Consultant's Corner

Practical Answers To Your Everyday Questions

1. What are the best Iron Supplements to Prescribe?

Is there one iron supplement better than another?

Question submitted by:
Dr. Charles Lynde
Markham, Ontario

The most commonly prescribed types of ferrous iron supplements can be differentiated with respect to their elemental iron concentration. These include ferrous sulfate (20%), ferrous gluconate (12%) and ferrous fumarate (33%).[1] There is little evidence to suggest significant differences in bioavailability amongst the various types of oral iron supplementation.[1] Some data has indicated that sustained-release iron formulations may result in decreased nausea and epigastric pain in comparison to conventional ferrous sulfate, although therapy adherence rates between these formulations have been found to be similar.[2] Furthermore, enteric-coated and sustained release formulations are not as well absorbed as the nonenteric-coated varieties.[1] As such, the prescription of oral iron supplementation should target adequate doses of elemental iron (between 150 to 180 mg per day, given in divided doses), with enhanced gastrointestinal absorption facilitated by concomitant ascorbic acid administration and consumption on an empty stomach.[1]

References
1. Johnson-Wimbley TD, Graham DY: Diagnosis and Management of Iron Deficiency Anemia in the 21st Century. Therap Adv Gastroenterol 2011; 4(3): 177–184.
2. McDiarmid T, Johnson ED: Clinical Inquiries. Are Any Oral Iron Formulations Better Tolerated than Ferrous Sulfate? J Fam Pract 2002; 51(6):576.

Answered by:
Dr. Theodore Xenodemetropoulos

Protocol for Immunizing Patients

2.

Could the expert comment on protocol for immunizing a patient who, in the past, failed to complete the recommended primary series (*i.e.*, Hepatitis A, Hepatitis B, and HPV vaccines).

Question submitted by:
Dr. Aileen Comerton
Ottawa, Ontario

The problem with assessing the best course of action for people who have failed to complete the recommended vaccination protocol is that there is very little empiric data to guide these decisions. Typically, we have only small studies, in vitro data, and/or surrogate markers of protection. We do know, in general, that extending the recommended dosing intervals by a "moderate" amount is theoretically unlikely to have a significant effect on vaccine efficacy.

For Hepatitis A, there is actually modest data that suggests that when the usual two doses are given as much as five years apart (as opposed to the recommended 6 to 12 months), seroconversion is still very high. However, this is an extremely effective vaccine, and this data can not be extrapolated to other vaccines. Also, there are theoretical reasons why shortening the interval between doses is likely to reduce efficacy, and it should be avoided. New protocols for these vaccines continue to be studied. For example, there is quite good evidence for the efficacy of HBV and HPV vaccines when given to adolescents as two doses, four to six months apart. This protocol has actually been adopted in some jurisdictions. However, validation of the duration of protection, and the need for, and timing of, booster doses will have to await long-term follow-up studies. I would suggest that for any given individual, as the risk of infection with these pathogens increases, the wiser it becomes to simply restart the vaccination series and complete a "standard" protocol.

Answered by:
Dr. Michael Libman

How to Use Psychostimulants in Geriatric Depressive Disorder

3. How should you use psychostimulants, like methylphenidate or atomoxetine, in geriatric depressive disorders secondary to medical illness?

Question submitted by:
Dr. Gaetan Y. Lavoie
Sainte-Félicité, Quebec

Root cause analysis will help determine which medication is used. If one thinks of the patient as a diamond, existing on the five facets of the Diagnostics and Statistic Manual (DSM-IV-TR), this job is made easier. According to the DSM-IV-TR, the patient exists on five facets (also known as Axis) and this is the first parameter of root cause analysis.[1] Axis one is the primary mental health condition. Axis two is anything psychiatric that aggravates Axis one. Axis three examines other medical conditions the patient has been diagnosed with. Axis four consists of all psycho-social stressors. Finally, Axis five is the patient's Global Assessment of Functioning (GAF).

The second parameter is the thought process about the medication being used that follows the acronym TAIDCC.

- therapeutically indicated
- allergies checked,
- interactions
- duplications
- compliance and
- cost in side effects are all items to consider[2]

Basically, the DSM-IV-TR Axis and TAICDCC are matched together to ensure optimization of therapy.

Drug interaction disease states and polypharmacy will be the major concerns in psychogeriatrics, as well as a reduction in the metabolized isoenzyme systems, such as the CYP 2D6 system.[3] Using the root cause analysis and blending evidence-based medicine to make an evidence-informed decision is critical. Is Alzheimer's or dementia (vascular, lewy bodies, *etc*.) present, are there psycho-social stressors, is there a loss or bereavement, has the dose of an antidepressant been optimized and reflective of Axis one to three, and so many more questions need to be answered. At this point, low dose methylphenidate appears to have the best evidence in these patient populations, but it must be compared against all of the filters described above, especially cardiac status in the elderly.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Rev. Washington, DC: American Psychiatric Association 2000.
2. Lamoure J: Schizophrenia. Getting the Right Drug to the Right Patient. Pharmacy Practice 2007; 23(4):48–54, 63–64.
3. Lamoure J, Stovel J: Serotonin Syndrome: A Perfect Storm. How to Prevent, Recognize and Manage Serotonin Syndrome. Pharmacy Practice 2011; 27 (2):22–26, 30–31.

Resource

1. Lamoure J: Which Antidepressant Is Right for a Given Patient? The South African Depression and Anxiety Group (SADAG), http://www.sadag.org/index.php?option=com_content&view=article&id=1093&catid=64&Itemid=461 Accessed on March 21, 2012

Answered by:
Dr. Joel Lamoure

Should Levothyroxine be used to Normalize TSH?

4.

An asymptomatic patient on levothyroxine, shows low TSH but FT4, FT3 values well within normal limits on several consecutive tests. Do you decrease the levothyroxine to normalize the TSH?

Question submitted by:
Dr. John E. Dawson
Ottawa, Ontario

A low TSH with a normal FT4 and FT3 suggests Iatrogenic thyrotoxicosis, and a reduction in the dose of thyroxine is generally warranted. You have not specified how low the TSH is. If it is minimally below the reference range, then the risks are probably not increased; however, if the TSH is significantly suppressed or undetectable, this may increase the risk of increasing bone turnover, osteoporosis and atrial fibrillation, and the dose should be reduced accordingly to normalize the TSH.

Answered by:
Dr. Hasnain Khandwala

Initiating Antiviral Treatment for Herpes Zoster

5.

When a patient presents with herpes zoster on day three of infection with fresh lesions, is it still appropriate to initiate antiviral treatment?

Question submitted by:
Dr. Judy Chow
Ottawa, Ontario

All of the controlled clinical trials of antiviral therapy for shingles have initiated treatment within 72 hours of rash onset, an arbitrary criterion that does not necessarily reflect the duration of viral replication. Many diagnoses are delayed, and patients are unable to initiate treatment within this time frame. Unfortunately, there is not much evidence on the efficacy of treatment started after four or more days of symptoms. However, in the trials, there was no difference in pain outcomes when therapy was begun before vs. after 48 hours. There is also some uncontrolled data suggesting that initiation of treatment later than 72 hours has some benefit. For those still forming new lesions, and especially those at high risk of postherpetic neuralgia (*e.g.*, the elderly), it is reasonable to treat even after 72 hours of symptoms. There does not appear to be any benefit for treating longer than seven days.

Answered by:
Dr. Michael Libman

Treating Eczema in Children

6.

What is the best way to treat eczema in a five-year-old that does not sting?

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

When selecting therapy for active eczema, one has to realize that some common treatments can actually be quite irritating. For instance, calcineurin inhibitors often give a burning sensation when applied. This tends to settle down after a few days. While an adult may be able to accept the pain, children will often complain about it and may not allow re-application. Furthermore, many cream formulations of steroids may sting slightly upon application due to stabilizers and preservatives. In general, ointment based treatments are less irritating. Therefore, a therapy approach that includes soothing baths, moisturizer, and an ointment based steroid is usually the less stinging option.

Answered by:
Dr. Scott Murray

Methotrexate and Misoprostol to Induce Therapeutic Abortion?

7.

Can we still use methotrexate and misoprostol to induce a therapeutic abortion (TA) and if so, what is the percentage of efficacy?

Question submitted by:
Dr. Gilbert Blanchard
Bas-Caraquet
New Brunswick

Methotrexate (MTX) and misoprostol (MP) are not approved by Health Canada for the purpose of TA. The Society of Obstetricians and Gynaecologists of Canada (SOGC), however does support the off label use of these agents for this purpose. Namely, "Medical abortion with misoprostol and methotrexate should be considered in carefully selected patients who will be compliant with follow-up. A follow-up system must be in place to provide for surgical evacuation of the uterus if medical abortion fails."[1]

MTX and MP can be used for TA in women with a fetus of less than eight weeks gestational age (GA). The success rate is 90% in women up to 49 days and declines beyond this point. In 78% of women, the products of conception (POC) will pass within 24 hours of the first or second dose of MP. The remainder of women will have a more prolonged course of bleeding, with 10% going on for several days or weeks and up to 5% having retained POC, requiring surgical evacuation. In 1% of patients, an ongoing viable gestation requiring surgical evacuation will occur. MP alone can also induce abortion in the first trimester with similar success rates. For this reason, single agent MP has become the regimen of choice, thus avoiding the possible teratogenic effects of MTX to the fetus if the TA fails and the pregnancy continues. The SOGC is in the process of updating the 2006 guideline to reflect this change in practice. Close monitoring with ultrasound and serial ß HCG levels is critical in the overseeing medical TA. This method requires more patience and commitment than a surgical termination. It can be associated with unpleasant side effects from the medications and prolonged vaginal bleeding, which can be distressing to the unprepared patient. For the appropriate patient, however, it allows for privacy, minimal surgical intervention, and autonomy over the process.

Reference
1. Davis, V.D: Induced Abortion Guidelines: SOGC Clinical Practice Guideline 2006 No 184: www.sogc.org/guidelines/documents/gui184E0611.pdf. Acessed March 21, 2012.

Answered by:
Dr. Cathy Popadiuk
Dr. Vyta Senikas, acting Executive Vice President, SOGC

Treatment for Acute Onset of Seizures in Children

8.

Manufacturers of rectal valium state that it is contraindicated for children under 6-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 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 is using lorazepam, ideally intravenously, but by the rectal or nasal route if intravenous access is problematic.

Answered by:
Dr. Michael Rieder

Kynurenine and Depression

9. Please tell me about kynurenine and depression.

Question submitted by:
Anonymous

Kynurenine is a major metabolite of tryptophan that is produced when tryptophan is metabolized by an oxidative hepatic pathway through the kynurenine pathway. Two metabolites that are produced are serotonin and kynurenine. Kynurenine is subsequently metabolized into kynurenic acid and also quinolic acid. Both agents impact on the N-methyl-D-aspartate (NMDA) receptor. Serotonin has played a major role in depression since the original 1969 Lancet article.[1]

Depression, as such, may be postulated to occur as a result of an imbalance in the oxidative hepatic pathway and from the activation of the kynurenine pathway. In major depressive disorder, there is a decrease in the plasma kainic acid, which is linked to genetic variations. These genetic variations were listed as tryptophan hydroxylase 2 (TPH2), kynurenine 3 mono-oxygenase (KMO), and kynurenine amino transferase 3 (KAT III), which had an impressive p-value showing statistical significance and support for a genetic variation in the kynurenine pathway.[2]

Although not surprising, this supports the clinical hypotheses that inflammatory and cytokene responses may impact depression. Also, genetic variations have a great role to play in affecting the production of kyurenine. Rate-limiting enzymes of kynurenine formation, which include tryptophan 2,3-dioxygenase, and indoleamine 2,3-dioxygenase are activated by stress hormones and/or by proinflammatory cytokines. As such, life stresses that affect cortisol and prolactin may also impact on the production of kyurenine, and potentially, as noted before, on inflammatory processes.[3]

In closing, I believe that kynurenine allows us to go several steps back from the landmark Lancet paper in 1969 that formulated the serotonin hypothesis on depression. Now we can truly start to see the interface of metabolic, genetic, and oxidative pathways from the essential amino acid, tryptophan. New work on brain derived neurotrophic factor (BDNF) and cytokines will open up more channels across time. Most critical to us as clinicians is the interface with our patients with a multifactorial response to treating depression. That is, treatment of psychological and physical pain, addressing autoimmune disorders, the impact of sleep, and many more Axis III concerns impacting on mood and depression. This may allow us to more effectively target psychiatric interventions, beyond mere antidepressant selection.

References
1. Dantzer R, O'Connor J, Freund G., *et al*: Nature Reviews Neuroscience 2008. (9): 46–56.
2. Claes S, Myint A, Domschke K: The Kynurenine Pathway in Major Depression: Haplotype Analysis of Three Related Functional Candidate Genes. Psychiatry Res 2011; 188(3):355–360.
3. Oxenkrug G: Tryptophan – Kynurenine Metabolism as a Common Mediator of Genetic and Environmental Impacts in Major Depressive Disorder: The Serotonin Hypothesis Revisited 40 Years Later. Isr J Psychiatry Relat Sci 2010; 47(1):56–63

Answered by:
Dr. Joel Lamoure

Herpes Simplex Virus Type-specific Serology

10.

Can herpes simplex virus typing be useful in deciding if a patient has had genital herpes or not?

Question submitted by:
Dr. Bernard Sequin
Ottawa, Ontario

Herpes simplex virus (HSV) type-specific serology is of limited value in diagnosing genital herpes. This is because, in Canada, about 50% of genital HSV infections are actually caused by HSV-1. It is speculated that recent improvements in hygiene have resulted in lower rates of herpes labialis in children and, thus, greater numbers reaching adolescence without immunity to HSV-1. Oral-genital exposure in these individuals may lead to genital HSV-1. Thus, absence of HSV-2 antibodies does not rule out genital HSV infection. In addition, the majority of people found to be seropositive for HSV-2 antibodies do not report ever having symptoms of genital HSV. These individuals presumably had subclinical infection. They are probably just as infectious as known HSV-2 carriers during their periods without symptoms. Interestingly, genital HSV-1 infections appear to relapse less often than HSV-2.

Answered by:
Dr. Michael Libman

Is there a Cure for Onychomycosis?

11. Is there a cure for onychomycosis?

Question submitted by:
Dr. James Beacon
Kingston, Ontario

Onychomycosis is the infection of the nail plate by dermatophytes. This is a very common problem, especially in the elderly and it is almost totally resistant to topical therapy. The best therapy for onychomycosis is systemic therapy. While response rates are quite good for terbinafine and itraconazole, long-term "cures" are not always seen. Comparative studies between three to four months of oral terbinafine and pulse therapy with itraconazole were undertaken. Median duration of follow-up was 54 months. At the end of the study, mycological cure without second intervention treatment was found in 34 (46%) of the 74 terbinafine-treated subjects and 10 (13%) of the 77 itraconazole-treated subjects. Mycological and clinical relapse rates were significantly higher in itraconazole vs. terbinafine treated patients (53% vs. 23% and 48% vs. 21%, respectively). Of the 72 patients who received subsequent terbinafine treatment, 63 (88%) achieved mycological cure and 55 (76%) achieved clinical cure.

So oral terbinafine seems to be the best option to try, but a "cure" may require repeat therapy and the patient must appreciate that there may be relapses or failure.

Resource
1. Sigurgeirsson B, Olafsson JH, Steinsson JB, *et al*: Long-term Effectiveness of Treatment with Terbinafine vs. Itraconazole in Onychomycosis: A 5-year Blinded Prospective Follow-up Study. Arch Dermatol 2002; 138(3):353–357.

Answered by:
Dr. Scott Murray

The Normal Reference Range for Serum Ferritin

12. What is a normal serum ferritin?

Question submitted by:
Dr. Sliwowicz
Ajax, Ontario

The normal reference range for any laboratory value really depends on the laboratory equipment, the reagents used, and the population that is being tested. Thus, reference ranges may vary widely from laboratory to laboratory and from location to location. A specific reference range for a laboratory requires sampling from a number of people from the population of interest and determining the mean and two standard deviations from the mean. Statistically, 2.5% of the population will have values less than this range and another 2.5% of the population will have values greater than this range. At our local laboratory, the ranges for normal ferritin are 30 to 400 µg/L (adult male) and 13 to 150 µg/L (adult female). All serum ferritin values should be evaluated with the reference ranges provided by the same laboratory that performed the testing. We would encourage clinicians to become familiar with normal reference ranges of their reporting laboratory.

Answered by:
Dr. Cyrus Hsia and
Dr. Kang Howson-Jan

Long-term Bisphosphonate Use

13.

A 60-year-old woman with no fractures and a T score of -2.5 has been on risedronate for five years. Her bone density study shows a slight decline. Can she come off risedronate, and when should a study be done again?

Question submitted by:
Dr. Gayle Garber
Conception Bay S, Newfoundland

Long-term use of bisphosphonates (BP) has recently come under scrutiny because of the association between their use and atypical femoral fractures. These fractures, though quite uncommon, have mostly been described in patients exposed to long-term (> five years) bisphosphonate use.

The Fracture Intervention Trial Long-term Extension (FLEX) study demonstrated that, though lumbar spine bone mass density (BMD) decreased in women after discontinuing alendronate after five years, no significant increase in clinical vertebral fractures was seen.[1] An increase in nonclinical vertebral fractures was, however, present. Based on these results and the risks associated with long-term BP use, some advocate a drug holiday after five years of BP use in low-risk patients, with periodic monitoring of BMD and fracture risk.

Your patient, however, continues to demonstrate osteoporosis and an ongoing decrease in BMD, despite continuing therapy. I feel that her risk of sustaining an osteoporotic fracture would outweigh the small risk of atypical fractures. You may also wish to evaluate why her BMD is decreasing despite treatment. I would hesitate to stop therapy at this point. She may also benefit from a referral to an osteoporosis specialist.

Reference
1. Schwartz AV, Bauer DC, Cummings SR, *et al*: Efficacy of Continued Alendronate for Fractures in Women with and without Prevalent Vertebral Fracture: The FLEX Trial. JMBR 2010; 25(5):976–982.

Answered by:
Dr. Hasnain Khandwala

Current Recommendations for TB Testing

14.

What are current recommendations for TB skin testing?

Question submitted by:
Dr. B. Bennett
Thunder Bay, Ontario

Current recommendations for tuberculin skin testing, or the recently introduced interferon- (INF-) release assays, emphasize that such testing is to be targeted for one purpose: to identify persons at high risk for TB who would benefit by treatment of latent tuberculosis infection (LTBI). This includes those at high risk of recent infection with tuberculosis and those with infection of any duration at increased risk of progression to active tuberculosis. The identification of these groups should be flexible, and based on local epidemiologic information from cases of tuberculosis. Examples of the first group include recent contacts of a known case of active disease, recent immigrants from certain high transmission regions, and those working in institutions where exposure is relatively common. Examples of the second group include HIV infected individuals, intravenous drug users, those with typical fibrotic lung lesions on radiography, and, in some areas, the homeless. Priorities should be set in conjunction with local public health authorities.

Answered by:
Dr. Michael Libman

How to Approach Platelet Dysfunction

15. How do you approach platelet dysfunction (low or high)?

Question submitted by:
Feryal Sharabyani
Laval, Quebec

Platelet dysfunction is different than having a low or high platelet count. There are numerous causes to consider in platelet dysfunction. Platelets have several functions, including adhesion, secretion, aggregation, and contraction. Platelets also require functioning von Willebrand factor (vWF) in sufficient numbers for proper function. Hereditary defects in any of these can lead to a bleeding disorder. The most common hereditary bleeding disorder is von Willebrand disease.

Acquired causes of platelet dysfunction are more common. Medications, such as ASA, NSAIDs, clopidogrel, and abciximab, should be considered in all patients. Systemic diseases, such as liver disease, chronic renal failure, and myeloproliferative neoplasms, should be considered. Platelet dysfunction should be considered when there is a bleeding diathesis and the work-up excludes abnormalities of platelet numbers, coagulation, and blood vessels. The work-up will require a hematology consultation and specific tests, such as von Willebrand screening, as necessary.

For an approach to low or high platelet count, we should consider the two separately.

There are several causes of low platelet count or thrombocytopenia. By definition, thrombocytopenia is present when a platelet count falls below the reference range that typically ranges from 150,000 to 450,000 per μ/L for most laboratories. This represents two standard deviations from the population mean platelet count, and, as such, 2.5% of the population will have platelet counts less than this. The presence of platelet clumping should be ruled out, as this would suggest pseudothrombocytopenia, a phenomenon that occurs in approximately 0.1 to 0.5% of the population when peripheral blood is collected using ethylenediaminetetraacetic acid (EDTA) as the anticoagulant. True causes of thrombocytopenia can then be classified into problems with marrow production, increased peripheral destruction, or sequestration. Common causes may differ slightly depending on the age of the patient. Typically, drugs and immune thrombocytopenia purpura are the main causes. In elderly patients, over 50- to 60-years-old, myelodysplastic syndromes should also be considered.

For a high platelet count or thrombocytosis, one should consider a primary marrow disease vs. a secondary reactive process. Any of the myeloproliferative neoplasms, and in particular essential thrombocythemia, can result in an elevated platelet count. Usually, there will be a chronic thrombocytosis and other clinical features, such as splenomegaly, the presence of gene mutations, such as the JAK2 mutation, and bone marrow features. More commonly, thrombocytosis is present due to infection/inflammation, recent surgery (especially postsplenectomy), and chronic iron deficiency anemia.

Answered by:
Dr. Cyrus Hsia and
Dr. Kang Howson-Jan

Is Aminolevulinic Acid an Effective Acne Treatment?

16.

In a previous issue of CME, Dr. Murray makes no mention of aminolevulinic acid for acne treatment. Are these not considered effective treatments for acne?

Question submitted by:
Dr. Jim Maytham
Kingsville, Ontario

There seems to be some short- term benefit in patients who undergo this therapy. So far, controlled trials have not established this as a first line therapy for acne.[1] In my experience, the inordinately high costs charged (usually in cosmetic rather than medical facilities) and the need for repeat treatments only makes this an alternative where standard therapies are contraindicated.

Reference
1. Hædersdal M, Togsverd-Bo K, Wulf H: Evidence-based Review of Lasers, Light Sources and Photodynamic Therapy in the Treatment of Acne Vulgaris. Journal of the European Academy of Dermatology and Venereology 2008; 22(3):267–278.

Answered by:
Dr. Scott Murray

Nonstreptococcal Bacterial Infections in the Airway

17. Please comment on the management of nonstreptococcal bacterial infections in the upper airway (*e.g.*, staphylococcal, *Haemophilus influenzae* type B-epiglottitis). Can we culture for these?

Question submitted by:
Dr. Tim Cuddy
Burlington, Ontario

The microbiological diagnosis of unusual upper airway infections is a challenge. Nonstreptococcal pharyngitis generally requires consulting with your local microbiology lab to see what services they offer. Some look only for Group A Streptococcus and may not even identify other hemolytic potential pathogens, such as groups C. and G. Gonococcal pharyngitis can be diagnosed with the proper transport medium and a specific request. Many labs will not be able to diagnose the "atypical" pathogens, such as Chlamydia and Mycoplasma. Very rare agents, such as Corynebacterium diphtheriae, require discussion with a microbiologist.

The availability of tests for the diagnosis of many respiratory viruses that can cause pharyngitis, such as influenza, has improved markedly thanks to the H1N1 pandemic. The relevance of organisms that are commonly carried in the nose and mouth, including Pneumococcus, Haemophilus, and Staphylococcal species is not established, and these agents are generally not identified from throat specimens. Specimens that actually represent the contents of pharyngeal abscesses should be identified as such and are best obtained with a needle and syringe.

The most frequently missed diagnosis in pharyngitis is infectious mononucleosis, which is diagnosed serologically. Since the advent of the Haemophilus vaccine, type B-epiglottitis has become rare, and the disease is now usually less virulent. Surface cultures of the epiglottis may not correspond to blood culture isolates, and their relevance is often unclear. Again, discussion with the lab is in order for these cases.

Answered by:
Dr. Michael Libman