1. How frequently should TSH be taken?

How frequently should TSH be taken when following treatment for hypothyroidism?

Submitted by:
John Dawson, MD
Ottawa, Ontario

Generally when the dose of levothyroxine is adjusted it may take about six weeks to eight weeks to get to a new steady state level and therefore, this is when the thyroid stimulating hormone (TSH) should be remeasured. If you measure the TSH before this, the TSH will be changed, but it will not yet be at a steady level.

Answered by:
Dr. Vincent Woo

2. Prednisone for allergic reactions

When should one prescribe prednisone for allergic reactions?

Submitted by:
Natalie Nimetz, MD
Guelph, Ontario

A short course (five days to seven days) of corticosteroids should be considered for all patients with immediate systemic reactions to:

- foods,
- medications,
- venom stings, as well as
- anaphylactoid reactions to triggers (*i.e.*, radiocontrast dye).

Delayed-type drug reactions leading to severe skin reactions (*e.g.*, urticarial vasculitis) may also require systemic steroid therapy. Systemic reactions to environmental triggers can also occur (*e.g.*, severe asthmatic reactions in response to animal dander) and would require systemic steroids. The most important role of systemic steroid therapy, in the setting of an acute systemic allergic reaction, would be to reduce the likelihood of a protracted or biphasic anaphylactic response.

Answered by:
Dr. Tom Gerstner

3. Following patients on systemic steroids

How should we follow patients that we have placed on systemic steroids to reduce their risk of osteoporosis?

Submitted by:
Mary McKenzie, MD
Toronto, Ontario

Fracture risk on systemic steroids is dose-dependant and occurs early, within the first three months of starting therapy. Studies have shown an increased risk of fracture with doses > 2.5 mg q.d. of prednisone equivalent[1] and adverse effects on markers of bone formation with 5 mg q.d.[2]

With regards to primary prevention and treatment of osteoporosis in high-risk patients using systemic steroids, the 2002 Canadian Osteoporosis Guidelines recommend the initiation of bone-sparing therapy with a bisphosphonate for those receiving > 7.5 mg of prednisone q.d. for longer than three months. Patients receiving > 2.5 mg of prednisone q.d. over a long-term period were also thought to be at increased risk of fracture and require further assessment (at least a bone mineral density [BMD] scan). These recommendations were based on retrospective cohort data out of the United Kingdom.[3]

The 2000 American College of Rheumatology recommendations differ slightly. For patients beginning therapy with > 5 mg of glucocorticoid for at least three months, a bisphosphonate is recommended. In patients already receiving long-term (> 5 mg) glucocorticoid therapy, a BMD scan is recommended before the initiation of a bisphosphonate. If the T-score is not in the normal range (< -1), then a bisphosphonate should be initiated. If it is normal, then an annual or biannual BMD scan is recommended.

Every patient on systemic steroids should be counselled on:

- lifestyle modification (*i.e.*, smoking and alcohol cessation),
- weight-bearing exercises,
- calcium maintenance (1 g q.d.) and
- vitamin D (800 IU q.d.) supplementation.

References
1. van Staa TP, Geusens P, Pols HA, et al: A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. QJM 2005; 98(3):191-8.
2. Ton FN, Gunawardene SC, Lee H, et al: Effects of low-dose prednisone on bone metabolism. J Bone Miner Res 2005; 20(3):464-70.
3. van Staa TP, Leufkens HG, Abenhaim L, et al: Use of oral corticosteroids and risk fractures. J Bone Miner Res 2000; 5(6):993-1000.

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

4. Warfarin and thromboembolic complications

Can patients taking warfarin (with an international normalized ratio of 2.0 to 3.0 for stroke prevention) develop thromboembolic complications and how should they be investigated?

Submitted by:
David Johns, MD
Dundas, Ontario

Yes, patients taking warfarin can certainly develop thromboembolism. Depending on the indications, warfarin generally significantly reduces the risk for thromboembolism, but does not reduce it to what would be expected in the normal population. For example, warfarin administered for stroke prevention in patients with atrial fibrillation has been reported to reduce the risk of ischemic stroke by 68% (whereas the risk is reduced by only 44% for patients on 325 mg of acetylsalicylic acid). For patients in a hypercoagulable state (*i.e.*, patients with malignancy and/or remote thromboembolism), coumadin is likely to be less protective. Of note, the incidence of hemorrhagic complications generally increases in warfarin-treated patients, particularly in:

- overly anticoagulated patients,
- patients with poorly controlled hypertension and
- the elderly population.

Answered by:
Dr. Igal A. Sebag

5. Managing a cold thyroid nodule

What are the steps to take with a cold thyroid nodule and what are the follow up measures?

Submitted by:
I. D'Souza, MD
Willowdale, Ontario

It is recommended that if a cold nodule is found by a thyroid scan, a fine needle aspiration biopsy of the thyroid nodule should be performed to ascertain the nature of the nodule or cyst.

Follow up will depend on the results of the fine needle aspiration biopsy.

Answered by:
Dr. Vincent Woo

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6. Assisting cannabis withdrawal

? Are there any drugs to assist in cannabis withdrawal?

Submitted by:
Réjean Falardeau, MD
Bromont, Quebec

Until the 1990s, it was generally believed that cannabis use did not result in a true dependency syndrome. However, recent human studies have consistently demonstrated that a significant number of chronic cannabis users have difficulty quitting or, with cessation of use, develop a time-dependent set of withdrawal symptoms, including:

- Decreased appetite
- Anxiety
- Irritability
- Stomach pain
- Depression
- Sleep difficulties

At present, most treatment programs for cannabis dependence or abuse depend on individual or group psychotherapeutic interventions, such as:

- cognitive-behavioural relapse prevention,
- motivational enhancement therapy,
- coping-skills therapy and
- aversion therapy.

Published studies of pharmacologic interventions for cannabis abuse or withdrawal symptoms are scarce. A handful of small clinical trials have examined the effects of bupropion, oral Δ9-tetrahydrocannabinol (THC) (a cannabinoid agonist) and divalproex on withdrawal symptoms. Bupropion use was associated with increased irritability and depressed mood compared to placebo; divalproex decreased cannabis cravings and increased appetite but worsened mood and cognitive performance. Compared to placebo, the administration of oral THC during abstinence, following a period of daily cannabis use, decreased cannabis craving, increased appetite, and reduced anxiety and sleep disturbances, but had no effect on other withdrawal symptoms. A single animal study has suggested a role for lithium in the prevention of cannabis withdrawal symptoms via oxytocinergic neuronal activation.

Overall, results from these few studies suggest that oral THC and potentially lithium may be useful in the treatment of cannabis withdrawal symptoms. However, the use of pharmacotherapy in the treatment of cannabis abuse is a new and unexplored area of research; use of drugs for cannabis withdrawal symptoms is, at present, largely experimental.

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

Answered by:
Dr. Hany Bissada; and Ms. Jodi Taryn Heshka

7. Correcting an undescended testis

? At what age should an undescended testis be corrected to avoid the risk of infertility and/or cancer?

Submitted by:
J. V. Patidar, MD
Edmonton, Alberta

A palpable undescended or cryptorchid testis is found in 3% to 5% of newborns and in 30% of babies born prematurely. Bilateral undescended testis occurs in 15% of newborns with cryptorchidism. Most undescended palpable testes later descend spontaneously, so that only 0.7% to 1% of one-year-old infants have a persistent undescended testis. The incidence does not change after one year of age.

The risks related with an undescended testis are:

- testicular cancer,
- infertility,
- trauma,
- testicular torsion and
- psychological effects.

Although these risks are low, they can cause potential morbidities in patients.

The main goals of treatment are the preservation of fertility and hormonal production and the diagnosis of potential testicular malignancies. Other benefits include correction of associated hernias and the prevention of testicular torsion. Correction of the cryptorchid testis does not reduce the risk of cancer, but makes diagnosis easier because the testicle is readily palpable (in patients with cryptorchidism, the risk of testicular cancer is 3% to 5%, a four-fold to seven-fold increased risk compared with the 0.3% to 0.7% risk in the healthy population). Classically, treatment is offered after the patient is one-year-old, but some advocate treatment as early as six months because spontaneous descent is rare after this point.

Answered by:
Dr. Hugues Widmer

Classically, treatment is offered after the patient is one-year-old, but some advocate treatment as early as six months because spontaneous descent is rare after this point.

8. Combining H2 receptor blockers and PPIs

Is there any advantage in combining H2 receptor blockers and PPIs to treat peptic ulcer disease?

Submitted by:
S. Chaudhry, MD
Toronto, Ontario

Proton pump inhibitors (PPIs) act on the final common pathway by which the gastric parietal cell produce acid. Therefore, it should be 100% effective in suppressing gastric acid secretion and negate the need for medications that only partially suppress acid secretion (as in histamine-2 [H2] receptor blockers). However, patients represent a wide spectrum of:

- pathologic disease severity,
- symptomatolgy and
- response to treatment.

Severe peptic ulcer disease or gastroesophageal reflux disease states that do not respond satisfactorily to PPI q.d. therapy are usually upgraded to PPI therapy b.i.d. This is effective in most, but persistent symptoms have been described in a number of patients; this has been attributed to breakthrough acid secretions at night. Some data is available, in fact, to support the use of nightly H2 blocker administration in combination with PPI therapy b.i.d. to relieve the nocturnal acid breakthrough. Therefore, combining PPIs and H2 blocker therapy is only justified in the small number of patients that experience breakthrough nocturnal symptoms despite maximal PPI dosage.

Answered by:
Dr. Robert Bailey; and Dr. Ali Cadili

Combining PPIs and H2 blocker therapy is only justified in the small number of patients that experience breakthrough nocturnal symptoms despite maximal PPI dosage.

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9. Pimecrolimus, tacrolimus and cancer

Is there really a link between pimecrolimus, tacrolimus and cancer, or are atopic patients simply more at risk for cancer?

Submitted by:
Mona Lee, MD
North Vancouver,
British Columbia

Pimecrolimus and tacrolimus are topical calcineurin inhibitors indicated for the second-line treatment of short-term and intermittent atopic dermatitis. The US Food and Drug Administration reported 19 postmarketing reports linking tacrolimus with cancer-related events, including lymphomas and skin tumours, many at the site of topical application. A causal relationship has not been established.

In the spring of 2006, a Dear Doctor letter was distributed regarding a revised product monograph warning for pimecrolimus and tacrolimus, emphasizing that continuous long-term use of these agents should be avoided. While there is growing interest in the potential link between atopy and cancer, data regarding this association has been conflicting. On the one hand, the heightened immune surveillance associated with atopy may confer a protective effect against carcinogenesis. Conversely, recurrent inflammatory damage and repair may increase this risk.

Based upon epidemiologic studies, atopy has been linked to an increased risk of:

- lymphomas,
- childhood leukemias and
- gliomas.

Further studies are required to assign a causal attribution.

Answered by:
Dr. Sharlene Gill

While there is growing interest in the potential link between atopy and cancer, data regarding this association has been conflicting.

10. Routine drug screening and crystal meth

? Does crystal meth show up on a routine drug screen? For how long?

Submitted by:
Julie Curwin, MD
Sydney, Nova Scotia

Methamphetamine (S-N-methyl-1-phenyl-propan-2-amine) is a highly addictive sympathomimetic drug. Methamphetamine is metabolized by the liver, excreted almost entirely (> 90%) in the urine and has a half-life of approximately nine hours to 15 hours. Approximately 25% of methamphetamine is excreted unchanged, while the remainder appears in the urine as amphetamine or other metabolites. Excretion depends heavily on:

- urinary pH,
- amount used,
- fluid intake and
- renal flow rate.

Peak serum levels of methamphetamine depend on the route of ingestion; levels peak within two hours to four hours after oral ingestion, but within minutes of smoking or intravenous injection. Urinary methamphetamine can be detected routinely by standard commercial immunoassay techniques. The assay can detect methamphetamine for up to 72 hours after use of the drug.

Resources
1. Caldwell J: The metabolism of amphetamines in mammals. Drug Metab Rev 1976; 5(2):219-80.
2. Cho AK, Wright J: Pathways of metabolism of amphetamine and related compounds. Life Sci 1978; 22(5):363-72.
3. Couper FJ, Logan BK: *Drugs and Human Performance Fact Sheets.* National Highway Traffic Safety Administration. 2004, pp. 3-100.
4. National Institute on Drug Abuse (NIDA) Community Drug Alert Bulletin-Methamphetamine. 1998.
5. Shimosato K, Tomita M, Ijiri I: Urinary excretion of p-hydroxylated methamphetamine metabolites in man. Arch Toxicol 1986; 59(3):135-40.
6. Beckett AH, Rowland M: Urinary excretion of methylamphetamine in man. Nature 1965; 206(990):1260-1.

Answered by:
Dr. Hany Bissada; and Ms. Jodi Taryn Heshka

Approximately 25% of methamphetamine is excreted unchanged, while the remainder appears in the urine as amphetamine or other metabolites.

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11. LABAs and COPD

? Are LABAs of any clinical benefit in COPD?

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

Long-acting ß2-agonists (LABAs), such as salmeterol or formoterol, have a duration of action lasting 12 hours and are taken as inhaled medications b.i.d., either alone or in combination with inhaled corticosteroids, for the treatment of chronic obstructive pulmonary disease (COPD). In COPD, there is evidence that LABAs:

- are effective bronchodilators (*i.e.*, improve forced expired volume in one second),
- improve exercise tolerance (*i.e.*, on standardized cardiopulmonary exercise testing),
- relieve dyspnea and
- improve health-related quality of life.

The Canadian Thoracic Society recommends the use of a long-acting bronchodilator (either a LABA or long-acting anticholinergics, such as tiotropium) for patients with persistent dyspnea and exercise intolerance, despite the regular use of a short-acting bronchodilator (at least b.i.d.).

Resource
1. O'Donnell DE, Aaron S, Bourbeau J, et al: State of the art compendium: Canadian Thoracic Society recommendations for the management of chronic obstructive pulmonary disease. Can Respir J 2004; 11(SupplB):3B-59B.

Answered by:
Dr. Paul Hernandez

LABAs, such as salmeterol or formoterol, have a duration of action lasting 12 hours and are taken as inhaled medications b.i.d., either alone or in combination with inhaled corticosteroids, for the treatment of COPD.

12. Chronic constipation vs. IBS

How can we distinguish chronic constipation from IBS?

Submitted by:
Guy Tellier, MD
Saint-Jérôme, Quebec

According to the Rome III diagnostic criteria for irritable bowel syndrome (IBS) released in 2006, IBS by definition primarily requires pain. Recurrent abdominal pain or discomfort must occur at least three days per month, in the last three consecutive months with symptom onset of at least six months prior to diagnosis. In addition, the pain must be associated with two or more of the following:

- improvement with defecation,
- onset associated with a change in frequency of stool and/or
- onset associated with a change in the form (appearance) of stool.

Therefore, the constipation itself is not the predominant complaint.

If a patient presents with constipation but without pain, IBS cannot be diagnosed; however, dysfunctional bowel or primary constipation should be considered in the differential diagnosis. Therefore, secondary causes for constipation must be ruled out. Anorectal motor abnormalities or colorectal cancer should be considered. In addition, colonic inertia may be caused by:

- medications,
- metabolic dysfunction, or
- neurological conditions.

A primary work-up should include:

- full history,
- physical exam (including rectal exam),
- investigations including thyroid stimulating hormone,
- random glucose level,
- calcium levels,
- magnesium levels,
- phosphate levels, as well as
- an abdominal x-ray and/or
- barium enema.

If worrisome features arise or no cause for secondary constipation can be found, referral to a gastroenterologist for possible colonoscopy should be considered.

Answered by:
Dr. Robert Bailey; and Dr. Marilyn Zeman

13. Glucosamine use in shellfish allergy

Why is glucosamine use contraindicated in shellfish allergy?

Submitted by:
L. Pilot, MD
Saskatoon, Saskatchewan

Glucosamine, which plays a role in cartilage formation and repair, has been suggested to restrict the progression of knee osteoarthritis. Sold as a nutritional supplement, a warning label instructs patients allergic to shellfish to consult a physician because glucosamine is derived from crab, lobster or shrimp shells. As there are no clinical trials to establish its safety in this population, it seems prudent to advise patients with shellfish allergy to avoid this therapy. However, shellfish allergy is caused by IgE antibodies to tropomyosin in the flesh of the shellfish and not the shell, suggesting it should be safe in these patients. Gray, *et al*[1] studied six patients with a known systemic reaction to shellfish and skin test positivity. All six were skin tested to a 1/20 wt/vol extract of glucosamine (all negative) as well as repeated skin testing to crab, lobster and shrimp (all positive to one or more of these). All patients then underwent successful oral challenges to glucosamine. Although this suggests that glucosamine is probably safe in these patients, the authors indicate that this is a pilot study requiring confirmation of a larger trial. At this point, if a shellfish allergic patient wishes to proceed with this therapy, further assessment for skin test reactivity followed by an oral challenge in a controlled setting would be advised.

Reference
1. Gray HC, Hutcheson PS, Slavin RG: Is glucosamine safe in patients with seafood allergy? J Allergy Clin Immunol 2004; 114(2):459-60.

Answered by:
Dr. Tom Gerstner

At this point, if a shellfish allergic patient wishes to proceed with this therapy, further assessment for skin test reactivity followed by an oral challenge in a controlled setting would be advised.

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14. Treating pneumonia in patients with COPD

What would be an appropriate antibiotic choice to treat pneumonia for a patient with significant co-morbidity (*e.g.*, chronic obstructive pulmonary disease [COPD]) who has recently received a fluoroquinolone?

Submitted by:
Mark Enright, MD
Collingwood, Ontario

Management of community-acquired pneumonia (CAP) is based upon a number of factors.[1] Empiric antibiotic therapy is determined by the most likely organisms responsible for CAP. In patients without modifying factors, the most common bacterial organisms include:

- *Streptococcus pneumoniae*,
- Chlamydia pneumoniae and
- Mycoplasma pneumoniae.

For any patient that needs repeated antibiotics to treat a lower respiratory tract infection within a three month period, it is sensible to choose another class of antibiotics to minimize the risk of treatment failure due to the emergence of antibiotic resistance. The patient described in this question has two modifying factors (*i.e.*, COPD and recent treatment with a fluoroquinolone antibiotic) and as a result, other pathogens must be covered, including *Haemophilus influenzae* and enteric gram-negative rods.

A respiratory fluoroquinolone would normally be part of the initial management of a COPD patient with CAP. However, as the patient in this question was recently treated with a fluoroquinolone, the Canadian Guidelines for the initial management of CAP would recommend that:

1. If the patient was well enough to be managed as an outpatient or in a medical ward, that they be treated with either amoxicillin-clavulanate acid or second generation cephalosporin and a macrolide
2. If the patient required management in an ICU and infection with pseudomonas aeruginosa was not a concern then they should be treated with an intravenous third generation cephalosporin (*e.g.*, ceftriaxone or cefotaxime) or ß-lactam/ß-lactamase inhibitor combination and a macrolide.[2] Dx

References
1. Fine MJ, Auble TE, Yealy DM, et al: A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336(4):243-50.
2. Mandell LA, Marrie TJ, Grossman RD, et al: Summary of Canadian Guidelines for initial management of community-acquired pneumonia: An evidence-based update by the Canadian Infectious Disease Society and the Canadian Thoracic Society. Can J Infect Dis 2000; 11(5):237-48.

Answered by:
Dr. Paul Hernandez