Chronic urticaria: What diagnostic evaluation is best?

Evidence-based answer

A detailed history and 6-week trial of an H1 antihistamine are the best diagnostic evaluations for chronic urticaria. More extensive diagnostic workup adds little, unless the patient's history specifically indicates a need for further evaluation (strength of recommendation: B, inconsistent or limited-quality evidence).

Evidence summary

Chronic urticaria affects 1% of the general population and is usually defined as the presence of hives (with or without angioedema) for at least 6 weeks.

History and physical are key, a few tests may be useful

A systematic review of 29 studies involving 6,462 patients done between 1966 and 2001 found no strong evidence for laboratory testing beyond a complete history and physical. However, the authors recommended that patients with chronic idiopathic urticaria have an erythrocyte sedimentation rate (ESR) measurement, white blood cell (WBC) count, and differential cell count.

Is aggressive testing worth the effort?

It would appear not. A prospective study of 220 patients, representative of the studies included in the systematic review, compared 2 strategies to evaluate the cause of chronic urticaria:

1. Detailed history taking and limited laboratory testing (hemoglobin, hematocrit, ESR, WBC count, and dermatographism test [hives associated with a scratch])
2. Detailed history taking and extensive laboratory evaluation with 33 different tests, many of them special and invasive (radiographs, vaginal cultures, and skin biopsies).

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Detailed history taking and limited laboratory tests found a cause for urticaria in 45.9% of patients, compared with 52.7% of patients who underwent detailed history taking and extensive laboratory screening.4 This translates into testing 15 patients aggressively to diagnose one potentially reversible cause of chronic urticaria.

Among patients evaluated with a detailed history and extensive diagnostic workup, 33.2% had physical urticaria (triggered by pressure, cold, heat, and light). Other diagnoses included adverse drug reactions (8.6%), adverse food reactions (6.8%), infection (1.8%), contact urticaria (0.9%), and internal disease (1.4%). No cause was identified in 47.3% of the patients.4

**Recommendations**

The British Association of Dermatologists has issued the following guidelines for evaluation and management of urticaria in adults and children5:

- The diagnosis of urticaria is primarily clinical.
- Diagnostic investigations should be guided by the history and should not be performed in all patients.6

### Differential diagnosis of urticaria

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<th>Differential Diagnosis</th>
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<td>Bullous pemphigoid (prior to vesicle formation)</td>
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<td>Dermatitis herpetiformis</td>
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<td>Drug eruption</td>
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<td>Erythema marginatum</td>
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<td>Erythema multiforme</td>
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<td>Papular urticaria</td>
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<td>Pruritic urticarial papules and plaques of pregnancy (PUPPP)</td>
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<td>Still's disease</td>
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<td>Urticaria pigmentosa</td>
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<td>Urticarial vasculitis</td>
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### References

Dear EBP Readers,

The rarest questions in Evidence-Based Practice are those about cost effectiveness. There are at least 4 reasons why this might be so. First, cost-effectiveness analyses can only be done when the magnitude of effect of a medical intervention is well documented. Second, they require quantification of nebulous outcomes such as quality of life. Third, most of our authors are not likely familiar with this type of research. Finally, answering a question about cost effectiveness requires knowing what medical services actually cost.

I learned how tough assessing cost can be after I had a series of medical procedures last year for an impacted kidney stone. As the bills rolled in, it became clear that the charges had no relation to the cost of the services. Here are a few choice numbers.

First off, let me thank my insurance company. After paying them a total of $90,000 in premiums over 10 years of perfect health (and $60 cash), I was able to access $47,000 worth of medical care. As a matter of fact, my insurance company arm-twisted the medical establishment into accepting only $32,700 for all this good stuff.

So where’s my rebate?

Also, why did my anesthesiologist get more insurance money than my urologist for my kidney stone surgery? I can easily envision the anesthesiologist reading Field & Stream while my urologist was actually working. Why did the radiology department bill $1,100 for renal ultrasound but accept only $180 for the same service? Do you get an 85% discount if you’re skinny and your kidneys are easy to get at?

I wish I could remember some of it!

So ultimately, I am left with absolutely no idea how much any of this really cost. But, then again, having a painful kidney stone removed is . . . priceless.

Regards,

Jon O. Neher, MD
This RCT assigned 7,376 patients with moderate or severe COPD without asthma to receive either tiotropium 18 µg daily plus placebo salmeterol BID or salmeterol 50 µg BID plus placebo tiotropium daily for 1 year. Patients were allowed to continue other COPD medications such as inhaled glucocorticoids. Outcomes included time to first COPD exacerbation, risks and annual rates of COPD exacerbations, as well as adverse events and mortality.

Time to first COPD exacerbation was longer in the tiotropium group (187 days vs 145 days in the salmeterol group; HR 0.83; 95% CI, 0.77–0.90; \( P < .001 \)). Tiotropium was also superior to salmeterol when comparing risk of moderate COPD exacerbations (NNT for 1 year = 36), severe COPD exacerbations (NNT = 48), exacerbations leading to use of antibiotics (NNT = 31), and exacerbations leading to use of systemic glucocorticoids (NNT = 26). This benefit of tiotropium over salmeterol persisted regardless of current smoking status or concurrent inhaled steroid use.

**Bottom line:** Prior to this study, the evidence was weak for choosing an anticholinergic over a beta2-agonist as a long-acting inhaled bronchodilator for patients with moderate or severe COPD. This evidence is convincing that the long-acting anticholinergic (tiotropium) is more likely to be effective than a long-acting beta2-agonist (salmeterol) for prevention of COPD exacerbations.

Our review of data from an electronic health record of 130 family physicians and general internists showed that these primary care physicians were using salmeterol and tiotropium in roughly even numbers. Based on this finding, we believe this study justifies a change in practice: use tiotropium when starting a patient on a long-acting bronchodilator, or switch to tiotropium if a patient is not well controlled with salmeterol.

**Bottom line:** The use of the implantable contraceptive rod between 1 and 3 days postpartum does not interfere with breastfeeding, and early postpartum insertion increased the chances of a woman using contraception, compared with 87% in the standard insertion group \( (P = .04) \).

### Relevant

**Relevant:** Is the topic relevant to family medicine?

**Valid:** Are the findings scientifically valid?

**Change in practice:** Would this change practice?

**Medical care setting:** Is this implementable in clinic, etc?

**Implementable:** Can we implement this immediately?

**Clinically meaningful:** Are results clinically meaningful?

### Tiotropium and COPD exacerbations


### Postpartum use of contraceptive implant


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**Postpartum use of contraceptive implant**

This randomized controlled noninferiority trial included 69 healthy peripartum women who expressed an interest in implantable contraception (Implanon®). The trial assigned women to postpartum insertion that was early (1–3 days) or standard (4–8 weeks).

Early insertion was noninferior to standard insertion in time to lactogenesis (defined as the time at which the mammary glands begin producing copious amounts of milk; 64.3 vs 65.2 hours; mean difference –1.4 hours; 95% CI, –10.6 to 7.7 hours). No significant differences were noted between the 2 groups in the rates of supplementation with formula, the rate of exclusive breastfeeding, or in the fat and energy content of the breast milk. Bleeding patterns were similar between the 2 groups at 6 months. At 6 months, 100% of patients in the early insertion group were using some form of contraception, compared with 87% in the standard insertion group \( (P = .04) \).

### Relevant

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<th>Relevant</th>
<th>Medical care setting</th>
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SSRIs associated with small increase in birth defects

This retrospective cohort study used the Finnish birth registry (>600,000 births, still births, & terminations) to identify relationships between SSRI exposure in pregnancy and congenital anomalies. Registry data were matched with a national prescription database. Congenital anomalies were compared between children whose mothers took SSRIs 1 month before conception through the first trimester and children with no such SSRI exposure. Results were adjusted for other known risks for congenital abnormalities.

6,976 offspring were exposed to SSRIs during early pregnancy, most commonly citalopram (2,799), followed by fluoxetine (1,818), paroxetine (968), and sertraline (869). The rate for all congenital anomalies was 434/10,000, compared with 355/10,000 in those with no exposure (adjusted odds ratio [AOR] 1.08; 95% CI, 0.96–1.22). There was a much higher rate of fetal alcohol spectrum disorders among liveborn children with SSRI exposure (AOR 9.6; 95% CI, 4.6–20).

Fluoxetine specifically was associated with higher risk of ventricular septal defect (AOR 2.03; 95% CI, 1.28–3.21). Paroxetine was associated with higher risk of right ventricular outflow tract anomalies (AOR 4.68; 95% CI, 1.48–14.74). Citalopram was associated with higher risk of neural tube defects (AOR 2.46; 95% CI, 1.2–5.07).

Bottom line: The overall rate of congenital abnormalities was no higher among SSRI-exposed than unexposed children. However, exposures to fluoxetine, paroxetine, and citalopram were each associated with significant risk of specific types of anomalies. Fetal alcohol syndrome was also more common among exposed children overall. When considering drug treatment for depressed pregnant women, provide counseling about the unique risks of SSRIs, and discourage excessive alcohol consumption.

Article Reviewer and Summary Author: Kate Rowland, MD

Sleep counseling for children: Pediatric sleep counseling not quite ready for primary care

This RCT enrolled 108 children whose parents identified them (through a standardized questionnaire) as having moderate to severe behavioral sleep problems at the time of kindergarten enrollment. The families were randomized to receive either three 2-hour sleep counseling sessions from a trained psychologist and nurse and follow-up phone calls or no intervention. The children were evaluated at 3, 6, and 12 months after the intervention. The primary outcome was the score on the Child Sleep Habit Questionnaire (CSHQ), a validated 100-point scale in which higher scores indicate increased problems with sleep.

At 3 months, children in the intervention group had a mean score of 46 compared with a mean score of 48 for children in the control group (mean difference –2; 95% CI for difference, –4.6 to –0.2, P=.03); at 6 months the intervention group scored 45 compared with 49 in the control group (mean difference –4.0, 95% CI, –6.5 to –1.4, P=.003). Similar effects were seen at 12 months.

Bottom line: The 2- and 4-point improvements in the 100-point CSHQ are not clinically meaningful. We also think that most physicians are unable to access a trained sleep counselor to provide 6 hours of sleep information and patient education.

Article Reviewer and Summary Author: Kate Rowland, MD

Erratum
The December 2011 Diving for PURLs article, entitled “A simple 2-step model for diagnosing obstructive sleep apnea,” noted that Medicare will not cover CPAP treatment for OSA diagnosed in a home setting.

However, Medicare does cover CPAP for OSA diagnosed with some forms of home testing, but it currently does not cover CPAP for OSA diagnosed with ApneaLink on a national level.
What is the most effective therapy for vasomotor rhinitis?

Evidence-Based Answer
Symptoms of vasomotor rhinitis (VR) may be reduced with:
- Intranasal fluticasone propionate (SOR: A, based on a meta-analysis of RCTs)
- Intranasal azelastine (SOR: B, based on one RCT)
- Intranasal ipratropium bromide (SOR: B, based on one RCT)
- Acupuncture (SOR: C, based on one low-quality RCT)

A meta-analysis was performed of 3 randomized, placebo-controlled trials evaluating use of intranasal fluticasone propionate in 983 adult patients with VR. Patients with and without nasal eosinophilia were randomized to 3 groups: 200 mcg fluticasone per nostril daily, 400 mcg fluticasone per nostril daily, and placebo. The primary outcome was change over a 28-day treatment period in total nasal symptom score (TNSS; a 300-point symptom score of the patient’s ratings of nasal obstruction, postnasal drip, and rhinorrhea). The mean change in TNSS was –84 in the 200-mcg group, –82 in the 400-mcg group, and –64 in the placebo group (P<.002 for both treatment groups vs placebo).

Two multicenter, randomized placebo-controlled trials with 426 adult patients evaluated the efficacy of intranasal azelastine for VR. Patients were randomized to receive 1.1 mg azelastine per nostril daily or placebo nasal spray for 21 days in 2 parallel groups. The primary outcome, change in total VR symptom score (patient report of nasal congestion, postnasal drip, sneezing, and rhinorrhea graded as 0=none to 3=severe during the previous 12 hours), was reduced by 24% and 22% in the azelastine groups, but by only 11% and 12% in the placebo groups (P<.002 for both treatment groups vs placebo).

Another RCT evaluated 233 adult patients randomized to ipratropium 0.03% nasal spray 2 sprays per nostril 3 times daily or placebo. The primary outcome measures of duration and severity of rhinorrhea decreased 34% and 30%, respectively, in the ipratropium group compared with 19% and 15% in the placebo group (P<.05 for both comparisons).

Finally, a 2009 RCT included 24 adult patients randomized to acupuncture or sham laser for treatment of VR. The primary outcome of change in nasal sickness score (NSS; a 27-point scale assessed by patient response to a questionnaire) was –5.2 points for acupuncture compared with –2.0 points for placebo (P<.01). Limitations included small study size and a significant baseline difference in NSS between groups.

Is a carotid bruit a good predictor of underlying carotid stenosis in an asymptomatic person?

Evidence-Based Answer
No. A carotid bruit is a poor predictor of carotid stenosis in asymptomatic patients. In addition, the absence of a bruit is not reassuring. (SOR: B, based on conflicting cohort studies.)

In a prospective cohort study, 2,736 apparently healthy asymptomatic patients from a preventive cardiology clinic were assessed. Participants were referred for an evaluation of their risk factors and a routine ambulatory cardiovascular screening. They all were examined for carotid bruits and had ultrasound examinations of the carotid arteries. Hemodynamically significant stenosis was defined as >50% stenosis. The participants’ mean age was 52 years. Nearly half had hypertension.

Overall, 95 of 114 subjects with >50% stenosis had no bruit. The positive likelihood ratio (+LR) of carotid bruit for carotid artery stenosis >50% was 0.90 (95% CI, 0.34–2.41) and the negative likelihood ratio (–LR) was 1.00 (95% CI, 0.97–1.04). Thus, the presence or absence of a carotid bruit did not affect the likelihood of significant carotid artery stenosis.

In a prospective, multiethnic, community-based cohort study, 686 asymptomatic subjects were examined for carotid bruits and underwent carotid duplex scanning. The mean age was 68 years. About 60% of subjects were Hispanic, 20% African American, and 20% Caucasian. Carotid bruits were detected in 4.1% of subjects. Carotid stenosis ≥60% was found in 2.2% of subjects. Seven of 16 subjects with ≥60% stenosis...
had no bruit. Sensitivity and specificity of a bruit for stenosis were 56% and 98% (+LR 28 and –LR 0.45).

In a prospective cohort study, 153 patients undergoing coronary artery bypass grafting who had no previous history of cerebrovascular events were evaluated.3 They were all examined for cervical bruits and received carotid artery duplex scanning. The mean age was 57 years, and 94% were male. Bruits were detected in 7.8% of patients. The sensitivity and specificity of cervical bruit for detection of ≥50% ipsilateral internal carotid artery stenosis were 20% and 93.5%, respectively (+LR 3.1 and –LR 0.85).

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Do ACE inhibitors alter lung function in patients with asthma?

Evidence-Based Answer
No. Angiotensin-converting enzyme inhibitor (ACE-I) medications do not alter lung function in patients with asthma. (SOR: C, based on bench research.)

ACE-I medications increase the production of pulmonary bradykinin and frequently cause cough. Theoretically, they might alter pulmonary function or disease severity in patients with asthma.

A prospective, randomized double-blind study (n=21) evaluated the effects of oral enalapril 12 mg daily (n=10) and spirapril 12 mg daily (n=11) on airway responsiveness and symptoms.1 Patients were included if they demonstrated bronchial responsiveness to a methacholine challenge test (defined as a reduction in FEV1 by 20%). Baseline FEV1, forced vital capacity (FVC), and FEV1/FVC ratios were obtained.

After 3 weeks, no significant changes were noted in FEV1, FVC, or FEV1/FVC with either therapy. In addition, bronchial responsiveness to methacholine did not change with the use of either ACE-I agent. Six weeks after discontinuing treatment, there were still no changes in bronchial reactivity, FVC, FEV1, or FVC/FEV1. No P values or confidence intervals were provided. Limitations of the study included the small sample size and the use of baseline measures rather than a placebo arm.1

An older, double-blind crossover study (n=16) from Spain assessed the effect of an ACE-I on patients with asthma with increasing doses of captopril and placebo for 4 weeks.2 Asthma was defined using clinical and lung function criteria (based on the American Thoracic Committee of 1962). Half the patients received captopril 25 mg twice a day, which was increased up to 75 mg twice a day; the others received a placebo. After 4 weeks, individuals were all retested and the groups were crossed over.

Neither group had significant changes in spirometric results or methacholine responsiveness. Limitations to the study included small sample size and lack of clinical symptom scoring.2

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How long does prenatal RhoGAM last?

Evidence-Based Answer
The total body load of anti-D immunoglobulin G (IgG) 12 weeks after a single 300-mcg dose of intramuscular anti-D immunoglobulin given at 28 weeks' gestational age (GA) is variable, ranging from undetectable to more than 25 mcg. Similarly variable total body loads result if 100 mcg of the immunoglobulin is given at both 28 and 34 weeks' GA. In many patients, therefore, the residual anti-D IgG will be insufficient to prevent Rh sensitization with the birth of an Rh D-positive infant. Routine administration of anti-D immunoglobulin within 72 hours of delivery of an Rh D-positive infant is therefore recommended. (SOR: B, based on consistent cohort studies.)

In 2003, a randomized, multicenter cohort study followed serum concentrations of anti-D IgG in 14 pregnant Rh D-negative women who received 300 mcg anti-D immunoglobulin at 28 weeks’ GA.1 The serum half-life of anti-D IgG was about 17 days. Quantifiable
anti-D IgG concentrations (≥0.4 mcg/L) were observed in all women up to 37 weeks’ GA. These concentrations would equate to a total body load of at least 2.0 to 2.4 mcg anti-D IgG based on the average human blood volume of 5 to 6 L. However, by 39 weeks’ GA, quantifiable anti-D IgG concentrations were found in only 60% of treated women.

A larger 2003 cohort study evaluated 150 pregnant Rh D-negative women who also received 300 mcg anti-D prophylaxis at 28 weeks’ GA. Serum concentrations of anti-D IgG were assessed at the time of delivery. The measurement method was able to detect as little as 6.25 mcg/L anti-D IgG. Fifty-seven percent of preterm deliveries had mean residual total body loads of anti-D IgG above 20 to 25 mcg, which would be enough anti-D IgG to neutralize the transplacental passage of 1 mL Rh D-positive blood from a fetus. Only 13% of full-term deliveries had detectable total body loads of anti-D IgG above 20 to 25 mcg. No women were found to have detectable anti-D IgG concentrations when measured at 42 weeks’ GA.

The British preference for prophylaxis is to give Rh D-negative women 100 mcg anti-D immunoglobulin at both 28 and 34 weeks’ GA. From 1992 through 1996, a prospective cohort study evaluated anti-D IgG concentrations in 365 Rh D-negative women who received the 2-dose regimen at 28 and 34 weeks. The half-life was found to be <21 days. Similar to the findings of studies evaluating the 300-mcg dosing, anti-D IgG concentrations were detectable in only 13% of the study cohort at the time of delivery.

Based on low anti-D IgG concentrations found in many women late in their third trimester of pregnancy, the American College of Obstetricians and Gynecologists recommends administration of 300 mcg anti-D immunoglobulin within 72 hours of delivery of a Rh D-positive infant. This immunoglobulin dose is as much as 15 mL of fetal red blood cells.

What is the best imaging for suspected cholecystitis?

Evidence-Based Answer
Radionuclide scanning has slightly higher sensitivity and specificity than abdominal ultrasound. (SOR: A, based on meta-analyses.) However, ultrasound is the preferred initial test because it is readily available, does not use radiation or contrast dye, and provides a reasonable view of the anatomy of the upper abdomen. (SOR: C, based on expert opinion.)

Researchers conducted a meta-analysis of studies of radionuclide imaging and ultrasound for the diagnosis of suspected acute cholecystitis. The gold standard used to confirm the diagnosis was surgery, autopsy, or observation for recurrent disease.

Radionuclide scanning was evaluated in 22 studies with 2,466 patients and found to have a sensitivity of 97% (95% CI, 0.96–0.98) and specificity of 90% (95% CI, 0.86–0.95). This yielded a positive likelihood ratio (+LR) of 9.7 and a negative likelihood ratio (–LR) of 0.03. In 5 studies and 532 patients using ultrasound, the unadjusted sensitivity and specificity were 94% (95% CI, 0.92–0.96) and 78% (95% CI, 0.61–0.96), respectively. Adjusting the ultrasound studies for verification bias lowered the sensitivity to 88% (95% CI, 0.74–1.00) and increased specificity to 80% (95% CI, 0.62–0.98). This yielded a +LR of 4.4 and a –LR of 0.15.

A retrospective case-control study of computed tomography (CT) scans was conducted with 75 patients—23 with acute gangrenous cholecystitis, 25 with acute nongangrenous cholecystitis, and 27 without cholecystitis. The sensitivity and specificity CT for acute cholecystitis were 92% and 99%, respectively (+LR 92, –LR 0.08). For acute gangrenous cholecystitis, the corresponding figures were 29% and 96% (+LR 7.3, –LR 0.7).

An expert panel of the American College of Radiology concluded that the diagnosis of acute cholecystitis should be confirmed or excluded with ultrasound or radionuclide scanning. Abdominal ultrasound was chosen as the preferred initial imaging test for a variety of reasons: availability, lack of radiation, confirmation of the presence or absence of gallstones, evaluation of intrahepatic and extrahepatic bile ducts, and ability to exclude alternative diagnoses. CT was noted to be
helpful in negative or unclear situations, especially for identification of extrabiliary diseases and complications of acute cholecystitis.

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What are the causes of chronic perianal dermatitis in kids?

Evidence-Based Answer
Causes of chronic perianal dermatitis include bacterial, fungal, parasitic, and viral infections; contact with irritants and allergens; atopic dermatitis; pruritus ani; psoriasis; steroid-induced skin atrophy; lichen sclerosus; and seborrheic dermatitis, histiocytosis, inflammatory bowel disease, and sexual abuse. The most common bacteria are group A Streptococcus and Staphylococcus aureus. (SOR: C, extrapolated from mixed age and referral center cohorts.)

A prospective study evaluated 126 consecutive patients referred to an Austrian proctology clinic to determine the etiology of their perianal dermatitis. The ages of the patients ranged from 7 to 82 years and the duration of symptoms ranged from 6 days to 10 years, with half the patients having symptoms for more than a year. The investigators assessed all patients with a history, clinical exam, proctoscopy, microbiology and laboratory studies, patch testing, and biopsy if needed. Candida infection was the most common diagnosis (43%) followed by allergic contact dermatitis (26%), irritant dermatitis (20%), atopic dermatitis (6%), pruritus ani (5%), psoriasis (3%), steroid-induced skin atrophy (2%), lichen sclerosus (1%), and single patients with condyloma and herpes simplex. Because the authors did not report the distribution of ages, the exact frequency of these diagnoses within the pediatric population is not known. The researchers did not state if bacterial swabs were obtained, but no bacterial cases were found.

Citing their experience with seeing cases of perianal streptococcal dermatitis misdiagnosed, investigators in Germany reported a case series evaluating the relative frequency of perianal streptococcal dermatitis in 124 children referred to a colorectal surgery clinic for persistent perianal symptoms. Patients were 14 years of age and younger, with duration of symptoms ranging from 2 weeks to 2 years (mean duration 6 months). The investigators evaluated patients with history, examination, and microbiological analysis of perianal swabs; anoscopy and proctoscopy were used at each clinician’s discretion.

Perianal swabs revealed 21 patients (16%) with perianal streptococcal dermatitis. Group A beta-hemolytic streptococci accounted for 17 of the cases and group B beta-hemolytic streptococci accounted for 4 cases. Because this represents a referral population, the frequencies in primary care populations may be different.

Investigators in the United States reviewed culture results and final diagnosis of 26 patients aged 5 months to 12 years seen for perianal erythema in a referral setting. Cultures were positive in 23 patients; 11 grew only Staphylococcus aureus (6 were methicillin-resistant), 6 grew enteric flora, and 3 grew both Streptococcus and Staphylococcus. Again, there may be a referral bias and primary care clinics may see different frequencies.

A nonsystematic review provided an unreferenced differential diagnosis that included the above conditions but also added pinworm infestation, seborrheic dermatitis, histiocytosis, inflammatory bowel disease, and sexual abuse as causes of perianal dermatitis in children.

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“Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.”
What is the optimal interval for checking liver function tests (LFTs) in patients taking statins?

Evidence-Based Answer

Monitoring LFTs in asymptomatic patients taking statin medications is unlikely to provide clinical benefit, given the infrequency of statin-induced liver damage. New US Food and Drug Administration (FDA) prescribing information for all statins recommends monitoring at baseline and when clinically indicated. The American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute (ACC/AHA/NHLBI) guidelines recommend monitoring at baseline, 12 weeks, and then annually for all statins. (SOR: C, based on expert opinion.)

A meta-analysis identified 35 double-blinded placebo-controlled RCTs (n=74,102) in which adults with hyperlipidemia were allocated to statin monotherapy or placebo. All studies had to report adverse effects. Transaminase elevations were defined by each study, ranging from >1x upper limits of normal (ULN) to ≥3x ULN on 2 consecutive occasions. Discontinuation rates did not differ statistically (5.6% vs 6.1% P=.80). Risk difference (RD) per 1,000 patient-years of therapy indicated no increased risk of transaminase elevations for active medication versus placebo (RD −0.2; 95% CI, −0.7 to 0.2). Long-term follow-up (19 studies ≥1 year) showed no difference in transaminase elevations or discontinuation rates. Specific outcomes related to transaminase elevations were not reported.

A meta-analysis of 7 RCTs (n=29,395) evaluated safety of intensive therapy (80 mg atorvastatin or simvastatin) compared with pravastatin 40 mg, atorvastatin 10 mg, simvastatin 20 mg, or lovastatin 5 mg. Inclusion criteria were RCTs comparing different statin therapy intensity in adults with coronary artery disease and reporting cardiovascular events or mortality. Patients with comorbidities (renal failure, hepatic failure, advanced age, or alcohol abuse) or interacting medications (eg, other lipid-lowering drugs or inhibitors of cytochrome P450) were excluded. Elevated transaminases (>3x ULN) were more common with intensive treatment (1.5% vs 0.4%; OR 4.14; 95% CI, 2.3–7.44); however, discontinuation rates did not differ significantly (7.8% vs 5.3%).

Monitoring recommendations by the ACC/AHA/NHLBI published in 2002 include baseline, 12 weeks, then annually or more frequently if clinically indicated. As we were going to press, the FDA changed its safety label monitoring recommendations for liver enzymes in patients on statin medications. The FDA now recommends checking liver enzymes prior to starting a statin and “as clinically indicated” thereafter. Routine liver enzyme monitoring is no longer recommended for statins.

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Are low-carbohydrate diets safe and effective methods for losing weight?*

Evidence-Based Answer

Low-carbohydrate diets are as effective for weight loss as a low-fat diet for at least the first year. (SOR: A, based on a systematic review.) Constipation is a common adverse effect. (SOR: B, based on an RCT and patient reports.)

A systematic review of 13 RCTs studied the effects of a low-carbohydrate diet (LCD) versus a low-fat diet (LFD) in 1,222 volunteers older than 18 years with a body mass index (BMI) of more than 28 kg/m². An LCD was defined as less than 40 g carbohydrates per day, irrespective of calorie count; an LFD had 30% or less calories from fat.

Patients consuming an LCD lost more weight at 6 months (weighted mean difference [WMD] 4.02 kg; 95% CI, 4.54–3.5) and at 12 months (WMD 1.5 kg; 95% CI, 2.09–0.01) than patients consuming an LFD. Consuming an LCD was associated with higher low-density lipoprotein (LDL) cholesterol at 6 months (WMD 0.14 mmol/l; 95% CI, 0.08–0.20) and at 12 months (WMD 0.37 mmol/L; 95% CI, 0.28–0.46) than consuming an LFD. Consuming an LCD

*This HDA updates an answer published in Evidence-Based Practice. 2008;11(7):5.
was associated with greater increase in high-density lipoprotein (HDL) cholesterol at 6 months (WMD 0.04 mmol/L; 95% CI, 0.00–0.07; \(P=0.03\)) and at 12 months (WMD 0.06 mmol/L; 95% CI, 0.02–0.11) than consuming an LFD.\(^1\)

A subsequent RCT randomized 307 obese adults (mean BMI 36 kg/m\(^2\)) without serious medical conditions such as diabetes to either an LCD or LFD.\(^2\) The LCD started at 20 g carbohydrates per day for 12 weeks, then increased by 5 g/d until a stable weight was achieved. The LFD was calorie restricted and had 30% of calories from fat. All participants also received a series of comprehensive group sessions on behavior change and physical activity prescriptions.

Patients on the LCD lost significantly more weight from baseline compared with patients on the LFD (9.5% vs 8.4%; \(P=0.019\)) at 3 months; however, the difference was not significant at 6, 12, or 24 months. Constipation was significantly less frequent with the LFD than the LCD (17 vs 39 subjects, respectively; \(P=0.02\)).\(^2\)

A 2-year double-blind RCT studied the effect of different diets in 811 patients (mean age 55; mean MBI 33 kg/m\(^2\)) without diabetes or cardiovascular disease. 3 Diets provided a deficit of 750 kcal/d from baseline. The LFD derived 20% of calories from fat (65% from carbohydrates). The LCD derived 40% of calories from fat (35% from carbohydrates).

After 2 years, the LCD and LFD groups lost a similar amount of weight (4 vs 3.3 kg, respectively; \(P=0.37\)). LDL cholesterol decreased less with the LCD than the LFD (1% vs 6%, respectively; \(P=0.01\)), while HDL increased more (9% vs 6%, respectively; \(P=0.02\)).\(^3\)

An Internet-based registry\(^4\) has documented side effects attributed to an LCD in 429 individuals: constipation (40%), bad breath (40%), heart-related problems (33%), lipid problems (33%), difficulty concentrating (29%), kidney stones (19%), and reduced kidney function (19%), and occasional gout, diarrhea, mood swings, fatigue, and headaches.

Does the use of bronchodilators in mechanically ventilated patients without a prior history of obstructive lung disease improve patient outcomes?

Evidence-Based Answer

Bronchodilators do not alter important outcomes in mechanically ventilated patients without prior obstructive lung disease. (SOR: \(B\), based on an RCT and prospective cohort study.)

A 2007 prospective cohort study evaluated the effect of bronchodilators for 6 months in 206 mechanically ventilated patients.\(^1\) Patients with obstructive lung disease were excluded. Overall, 74 patients received bronchodilators (albuterol and ipratropium bromide) without a clear indication for them.

Patients treated with bronchodilators without indications were found to have a greater degree of hypoxemia with lower mean PaO\(_2\)/FiO\(_2\) ratio (188 vs 238 mmHg, \(P=0.004\)); they were also more likely to contract pneumonia during the intensive care unit stay (53% vs 33%; \(P=0.007\)). In addition, there was a mean extra cost of $449.35 for each patient who received bronchodilator therapy. No statistically significant difference was noted in the incidence of ventilator-associated pneumonia, tracheostomy, or mortality.\(^1\)

In another study, 282 hospitalized patients with acute lung injury and without prior pulmonary disease were randomized to receive an aerosolized \(\beta_2\) agonist (every 4 hours for up to 10 days) or placebo when on mechanical ventilation.\(^2\) The primary outcome studied was the number of ventilator-free days (VFDs).

No significant difference was noted in VFDs between the albuterol and placebo groups (14 vs 17 VFDs; 95% CI, –4.7 to 0.3; \(P=0.087\)). The study was discontinued early due to treatment futility based on preset parameters. Mortality rates prior to discharge were not significantly different between the albuterol and placebo pool (23% vs 18%; 95% CI, –4.0 to 15; \(P=0.30\)).\(^2\)


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What is the best treatment for iliotibial band syndrome (ITBS)?

Evidence-Based Answer
Corticosteroid injections are effective in decreasing running pain due to acute ITBS about 2 weeks after treatment. (SOR: B, based on 1 small RCT.) For chronic ITBS, a combination of NSAIDs, analgesics, medications, and physical therapy is more effective in improving total running time and distance than physical therapy alone, although pain reduction is similar. (SOR: B, based on 1 small RCT.) For subacute ITBS, phonophoresis is better than immobilization for faster recovery. (SOR: B, based on 1 small RCT.) Deep transverse friction massage does not produce any additional benefit to a standard physical therapy program of ultrasound, rest, icing, and stretching exercises. (SOR: B, based on 1 small RCT.)

A 2007 systematic review identified 4 RCTs (discussed below) that evaluated different combinations of conservative therapy for the treatment of acute (<14 days) and chronic (>14 days) ITBS, including physical therapy, NSAIDs, analgesics, corticosteroid injection, deep transverse friction massage, phonophoresis, and immobilization. Mean age in all trials was 22–29 years. All 4 of these RCTs were of limited quality due to small study size; lack of blinding of assessors, therapists, or patients; and crossover.

In a 2004 RCT (N=18) patients with acute ITBS were randomized to receive local iliotibial band injections of 40 mg methylprednisolone plus 10 mg 1% lidocaine or 20 mg 1% lidocaine alone. No statistically significant difference was noted in pain scores as measured by a 300-point pain scale assessed during a 30-minute treadmill test on days 0 and 7. However, while both the steroid group and control group had decreased pain during running at day 14 compared with day 7, there was a greater reduction for the steroid group (mean difference 37 vs 21 points; P=.01).

A 1991 RCT (N=43) evaluated the effectiveness of combination analgesic medications when added to physical therapy for 3 groups of patients with chronic ITBS (6–20 weeks of symptoms): group 1 received 50 mg diclofenac and physical therapy; group 2 received 400 mg ibuprofen, 500 mg paracetamol, 20 mg codeine phosphate, and physical therapy; and group 3 received physical therapy alone. Pain decreased in all the groups similarly from day 0 to 7. However, only group 2 improved total running time (15 vs 25 minutes) and distance from day 0 to day 7 (3.5 vs 5 km, respectively; P<.05).

A 1995 RCT (N=26) evaluated the comparative effectiveness of phonophoresis versus knee immobilization in patients with ITBS symptoms lasting 15–17 days. Patients were randomized to receive phonophoresis (ultrasound through 10% hydrocortisone cream) daily on weekdays over 2 weeks plus rest, ice, stretching, and ibuprofen or immobilization over 2 weeks plus rest, ice, stretching, and ibuprofen. The phonophoresis group was pain free on examination sooner (2 vs 8 days; P<.001). A greater proportion of subjects in the phonophoresis group recovered in <10 days than in the immobilization group (100% vs 62%, respectively; P<.001). One subject from the phonophoresis group and 3 from the immobilization group experienced pain during the 1-mile run.

In a 1992 RCT (N=17) patients with chronic ITBS symptoms (for 6 months to 1 year) were randomized to receive 2 weeks of deep transverse friction massage plus ice, stretching, and ultrasound or control therapy with just ice, stretching, and ultrasound. While total pain during running decreased significantly for both the groups (pain scores reduced >50% by day 7–14; P<.05), there were no differences observed in the pain reduction between the 2 groups.

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Email us at EBP@fpin.org.
Obesity in childhood

In last 30 years, childhood obesity more than doubled for children ages 2-5 and 12-19, and tripled for ages 6-11.

- ~1/3 of US children ages 4-19 eat fast food every day, adding ~6 lb per year per child
- Overweight adolescents have a 70% chance of becoming overweight or obese adults, increasing to 80% if at least 1 parent is overweight or obese
- ~60% of obese children ages 5-10 have at least 1 cardiovascular disease risk factor, 25% have 2 or more
- Estimated lifetime risk of type 2 diabetes for obese children born in the United States in 2000: 30% for boys, 40% for girls

Therapeutics

- Body mass index should be calculated and plotted at least annually; classification should be integrated with other information such as growth pattern, familial obesity, and medical risks (ie, diabetes mellitus) to assess child’s obesity risk
- Noncoercive feeding tactics, decrease watching TV at dinnertime, decrease away-from-home food (SOR: B)
- Community/school intervention: organized physical activity, education classes to teach healthier food preparation to parents and children, early home visits by nursing staff to support new parents in healthier lifestyles for newborn (breastfeeding, waiting to introduce solid foods, decreasing unhealthy snacks) (SOR: C)

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Tinnitus

Demographics

- Incidence: 10% to 15%; increases with age
- Prevalence: 2.8% overall in the United States; 9.6% older than age 65
- Almost 2:1 males to females
- Most commonly affected men: Caucasians, elderly, located in southern United States, veterans

Risk factors

- Zinc deficiency possibly associated
- Associated conditions: insomnia, hearing loss, anxiety, depression, posttraumatic stress disorder
- Increased suicide risk associated with depression

Morbidity/mortality

- Third most common service disability among veterans

Symptom management

- Antidepressants—Sertraline may reduce severity, but overall insufficient evidence to support use
  - GABA active drugs—Alprazolam may decrease intensity; gabapentin and baclofen not helpful
  - Acamprosate—may decrease severity for patients with sensorineural hearing loss
  - Botulinum toxin—may improve symptoms for patients with subjective tinnitus if injected subcutaneously around ear or directly into tensor veli palatine muscle, if tinnitus is associated with palatal myoclonus
  - Zinc—beneficial effects appear dose related, with benefit perceived at 50 mg/d and 220 mg/d, not 66 mg/d; conflicting evidence
  - Therapies proven NOT to help—misoprostol, intratympanic prednisone injections, ginkgo biloba, melatonin, hyperbaric oxygen therapy, acupuncture
- Acoustic therapy—noises with ambient sounds (soft music, white noise)

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How effective are pharmacologic agents for alcoholism?

**Bottom line**

Acamprosate reduces the risk of return to any drinking and increases abstinence duration. Naltrexone reduces the risk of return to heavy drinking and decreases the percentage of drinking days. Topiramate reduces the percentage of elevated alcohol intake days and increases the number of abstinence days. Disulfiram is not effective in reducing 12-month abstinence. (SOR: A, based on meta-analyses of RCTs.)

**Evidence summary**

**Acamprosate**

A Cochrane review of RCTs compared the efficacy of acamprosate with that of placebo in the treatment of alcohol dependence. Doses of acamprosate ranged from 1 to 3 g daily and treatment duration from 8 weeks to 1 year (most commonly 6 months). Primary outcome measures were return to any drinking and cumulative abstinence duration.

Return to any drinking (24 trials; n=6,172) was significantly lower with acamprosate compared with placebo (2,416 vs 2,447 events; risk ratio [RR] 0.86; 95% CI, 0.81–0.91; NNT 12.5). Cumulative abstinence duration (19 trials; n=5,224) was significantly increased with acamprosate compared with placebo (mean difference [MD] 11%; 95% CI, 5.1–17).

**Naltrexone**

Another Cochrane review of RCTs compared the efficacy of naltrexone with that of placebo in the treatment of alcohol dependence. Doses ranged from 50 to 150 mg daily of naltrexone in 43 trials using oral formulations and 150 to 400 mg injectable naltrexone every 4 weeks in 4 trials. Treatment duration ranged from 4 to 52 weeks (most commonly 12 weeks).

No significant difference was noted in the risk of return to any drinking (27 trials; n=4,693) with naltrexone compared with placebo (1,823 vs 1,576 events respectively; RR 0.96; 95% CI, 0.92–1.00). The risk of return to heavy drinking (28 trials; n=4,433) was significantly reduced with naltrexone compared with placebo (1,180 vs 1,286 events, respectively; RR 0.83; 95% CI, 0.76–0.9; NNT=10). The percentage of days in which alcohol was consumed was also significantly decreased with naltrexone compared with placebo (MD –3.9%; 95% CI, –5.7 to –2.0).

**Topiramate**

A meta-analysis included 3 RCTs of topiramate versus placebo (n=635) in the treatment of alcohol dependence. Doses ranged from 150 to 300 mg daily of topiramate, and treatment duration was 12 weeks. Days of elevated alcohol intake significantly decreased 23% with topiramate compared with placebo (95% CI, 16–34). Additionally, abstinence days were significantly increased with topiramate compared with placebo (MD 2.9 days; 95% CI, 2.5–3.3).

**Disulfiram**

Disulfiram was compared with placebo for the treatment of alcohol use disorders (hazardous and harmful use as well as alcohol dependence) in another meta-analysis. Doses ranged from 100 to 250 mg disulfiram daily, and the treatment duration was 12 months. In the 2 studies (n=733) comparing disulfiram with placebo, no significant difference was noted in abstinence at 1 year (OR 1.48; 95% CI, 0.98–2.23).

**REFERENCES**

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1. Which of the following statements is true about carotid bruits and carotid artery disease in asymptomatic persons?
   - Absence of a bruit does not rule out significant stenosis
   - Carotid bruits are found in approximately 20% of asymptomatic people
   - Hemodynamically significant carotid stenosis is defined as >30%
   - Nearly all patients with significant carotid stenosis have a bruit

2. Which of the following intranasal medications has been shown to be effective in treating symptoms of vasomotor rhinitis?
   - Intranasal antihistamine
   - Intranasal corticosteroid
   - Intranasal ipratropium
   - All of the above

3. When a 300-mcg dose of anti-D immunoglobulin is given at 28 weeks to a pregnant Rh D-negative woman, the clinician can expect
   - That a subsequent delivery of an Rh D-positive child at 40 weeks will not trigger the development of Rh-D antibodies
   - That a subsequent delivery of an Rh D-positive child at 39 weeks will not trigger the development of Rh-D antibodies
   - That more anti-D immunoglobulin will need to be given at the time of delivery if the child is Rh D-positive
   - Higher serum levels and better coverage than if anti-D immunoglobulin is given as two 100-mcg injections, given at 28 and 34 weeks

4. In imaging for cases of suspected acute cholecystitis, ultrasound is the recommended first test because it
   - Is more sensitive than radionuclide scanning
   - Is rapidly available and has minimal possible toxicity
   - Is more specific than computed tomography (CT) scanning of the abdomen
   - Has a higher positive likelihood ratio than either radionuclide scanning or CT

5. Which of the following statements is true regarding the use of angiotensin-converting enzyme inhibitors (ACE-I) in patients with asthma?
   - Treatment with an ACE-I is contraindicated in patients with asthma secondary to the possibility of exacerbation of asthma symptoms
   - Cough is not an adverse effect from treatment with an ACE-I in patients with asthma
   - Patients with asthma do not experience change in lung function when taking an ACE-I
   - Patients with asthma taking an ACE-I have an increase incidence of asthma exacerbations

6. For children with chronic perianal dermatitis, the differential
   - Includes bacterial and fungal infections
   - Does not include allergy or irritant dermatitis, which are adult conditions
   - Can be adequately addressed with a bacterial culture alone
   - Can be adequately be addressed with a history and inspection alone

7. When compared with low-fat diets, low-carbohydrate diets
   - Are as effective in producing weight loss during the first year
   - Have similar effects on low- or high-density lipoprotein cholesterol
   - Have similar rates of constipation and halitosis
   - Have been shown to be “heart safe” in long-term outcome studies

8. Which statement is true about the pharmacologic treatment of alcoholism?
   - Topiramate is not more effective than placebo in reducing the days of elevated alcohol intake
   - Acamprosate is not more effective than placebo in “return to drinking” events
   - Disulfiram is more effective than placebo in effecting a sustained abstinence
   - Naltrexone is more effective than placebo in reducing the risk of heavy drinking

Answer key: 1. a; 2. d; 3. c; 4. b; 5. c; 6. a; 7. a; 8. d

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