography, Society For Cardiovascular Magnetic Resonance, American Society Of Nuclear Cardiology, North American Society For Cardiac Imaging, Society For Cardiovascular Angiography And Interventions, And Society Of Interventional Radiology. J Am Coll Cardiol 2006; 48(7):1475-97.

Answered by: Dr. Bibiana Cujec

12. Urticarial Rash with Arthritis

My patient had a diffuse urticarial rash with arthritis while on trimethoprim-sulfamethoxazole 10 years ago. Can I give her hydrochlorothiazide? What about other sulphonamides?

Submitted by: David Cross, MD, Calgary, Alberta

A sulfonamide is any compound with an SO_2NH_2 moiety. Sulfonamides can be divided into two groups:

- the antibiotics which contain an aromatic amine group (sulfamethoxazole, sulfadiazine, sulfacetamide) and
- the non-antibiotic sulfonamides which do not contain the aromatic amine group (thiazides, furosemide, glyburide, sumatriptan, celecoxib).

The aromatic amine group is felt to be critical for development of hypersensitivity syndrome reactions and severe skin reactions such as toxic epidermal necrolysis.

Although there are many references to cross-reactivity between various sulfonamide medications, cross-reactivity among the sulfonamide antibiotics and non-antibiotic sulfonamides has not been well substantiated in the literature.

Nevertheless, if one is dealing with the potential for a severe reaction such as anaphylaxis, severe drug hypersensitivity and toxic epidermal necrolysis, it is prudent to proceed with caution and avoid using sulfonamide drugs.

In your case with an urticarial rash with arthritis suggesting a serum sickness reaction or drug hypersensitivity syndrome, I would be cautious in using hydrochlorothiazide or furosemide. If possible, an alternative diuretic such as ethacrynic acid or a potassium-sparing diuretic (triamterene, spironolactone or amiloride) would be preferable as these are not sulfonamides.

If there was no appropriate alternative, the patient would need to be started on a low dose of the non-antibiotic sulfonamide and closely monitored. Risks and benefits of this therapy would need to be discussed with the patient. There are reports of desensitization protocols for both sulphonamide antibiotics and non-antibiotic sulphonamides if the drug is absolutely necessary.

I would definitely avoid other sulphonamide antibiotics in your patient as these would also contain the aromatic amine group and a much higher risk of cross-reactivity.

Resource

1. Ponka, D: Approach To Managing Patients With Sulfa Allergy. Use Of Antibiotic And Nonantibiotic Sulfonamides. Can Fam Physician 2006; 52(11):1434-8.

Answered by: Dr. Richard Haber

The aromatic amine group is felt to be critical for development of hypersensitivity syndrome reactions and severe skin reactions such as toxic epidermal necrolysis.

13. Are Drug Allergies Permanent?

Are drug (antibiotic) allergies permanent or can lack of exposure diminish response over long periods of time?

Submitted by: Michel Bernier, MD, Ste-Foy, Quebec

Allergic drug reactions (also known as hypersensitivity reactions) account for about 6% to 10% of all adverse reactions.[1] Penicillin allergy is the most commonly reported medication allergy, with about 10% of patients reporting being penicillin allergic. However, large-scale studies have shown that at least 80% of these individuals are falsely labelled as allergic and can tolerate treatment with penicillin.[2] Careful history taking can identify many of those falsely labelled.

Epidemiologic data on hypersensitivity reactions are scanty and any available information requires cautious interpretation. However, overall reactions rates of 7% to 10% have been described.[3] To my knowledge there are no statistics available with regards to tolerance acquisition of drug allergy, whereas such similar data is available for venom and food allergy. This is in part likely due to the complex and heterogenic nature of drug allergy. There are many mechanisms (*e.g.*, T cell, IgE, immune complex, cytokine mediated) involved and each reaction in each patient presents with unique features with regards to host (genetic polymorphisms, age, race, gender) and environmental (*e.g.*, underlying illness), as well as drug (with multiple metabolites produced *in vivo*) factors. Certainly reactions that have been severe (Stevens-Johnson syndrome, toxic epidermal necrolysis, or interstitial nephritis) should be considered allergic indefinitely. Beeler, *et al*[4] showed evidence of persistence of drug reactive T cells for up to 12 years, highlighting those patients with severe delayed drug hypersensitivity reactions are potentially prone to react again to the incriminated drug, even years after strict drug avoidance. Those with reactions consistent with an IgE mediated mechanism, whether mild or life-threatening, would benefit from an allergy assessment, including intradermal testing procedures. Those allergic patients with non-life threatening reactions may be candidates for desensitization protocols if necessary. In general, the longer the interval since the reaction, the less likely he or she is still allergic and skin testing may help identify those that have "outgrown" their allergy. In fact, IgE antibody responses do dissipate over time (*i.e.*, over several years), especially for haptenic drugs. As is demonstrated for the penicillins, a large majority of patients do lose sensitivity over time (*i.e.*, several years).[5]

References
1. deShazo RD, Kemp SF: Allergic Reactions To Drugs And Biologic Agents. JAMA 1997; 278(22):1895-906.
2. Solensky R: Drug Desensitization. Immunol Allergy Clin North Am 2004; 24(3):425-43, vi.
3. Ilbia EO, Schwartz RH, Wiedermann BL: Antibiotic Rashes In Children. Arch Dermatol 2000; 136(7):849-54.
4. Beeler A, Engler O, Gerber BO, et al: Long-Lasting Reactivity And High Frequency Of Drug-Specific T Cells After Severe Systemic Drug Hypersensitivity Reactions. J Allergy Clin Immunol 2006; 117(2):455-62.
5. Adkinson, N: Chapter on Drug Allergy, Middleton's Allergy, Principles and Practice, pp 1679 (2003).

Answered by: Dr. Tom Gerstner

14. The Relationship Between NSE and Stroke Outcome

Neuron specific enolase (NSE) has been shown to have some utility in predicting brain outcomes post CPR. How about after stroke?

Submitted by: Peter Chee, MD, Richmond, British Columbia

A number of trials have attempted to look at the relationship between NSE and stroke outcome. Unfortunately, available data at this time does not show a great predictive utility. A recent systematic review concluded that levels of NSE probably do correlate with volume of infarcted tissue, but they do not seem to correlate with functional outcomes, or stroke severity.

Resource
1. Anand N, Stead LG: Neuron-Specific Enolase As A Marker For Acute Ischemic Stroke: A Systematic Review. Cerebrovasc Dis. 2005; 20(4):213-9. Epub 2005 Aug 22.

Answered by: Dr. Inge Loy-English

See prescribing summary on page 106

15. Management of Chronic IBS

Chronic irritable bowel syndrome (IBS), what to do for it?

Submitted by: Paul Stephan, MD, Thornhill, Ontario

IBS is a common disorder characterized by the presence of abdominal pain, altered bowel habits (diarrhea, constipation, or both) and accompanying symptoms of abdominal distension, gas and mucus. The presence of organic disease is ruled out in this disorder. Treatment is usually targeted at education, reassurance and dietary modification. Often, pharmacological treatments target key symptoms such as abdominal pain or bowel irregularity. Low dose antidepressants have been commonly used in attempts to modulate the perception and processing of visceral sensation in the central nervous system (CNS). There are several studies that confirm the efficacy of amitriptyline, a tricyclic antidepressant for the treatment of IBS. Selective serotonin reuptake inhibitors (SSRIs) are another class of antidepressants that have also been evaluated for the treatment of IBS. Serotonin (5-HT3) receptor antagonist can inhibit colonic motor activity and 5-HT3 is also found to be involved in afferent information processing at the CNS level. The clinical trials evaluating fluoxetine, citalopram and paroxetine demonstrated modest benefit in treating IBS patients compared to placebo. SSRIs are a valuable option in the treatment of IBS when conservative measures have failed.

Resources
1. Tabas G, Beaves M, Wang J, et al: Paroxetine To Treat Irritable Bowel Syndrome Not Responding To High-Fiber Diet: A Double-Blind, Placebo-Controlled Trial. Am J Gastroenterol 2004; 99(5):914-20.
2. Vahedi H, Merat S, Rashidioon A, et al: The Effect Of Fluoxetine In Patients With Pain And Constipation-Predominant Irritable Bowel Syndrome: A Double-Blind Randomized-Controlled Study. Aliment Pharmacol Ther 2005; 22(5):381-5.
3. Tack J, Broekaert D, Fischler B, et al: A Controlled Crossover Study Of The Selective Serotonin Reuptake Inhibitor Citalopram In Irritable Bowel Syndrome. Gut 2006; 55(8):1095-103. Epub 2006 Jan 9.

Answered by: Dr. Richmond Sy

16. Important Findings in COPD

What are the latest important findings in COPD? What are the results of recent trials in the prevention of COPD exacerbations?

Submitted by: Gary Stephan, MD, Thornhill, Ontario

Three key messages are contained in the most recent Canadian Thoracic Society COPD guidelines: use targeted screening and spirometry to establish an early diagnosis and initiate treatment of mild COPD, improve dyspnea and activity limitation in stable COPD by optimizing pharmacologic and nonpharmacologic management strategies and prevent and manage acute exacerbations of COPD.[1] With respect to the last message, evidence points to a multifaceted strategy to prevent exacerbations including, smoking cessation counselling, administering vaccinations against influenza and pneumococcus and use of appropriate inhaled medications.[1] Recent clinical trials have shown that long-acting bronchodilators, such as tiotropium bromide and long-acting β-2-agonists used in combination with inhaled corticosteroids (*e.g.*, fluticasone/salmeterol or budesonide/formoterol) reduce exacerbation frequency in patients with moderate to severe COPD.[1]

Reference
1. O'Donnell D, Hernandez P, Kaplan A, et al: Canadian Thoracic Society Recommendations For Management Of Chronic Obstructive Pulmonary Disease – 2008 Update - Highlights For Primary Care. Can Respir J 2008; 15(Suppl A):1A-8A.

Answered by: Dr. Paul Hernandez

17. BP Level When Treating Hypertension

How low should BP be allowed to get when treating hypertension and other comorbidities?

Submitted by: Yasmin Mussani, MD, London, Ontario

The relation between BP and CVD risk is continuous. A recent meta-analysis has confirmed that the benefit of BP lowering with antihypertensive medications is also continuous in terms of stroke, MI, heart failure and CV mortality reduction. The Canadian Hypertension Education Program (CHEP) recommends office/clinic BP targets of 140/90 mmHg for all hypertensives and 130/80 mmHg for individuals with diabetes mellitus or chronic renal failure based on clinical trial evidence of the efficacy and safety of achieving these BP levels. The CHEP also recognizes that most patients will require up to three or more antihypertensive medications in order to achieve and maintain these goals.

Patients with certain comorbidities such as coronary artery disease, cerebrovascular or peripheral vascular disease and heart failure frequently receive antihypertensive medications (ACE inhibitors, ARBs, β-blockers) that are considered vasculoprotective or cardioprotective independent of BP reduction based on landmark clinical trials, such as:

- HOPE
- EUROPA
- PEACE
- ONTARGET
- SAVE
- SOLVD
- AIRE
- TRACE
- VALIANT
- CHARM, *etc.*

These studies demonstrated major clinical benefit of taking these medications whether or not the participants had hypertension at baseline and with resultant BPs that were frequently well below the recommended hypertension target values above. For instance, patients with severe left ventricular systolic dysfunction and heart failure do quite well despite systolic BPs often well < 100 mmHg.

As a general rule, the lower the BP that can be safely maintained with well tolerated antihypertensive medications, the lower the CVD risk. Physicians should therefore reassure their asymptomatic patients with regard to the safety of optimal BP control and encourage long-term adherence to evidence-based CVD prevention therapy.

Answered by: Dr. George N. Honos

18. Prescribing Statins in the Elderly

Is it really effective to prescribe statins in the elderly > 80-years-old?

Submitted by: Daniel DesRoches, MD, Gatineau, Quebec

The role of statin therapy in patients who are > 80-years-old ("elderly") remains a topic of controversy. There are no studies examining specifically people > 80-years-of-age. The PROSPER[1] study, however, demonstrated that primary prevention patients (70 years to 82 years) did not show a significant risk reduction in CV events compared to those in secondary prevention. The same study suggested that patients who have coronary artery disease or diabetes, who are between the ages of 70 years and 82 years, have a significant benefit with a reduction in CV events. A recent meta-analysis demonstrated that statins reduce all cause mortality in elderly patients with coronary heart disease (CHD).[2] Thus, statins appear to be a verified medical therapy for elderly patients with CHD, diabetes mellitus and patients at high risk for CHD. Further studies exploring statin usefulness in primary prevention for patients > 75 years to 80 years are needed.

References
1. Shepherd J, Blauw GJ, Murphy MB, et al: Pravastatin in Elderly Individuals At Risk of Vascular Disease (Prosper): A Randomised Controlled Trial. Lancet 2002; 360(9346):1623-30.
2. Afilalo J, Duque G, Steele R, et al: Statins For Secondary Prevention In Elderly Patients: A Hierarchical Bayesian Meta-Analysis. J Am Coll Cardiol 2008; 51(1):37-45.

Answered by: Dr. Richard Sheppard

19. The Role of Melatonin for Insomnia

What role can melatonin play in the treatment of insomnia?

Submitted by: M. E. Robertson, MD, Kingston, Ontario

The hormone melatonin is the primary controller of circadian (day/night) biorhythms. Most of the melatonin in the human body is secreted by the pineal gland, which is 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 adversely affect the circadian biorhythms causing sleep problems, lethargy and mood disorders. Accordingly, melatonin has been used as a therapeutic agent in the treatment of circadian phase disturbances such as jet lag. Also, melatonin can be used in the treatment of insomnia, including initial and middle insomnia. It should be noted that melatonin is available OTC as a natural product in pharmacies and in health food stores. It is not licensed as an approved drug by Health Canada.

Answered by: Dr. Hany Bissada

20. Work-Up for a Patient with Dizziness

What is the practical work-up for the patient with dizziness?

Submitted by: Mark D. Poulin, MD, Côte-des-Neiges, Quebec

The term "dizziness" when used by patients may mean a variety of different sensations, including unsteadiness, imbalance, lightheadedness, disorientation and true vertigo, or a hallucination of movement. The first step in a work-up for the patient with dizziness, therefore, is the identification of the specific complaint, which will determine the focus of further investigation. The primary aim of the work-up is to differentiate whether the dizziness is caused by organic or non-organic (psychogenic) cause. Organic causes require a further differentiation between systemic and peripheral (inner ear) pathology.

Dizziness is associated with many common systemic conditions including CV (arrhythmias, hyper- or hypotension), endocrine and metabolic (diabetes, hypo- or hyperthyroidism, anemia) or neurologic (stroke, multiple sclerosis, small vessels disease) diseases. An iatrogenic dizziness is usually underappreciated and may result from side-effects of medications used for treatment of these common systemic diseases. Psychogenic dizziness is usually associated with a history of anxiety, panic attacks or depression. Thus, a detailed past medical history with specific inquiries on aforementioned conditions and medications is a critical part of the work-up of a dizzy patient. Systemic, organic causes of dizziness can be ruled out by history and general medical examination supplemented by blood work (complete blood count, TSH, glucose, B12 and folate levels), EKG, Holter monitoring, BP determination and brain MRI if indicated. More specific investigations for investigation of peripheral (end organ) causes often require special vestibular testing. The oto-neurologic evaluation with specific bedside manoeuvres (Hallpike test) and a laboratory cochleovestibular battery (hearing test, electronystagmography [ENG], electrocochleography [ECoG] and vestibular evoked myogenic potentials test [VEMP]) provides an objective basis for diagnosis of most common inner ear pathologies associated with dizziness:

- Benign positional vertigo
- Meniere's disease
- Recurrent vestibulopathy
- Acute vestibular neuronitis

Answered by: Dr. Jonathan Irish; and Dr. Vitaly Kisilevsky

21. Treatment Options for Oral Aphthosis

What are some treatment options for oral aphthosis?

Submitted by: Anonymous

Recurrent aphthous stomatitis (recurrent aphthous ulcers, aphthae, canker sores) is perhaps the most common oral concern of patients. It refers to painful, round or ovoid ulcerations of the oral mucosa with inflammatory halos in the absence of systemic disease.

Treatment is challenging but there are multiple agents available to lessen patient suffering and speed healing. Patients should be referred to a specialist if there is associated systemic disease, severe ulceration, or if cancer is suspected.

The treatment of underlying diseases (*i.e.*, anemia, malnutrition) can result in the disappearance of recurrent aphthous stomatitis. Patients should be advised to avoid exacerbating factors and irritating factors such as hard foods (*i.e.*, toast) and hard toothbrushes, acidic drinks and spicy foods.

Various OTC remedies can be tried to soothe lesions. Equal parts of diphenhydramine and aluminum hydroxide and magnesium hydroxide held in the mouth for five minutes before meals can promote relief.

For ulcers that occur more than monthly or are especially painful, other therapies can be tried. Topical anesthetics can relieve pain. Possible regimens include lidocaine viscous 2% solution (1 tsp in mouth for several minutes as needed) or 5% lidocaine gel applied to ulcers four times daily for two weeks or until ulcers heal.

Antimicrobial mouth rinses can speed healing and increase ulcer-free periods if used for prophylaxis. Chlorhexidine gluconate (0.12% or 0.2%) aqueous mouthwash should be swished in the mouth 4 times daily for as long as needed. Patients should be warned that it promotes teeth staining and red wine, tea and coffee intake should be reduced. Teeth should be brushed before use.

The application of a thin film of steroid gels as early as possible in an outbreak can speed healing. Fluocinonide 0.05% ointment with a protective bioadhesive (*i.e.*, a gentle emollient vehicle for oral use), in equal parts, should be applied to lesions three to four times per day for two weeks or until ulcers heal. The main risk of topical steroids is oral candidiasis and an antifungal agent may be added to more potent corticosteroids.

Oral anti-inflammatory antibiotic rinses may also be helpful. Tetracycline can be used as 250 mg in an oral suspension (5 ml in mouth for two minutes then swallowed) four times daily for seven days.

Systemic agents are reserved for extreme cases of severe recurrent aphthous stomatitis. These include oral steroids, dapsone, colchicine and thalidomide.

Answered by: Dr. John Kraft; and Dr. Charles Lynde

22. Acne Rosacea

What are current ideas about treating acne rosacea?

Submitted by: Jane Purvis, MD, Peterborough, Ontario

The newest theory of the etiology of rosacea is that high levels of an antimicrobial peptide (cathelicidin) and its processing serine protease are features of rosacea lesions. This suggests aberrant innate immunity contributes to the development of rosacea. This discovery may lead to new approaches in treating rosacea.

A systematic review of rosacea treatments in 2006 showed that topical metronidazole and topical azelaic acid (not commercially available in Canada) are effective therapies. There is some evidence that oral metronidazole and tetracycline are effective.

Recently, subantimicrobial doses of low dose doxycycline (40 mg q.d.) have been shown to reduce inflammatory lesions of rosacea. This approach lowers the incidence of tetracycline-induced adverse effects while maintainiing effectiveness and appears to reduce the risk of antibiotic resistant strains of bacteria. The 40 mg dose of doxycycline is not commercially available in Canada.

Resources
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Answered by: Dr. Richard M. Haber

23. Managing a Low Potassium Level

How should a low potassium level be treated?

Submitted by: David Hawkins, MD, Kelowna, British Columbia

Hypokalemia, defined as serum potassium < 3.5 mEq/L, is a common electrolyte disorder. Clinical complications include muscle weakness, paralysis, rhabdomyolysis and cardiac arrhymias. Special concern should occur in patients concurrently taking digoxin as the risk of toxicity is intensified. Approach to etiology can be organized as decreased intake, intracellular shifts and increased losses (either renal or GI). Diuretics (thiazide and loop) and diarrhea are the most common causes of hypokalemia. Treatment consists of potassium supplementation via the oral or IV route. Unfortunately, it is difficult to predict the quantity of potassium required for replacement. Severe hypokalemia (potassium < 2.8 mEq/L) should be treated with IV potassium with the maximum being 40 mmol/hr. Mild to moderate hypokalemia should be treated with 40 mmol q.d. to 100 mmol q.d. oral potassium in divided doses. More rapid oral correction can be achieved with potassium elixir as it is more rapidly absorbed than oral tablets.

Answered by: Dr. Manish M. Sood

24. Combining Warfarin and ASA Therapy

Should a 70-year-old patient with diabetes and atrial fibrillation be on both warfarin and ASA?

Submitted by: Steve Choi, MD, Oakville, Ontario

The 70-year-old patient with atrial fibrillation (AF) should be on warfarin particularly if the patient has another risk factor for thromboembolic events (*i.e.*, hypertension, heart failure or prior stroke or arterial embolism). There is no good reason to add ASA for either primary or secondary prevention of coronary artery disease (CAD). Warfarin decreases the risk of MI and although there have not been any studies directly comparing ASA with warfarin vs. warfarin alone for secondary prevention of MI, evidence suggests that combination therapy increases the risk of bleeding without a significant additive benefit on CV endpoints in patients with AF and stable CAD. In a post hoc analysis of the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) trials,[1] which included a high percentage of patients with CV disease or at high risk, combination therapy with warfarin plus ASA in comparison to anticoagulant alone, did not reduce the rate of MI. In addition, warfarin plus ASA was associated with a significant increase in the risk of major bleeding compared to warfarin alone. However, combined ASA and warfarin therapy is reasonable in selected patients with CAD, such as those with acute coronary syndromes or those who receive coronary stents, in whom the potential benefits may outweigh the increased risk of hemorrhage.

The indication for ASA for primary prevention of CV events is equivocal in patients with diabetes. Recommendations for routine use of ASA for primary prevention of CV events were made based on extrapolation from other high-risk subsets (*e.g.*, patients with known CAD).[2] The recently published Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial randomized > 2,500 patients with Type 2 diabetes and without a history of atherosclerotic disease to low-dose ASA (80 mg q.d. to 100 mg q.d.) or a control group. After a median follow-up of four years, ASA was not associated with a significant reduction in the primary composite endpoint, including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, transient ischemic attack and peripheral arterial disease. ASA therapy was associated with an increased risk of GI bleeding and retinal hemorrhage.[3] We need to rethink the need for combined ASA-warfarin therapy for prevention of CV events—usually only one of these medications is required.

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Answered by: Dr. Bibiana Cujec

Erratum

In the Febrary 2009, Volume 26, Number 2 issue of Diagnosis, two **Experts on Call** questions entitled "*Treating Skin Atrophy Due to Steroids*" (p. 24) and "*Using Calcipotriol on the Face*" (p. 44) were published with a few changes still to be made. The following are the revised questions and answers. We apologize to our readers for the error.

Treating Skin Atrophy Due to Steroids

Is there a treatment for atrophy of the skin secondary to the use of steroids?

Submitted by: André Rivard, MD, St-Jean-sur-Richelieu, Quebec

Topical steroids should not be applied for a prolonged period. Atrophy of the epidermis and dermis with telangiectatic skin may occur in some patients even after two to three weeks. Topical steroids have an antiproliferative effect and this may result in thinning of the epidermis and regressive changes in the connective tissue in the dermis. Striae, skin atrophy, telangiectasis, persistent erythema and purpura may occur. The face, dorsa of the hands, extensor surfaces of the forearms and legs and intertriginous (groin, axilla) areas are particularly susceptible. Infants, children and the elderly are prone to striae, atrophy and purpura; steroids should be used with caution.

Unfortunately, there is no special treatment for atrophy of the skin secondary to steroid use. Patients should discontinue applying any topical steroids to the affected area. Instead, consider the use of topical immunomodulators (*e.g.*, pimecrolimus, tacrolimus) which do not cause atrophy with prolonged use.

Answered by: Dr. Charles Lynde; and Dr. John Kraft

Using Calcipotriol on the Face

Can calcipotriol be used safely on the face? How is it best to treat facial psoriasis?

Submitted by: Alok Sood, MD, Toronto, Ontario

Calcipotriol cream is a synthetic 1,25-dihydroxyvitamin D analog indicated for treating psoriasis. It acts on vitamin D response elements in the nucleus, affecting gene expression and, relevant to psoriasis, results in reduced keratinocyte proliferation and inflammation. Although it is rapidly metabolized at the site of application with minimal systemic absorption, if applying large quantities (> 100 g per week), patients should be monitored for hypercalcemia.

Its main side-effect is lesional or perilesional irritation, burning/itching and irritant dermatitis affecting 5% to 10% of patients. Allergic contact dermatitis is very rare.

Since the skin on the face is thinner than other areas (trunk, palms/soles), it may be more susceptible to irritation. In open and uncontrolled studies, topical calcipotriol with application twice daily for six weeks has been shown to be effective and safe in treating psoriasis of the face and intertriginous areas.[1,2]

Facial psoriasis readily responds to mild topical corticosteroids. Low potency corticosteroids (*e.g.*, 1% to 2.5% hydrocortisone and hydrocortisone 17-valerate) can be used twice daily. Even with low-potency steroids, side-effects such as atrophy, telangiectasias and steroid-acne can still occur. Topical calcipotriol is an effective non-corticosteroid alternative for facial psoriasis, with twice daily application being more effective than once daily. Dx

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Answered by: Dr. Charles Lynde; and Dr. John Kraft