Should liver enzymes be checked in a patient taking niacin?

■ EVIDENCE-BASED ANSWER
No randomized trials directly address the question of frequency of liver enzyme monitoring with niacin use. Niacin use is associated with early and late hepatotoxicity (strength of recommendation [SOR]: B, based on incidence data from randomized controlled trials and systematic reviews of cohort studies). Long-acting forms of niacin (Slo-Niacin) are more frequently associated with hepatotoxicity than the immediate-release (Niacor, Nicolar) or extended-release (Niaspan) forms (SOR: B, based on 1 randomized controlled trial and systematic reviews of cohort studies).

The combination of statins and niacin at usual doses does not increase the risk of hepatotoxicity (SOR: A, based on randomized controlled trials). Screening has been recommended at baseline, 6 to 8 weeks after reaching a daily dose of 1500 mg, 6 to 8 weeks after reaching the maximum daily dose, then annually (SOR: C, based on expert opinion).

■ EVIDENCE SUMMARY
Three forms of niacin exist: immediate-release (IR), sustained-release/long-acting (SR/LA), and extended-release (ER), which is currently available only as Niaspan.1 Published incidence of niacin-induced hepatotoxicity varies according to the definition of hepatotoxicity, with a 0% to 46% rate of elevated hepatic enzymes. Hepatotoxicity includes mild liver enzyme elevations, steatosis, hepatitis, abnormal liver biopsies, or fulminant hepatic failure.2,3 Between 1982 and 1992, 11 case reports have linked IR nicotinic acid to a wide range of hepatotoxocities. For patients taking LA/SR niacin doses ≥3 g/d or switching from the IR to the LA product, 21 case reports have linked LA/SR niacin with adverse outcomes.3,4 In several of the LA/SR cases, patients were rechallenged with IR formulations with no recurrent hepatocellular damage.3,4 In these case reports, onset of hepatotoxicity ranged from 2 days to 18 months. In a retrospective cohort of 969 veterans taking LA/SR niacin, those who developed hepatotoxicity had onset between 1 and 28 months of initiating treatment.2 Studies evaluating the risk of hepatotoxicity with niacin alone and in combination with statins are summarized in the Table.

What are Clinical Inquiries?
Clinical Inquiries answer recent questions from the practices of family physicians. Practicing family physicians choose the most relevant questions submitted through a web-based voting system operated by the Family Physicians Inquiries Network (FPIN; online at www.fpin.org).

FPIN is national, not-for-profit consortium of family medicine departments, community residency programs, academic health sciences libraries, primary care practice-based research networks, and other specialists. Once questions are selected, FPIN editors then organize teams of clinicians and librarians to answer them based on systematic review of the world literature. Answers are developed through an explicit, systematic method:

• FPIN librarians and editors identify questions recently answered in best evidence sources (e.g. Cochrane Reviews, Clinical Evidence, the US Preventive Services Task Force, Evidence Based Guidelines, a published systematic review).
• FPIN librarians then conduct systematic and standardized literature searches of best evidence sources, Medline, and other databases in collaboration with an FPIN clinician or clinicians. If a best evidence source has been identified, the search begins from the date of the search conducted for that source. Otherwise, the searches are comprehensive.
• FPIN clinicians and editors then choose the highest quality original research sources, and critically appraise the research and integrate the findings in the Evidence Based Answer and Evidence Summary section of Clinical Inquiries. Authoritative sources are also quoted in the “Recommendations from Others” section of the Clinical Inquiry.
• Each Clinical Inquiry is reviewed by 4 or more peers or editors before publication in JFP.
• FPIN medical librarians are accountable for the thoroughness of the literature search, for recording the databases searched, search hedges used and the search terms. The details of each search is available to any interested reader (contact managingeditor@fpin.org).
• Finally, a practicing family physician or other clinician writes an accompanying commentary to provide a clinical perspective.
Because LA/SR niacin has an active metabolite (nicotinamide), hepatotoxicity is more likely to occur with the LA/SR formulation than with IR niacin. In a small prospective comparative study of IR and LA/SR niacin (n=46), 0/23 patients taking IR niacin exhibited hepatic toxicity, compared with 12/23 (52%) of patients taking the LA/SR formulation. In this study, patients receiving 1 g/d of LA/SR niacin had increases in transaminases similar to those of patients on 3 g/d of IR niacin. It is therefore recommended that if a patient cannot tolerate IR niacin and is switched to the LA/SR form, the dosage be reduced by 50% to 70%. At doses >2 g/d of LA/SR niacin, mean transaminases approached 3 times the upper limit of normal (ULN), supporting recommendations not to exceed this dose for LA/SR niacin.

Several LA/SR products exist, and their differing pharmacologic and clinical properties necessitate monitoring as though starting anew when changing from one LA/SR formulation to another. Because of the unfavorable risk-benefit ratio of LA/SR formulations compared with other niacin formulations, production and marketing of many

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**Table: Studies of niacin toxicity**

<table>
<thead>
<tr>
<th>Author, evidence</th>
<th>Pts/duration of Rx</th>
<th>Lipid therapy</th>
<th>Hepatotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray, retrospective cohort</td>
<td>896 pts/1–3 mos</td>
<td>LA/SR (Slo-Niacin) avg 1500 mg/d</td>
<td>2.2% probable, 4.7% possible or probable</td>
</tr>
<tr>
<td>Capuzzi, open-label, prospective</td>
<td>517 pts/≤96 wks</td>
<td>ER (Niaspan) 1000–3000 mg/d</td>
<td>&lt;1% w/ transaminases &gt;3 times ULN</td>
</tr>
<tr>
<td>McKenney, randomized, double-blind, placebo-controlled</td>
<td>46 pts/30 wks</td>
<td>LA/SR niacin or IR niacin: titrated from 500 mg/d to 3000 mg/d</td>
<td>52% SR pts with ↑ transaminases (78% SR pts withdrew); 0% IR pts with ↑ transaminases</td>
</tr>
<tr>
<td>Grundy, randomized, double-blind, placebo-controlled</td>
<td>97 pts/16 wks</td>
<td>ER (Niaspan) 1000–1500 mg/d</td>
<td>0% with transaminases &gt;3 times ULN</td>
</tr>
<tr>
<td>Zhao, randomized, double-blind, placebo-controlled</td>
<td>80 pts/38 mos</td>
<td>LA/SR niacin (Slo-Niacin) 250 mg twice daily titrated to 1000 mg twice daily or switched to IR (Niacor) titrated to 3000–4000 mg/d + simvastatin 10 mg/d titrated to maintain LDL-C</td>
<td>3% w/ transaminases &gt;3 times ULN (transient—resolved with temporary halt or decrease in med)</td>
</tr>
<tr>
<td>Parra, randomized, double-blind</td>
<td>74 pts/9 wks</td>
<td>IR niacin titrated to max of 3000 mg/d + fluvastatin 20 mg/d</td>
<td>0% with transaminases &gt;3 times ULN</td>
</tr>
<tr>
<td>Davignon, randomized, placebo-controlled</td>
<td>168 pts/96 wks</td>
<td>LA/SR niacin (Nicobid) 1000 mg twice daily vs Nicobid 1000 mg twice daily + pravastatin 40 mg nightly</td>
<td>3% &gt; 3 times baseline transaminases (Nicobid alone) vs 1.2% &gt;3 times baseline transaminases (Nicobid + pravastatin)</td>
</tr>
</tbody>
</table>

LA/SR, long-acting/sustained release; IR, immediate release; ER, extended release; ULN, upper limit of normal; LDL-C, low-density lipoprotein cholesterol.
LA/SR niacin brands has ceased. The ER formulation (Niaspan), only available by prescription, has a balanced metabolism resulting in less hepatotoxicity (<1%). Expert opinion mandates continued annual monitoring of liver function tests (LFT) for all patients, including those on a stable ER niacin dose, no new risk factors for hepatotoxicity, and a series of normal LFTs.

RECOMMENDATIONS FROM OTHERS
Elevated hepatic enzymes <3 times the ULN may occur but usually resolve with continued therapy or reduced doses. Enzymes >3 times the ULN require discontinuation of therapy. The American Society of Health-System Pharmacists (ASHP) recommends screening at baseline, every 2 to 3 months for the first year and every 6 to 12 months thereafter. The ASHP also recommends that patients be started on IR niacin products, with consideration of ER products only when IR products are not tolerated or alternative products are ineffective. ASHP makes no mention of LA/SR products in their recommendations. They recommend more frequent monitoring for high-risk patients—risks include doses >2 g/d for LA/SR and >3 g/d for IR; LA/SR formulations; switching between formulations; taking concomitant drugs that interact (ie, sulfonylureas); excessive alcohol use (undefined); and pre-existing liver disease (based on a bivariate analysis of factors associated with increased risk of hepatic toxicity from a single retrospective cohort study)—and for patients who demonstrate signs/symptoms of toxicity (nausea, vomiting, malaise, loss of appetite, right upper quadrant pain, jaundice, and dark urine). The National Cholesterol Education Program Expert Panel update in 2004 recommended obtaining ALT/AST initially, 6 to 8 weeks after reaching a daily dose of 1500 mg, 6 to 8 weeks after reaching the maximum daily dose, then annually or more frequently if indicated.

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CLINICAL COMMENTARY
Risk of toxicity with long-acting niacin is significant enough to avoid use
Our clinical experience is that once our patients are on stable doses of most medicines and have had a series of normal lab tests, we are unlikely to find toxicities from continued routine testing. That appears to be the case with niacin and liver toxicity, but long-term data are lacking for asymptomatic late reactions to usual niacin doses. The risk of toxicity with “long-acting” forms of niacin is significant enough that I see no reason to use them at all. If one wants to save money, use IR niacin. If cost is not an issue or regular niacin is not tolerated, I use the ER Niaspan. Both of these forms have very low rates of liver toxicity.

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REFERENCES
One of the largest and most recent of these studies reports adjusted odds for development of coronary artery disease of 1.45 (95% confidence interval [CI], 1.25–1.68) for subjects in the top third of hs-CRP levels compared with those in the bottom third. Odds ratios (OR) for other predictors of coronary artery disease are higher than this, in particular total cholesterol (OR=2.35; 95% CI, 2.03–2.74), cigarette smoking (OR=1.87; 95% CI, 1.62–2.22), and elevated systolic blood pressure (OR=1.50; 95% CI, 1.30–1.73). This shows that hs-CRP does not contribute as much as these factors to the established risk profile for coronary heart disease.

These same authors go on to provide a systematic review of 22 prospective studies of hs-CRP involving 7068 patients, which showed that an elevated hs-CRP was associated with higher odds of developing coronary artery disease (OR=1.58; 95% CI, 1.48–1.68). They also examined the largest 4 studies in their review (which included 4107 cases) and found a slightly lower OR of 1.49 (95% CI, 1.37–1.62). This meta-analysis included only studies published since 2000 because earlier studies, which had yielded higher odds for hs-CRP, suggested a pattern consistent with publication bias.

Two very recent studies evaluating statin therapy for CVD suggest that CRP may be monitored as an independent factor for predicting CVD outcomes for patients undergoing aggressive lipid therapy. These randomized, masked trials suggest that CRP is directly predictive of recurrent events among patients with known CVD. Its usefulness may be greatest when trying to decide whether to pursue aggressive (high-dose) statin therapy for these patients.

It is not clear whether hs-CRP is a direct, causative marker for atherosclerosis or whether it is simply a proxy marker elevated in conjunction with other known risk factors. This issue, combined with the fact that its elevation does not contribute as significantly as other risk factors, makes hs-CRP an inappropriate screening test for cardiovascular disease in the healthy adult.
population. If results continue to accrue supporting the relationship between statin therapy and reduction of CVD outcomes attributable to CRP, we may find that monitoring CRP levels becomes appropriate in the management of patients with known moderate or severe risk or known disease.

**RECOMMENDATIONS FROM OTHERS**

A consensus statement from the American Heart Association and the Centers for Disease Control and Prevention discourages use of hs-CRP for screening in the healthy adult population. It offers support for using hs-CRP for assessment of patients at medium risk levels for whom the test will alter treatment decisions. Guidelines from the Institute for Clinical Systems Improvement for lipid management in adults state that, “non-traditional risk factors (C-reactive protein [CRP] and total homocysteine) have been shown to have some predictive values in screening vascular disease. The value of screening for these risk factors is not yet known.”

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**REFERENCES**


It is not clear whether hs-CRP is a causative marker for atherosclerosis or simply a proxy marker.


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**CLINICAL COMMENTARY**

hs-CRP may be useful as a risk marker in some moderately high-risk patients

Elevated hs-CRP is not a standard cardiovascular risk factor, but may be useful for patients with Framingham Risk scores of 10% to 20%. The updated National Cholesterol Education Panel Adult Treatment Panel III guidelines list elevated hs-CRP (>3 mg/L) as an influencing factor in deciding whether to use an LDL-lowering drug for moderately high-risk patients with LDL-cholesterol values <130 mg/dL. However, no prospective studies prove that elevated hs-CRP should guide therapy. The JUPITER trial is a prospective, placebo-controlled trial evaluating cardiovascular events with statin therapy in primary prevention patients with LDL values <130 mg/dL and hs-CRP values >2 mg/L. When this study is completed, the definitive clinical utility of hs-CRP will be known. Until then, hs-CRP is a risk marker that may be useful for some moderately high-risk patients.

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How should we follow up a positive screen for anemia in a 1-year old?

### EVIDENCE-BASED ANSWER

Healthy infants who test positive for anemia on routine screening at 1 year of age are most likely iron-deficient and may be treated empirically with a trial of iron therapy (3–6 mg of elemental iron/kg/d). Documentation of response to iron confirms the diagnosis of iron-deficiency (strength of recommendation [SOR]: B; evidence from randomized controlled trials with some conflicting results; lack of evidence for long-term benefits/harms of screening strategies).

In these cases, further testing with a complete blood count, mean corpuscular volume, red cell distribution width (RDW), serum ferritin concentration, as well as hemoglobinopathy screening when appropriate, may be effective in determining the cause of anemia (SOR: C, expert opinion).

### EVIDENCE SUMMARY

A prospective study of 1128 children identified as anemic with a screening hemoglobin level showed that subsequent testing—which included mean corpuscular volume, protoporphyrin, transferrin, and ferritin measurements—did not reliably distinguish potential responders from nonresponders to a 3-month trial of empiric iron therapy. In fact, more than half of the responders would have been missed if treatment had been restricted to infants with abnormal mean corpuscular volume or iron studies. Because of the simplicity, low cost, and relative safety of iron therapy for infants, this trial suggests that a therapeutic trial of iron be given first, reserving further work-up for the small number of infants that still have unexplained hemoglobin concentrations of <11.0 g/dL after a therapeutic trial. Similar results were found in a prospective controlled treatment trial among Alaskan Native children as well as a trial of empiric iron therapy among infants with anemia.

*This study was supported by a grant from the Health Resources and Services Administration (#T32-HP14001).*
Another prospective study of 970 healthy infants identified 62 infants with a heel-stick capillary hematocrit of <33%. Of these, 31 had repeat hematocrit values of <33% as confirmed by subsequent heel-stick complete blood count measurement. Twenty of these anemic infants (65%) completed the study protocol, which included a 1-month trial of iron, a follow-up complete blood count, and hemoglobin electrophoresis for those infants with persistent microcytosis or positive sickle preparation (performed at initial screening for all African American infants). Six infants (30%) had an increase in hemoglobin concentration of 1.0 g/dL or more and were presumed to be iron-deficient; they went on to receive an additional 2 months of iron therapy. Two of these were found to have co-existing alpha-thalassemia. Of the remainder, 11 (55%) were determined to have a low-normal hematocrit (mean=31.5 ± 0.9), 1 had alpha thalassemia alone, 1 had coexisting alpha-thalassemia and hemoglobin AS, and 1 had hemoglobin SC. Review of data showed that abnormal diagnoses (iron deficiency, thalassemia, and sickle cell trait or disease) were found in 9 of 11 infants with high RDW and in none of the 9 with normal RDW. The authors concluded that RDW alone appears to be predictive of identifiable causes of anemia when used to screen healthy 12-month-old babies.

A recent Cochrane review suggests there is a clinically significant benefit for the treatment of iron-deficiency anemia; however, there is a need for further randomized controlled trials with long-term follow-up. A randomized controlled trial of iron supplementation vs placebo in 278 infants testing positive for iron-deficiency anemia demonstrated that once daily, moderate-dose ferrous sulfate (FeSO₄) therapy (3 mg/kg/d of elemental iron) given to fasting 1-year-old infants results in no more gastrointestinal side effects than placebo therapy. Another study demonstrated that iron sulfate drops (40 mg elemental iron divided 3 times a day) or a single daily dose of microencapsulated ferrous fumarate sprinkles (80 mg elemental iron) plus ascorbic acid resulted in a similar rate of successful treatment of anemia without side effects.

Further work-up should be reserved for those infants having unexplained hemoglobin concentrations <11.0 g/dL

In a retrospective cohort study of 1358 inner-city children aged 9 to 36 months who underwent screening, 343 (25%) had anemia (Hgb <11 g/dL); of these, 239 (72%) were prescribed iron and 95 (28%) were not. Responders were defined as those with a hemoglobin value of greater than 11 g/dL or an increase of 1 g/dL documented within 6 months of the initial screening visit. Follow-up rates for both groups were low (~50%), but of those prescribed iron, 107 of 150 (71%) responded to treatment compared with 27 of 48 (68%) of those who did not receive iron. Since similar response rates were seen among infants who did and infants who did not receive iron therapy, proving the benefit of routine screening followed by a trial of iron may be problematic in populations with higher rates of anemia, low follow-up rates, and high spontaneous resolution rates.

**RECOMMENDATIONS FROM OTHERS**

The United States Preventive Services Task Force, American Academy of Family Physicians, and American Academy of Pediatrics recommend screening infants for iron-deficiency anemia but do not address appropriate follow-up for positive screens.

The Centers for Disease Control and Prevention (CDC) guidelines recommend performing a confirmatory hemoglobin and hematocrit after a positive anemia screening. If anemia is confirmed and the child is not ill, then treat with iron replacement (3 mg elemental iron/kg/daily) for 4 weeks followed by a repeat test. An increase in hemoglobin concentration ≥1 g/dL or in hematocrit ≥3% confirms the diagnosis of iron-deficiency anemia. If iron-deficiency anemia is confirmed, they recommend continuing iron therapy for 2 more months (3 months total treatment), and rechecking hemoglobin or hematocrit 6 months after successful treatment is completed. Nonresponders, despite compliance with the iron
supplementation regimen and the absence of acute illness, should undergo further evaluation including mean corpuscular volume, RDW, and serum ferritin concentration.12

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■ CLINICAL COMMENTARY

Treating anemia without testing for the cause is the approach of most FPs

For infants 9 months to 1 year of age, there is no consensus regarding appropriate follow-up of positive screens for anemia. It is known that most of them have iron deficiency anemia and empiric treatment with iron supplements have been studied in several prospective trials.

It is also unclear which red cell indices should be tested for diagnosing the different types of anemia. One study found RDW testing alone could predict the cause of anemia. Based on my clinical experience with inner-city Hispanic babies, CDC guidelines seem to include appropriate follow-up. A Cochrane review suggests the need for further randomized controlled trials with long-term follow-up. There is evidence that treating anemia without initial testing for the cause is the approach of choice of most physicians, and there is some evidence that further testing may delay or result in nontreatment of infants who would have benefited from iron therapy.

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REFERENCES


■ CORRECTION

The authors of an article in the October 2004 issue of The Journal of Family Practice have requested a correction to the article’s title and Practice Recommendation. The new title and recommendation (below) omit an earlier mention of breast cancer.

[Title]
Raloxifene reduces risk of vertebral fractures in postmenopausal women regardless of prior hormone therapy

[Practice Recommendation]
Consider prescribing raloxifene 60 mg/d for postmenopausal women, regardless of whether they have used hormone therapy, to reduce the incidence of vertebral fractures

The authors wish to note that raloxifene is not approved in the United States for use in reducing the incidence or risk of breast cancer.
What is the best treatment for analgesic rebound headaches?

**EVIDENCE-BASED ANSWER**
Abrupt discontinuation of the offending analgesic(s), and treating rebound headaches with dihydroergotamine (DHE) as needed, results in significant improvement for most patients (strength of recommendation [SOR]: C; based on case series). Amitriptyline does not affect the frequency or severity of rebound headaches, but it may improve quality of life (SOR: B, low-powered randomized controlled trial). Prednisone or naratriptan (Amerge) lessen acute withdrawal symptoms from analgesics and reduce the need for rescue medications during the first 6 days of treatment; however, they do not affect headache frequency or severity (SOR: B, low-quality randomized controlled trial).

**EVIDENCE SUMMARY**
Analgesic rebound headaches are seen in 1% of the population, mostly middle-aged women with underlying migraines. Also termed analgesic-overuse headaches, they are defined by the International Headache Society guidelines as headaches occurring more than 15 days per month, mild to moderate in intensity, developing or worsening with analgesic overuse, and resolving or reverting to the prior underlying headache pattern within 2 months of discontinuing the analgesic(s).

A case series studied 50 patients with rebound headaches for 5 or more days a week at baseline. Patients were educated regarding analgesic overuse headaches, after which their analgesics were abruptly discontinued, and they were followed up to a year. Subcutaneous DHE was used as needed for symptomatic relief of excruciating headaches. At study completion, 78% of patients had adequately stopped analgesics. The goal of greater than 6 consecutive headache-free days was achieved in 74% patients in an average of 84 days.

A 9-week double-blind, placebo-controlled trial randomized 20 nondepressed patients with analgesic overuse headache to receive amitriptyline or active placebo (trihexyphenidyl). Patients were admitted to the hospital for 1 week and withdrawn from all analgesics. The 2 groups had similar baseline characteristics. During the hospitalization, the amitriptyline treatment group received intravenous amitriptyline escalating from 25 to 75 mg. During the following month, oral study medications were continued, and patients took low doses of aspirin or acetaminophen, as needed. There was no significant difference between the 2 groups with regard to analgesic use. At completion of this low-powered study, no difference was found between the 2 groups in headache frequency or analgesic use, although certain components of a quality-of-life scale were better in the amitriptyline group.

An open-label trial of patients with chronic migraine and analgesic overuse in a headache subspecialty center abruptly withdrew 150 participants from analgesics and quasi-randomized them to 3 groups: prednisone (tapering from 60 to 20 mg over 6 days), naratriptan (Amerge) (2.5 mg twice daily for 6 days), or no prophylactic treatment. Patients given the active substances were told it would reduce withdrawal symptoms; patients given placebo were not given this advice. All patients received education about the pathophysiology of rebound headaches, kept a headache diary, and were phoned weekly to ensure compliance. In addition, they all received capsules containing gradually increasing doses of atenolol, nortriptyline, and flunarazine (a calcium channel blocker not FDA-approved). Indomethacin and chlorpromazine were used as needed. Results from the first 6 days showed no difference in headaches between the 3 groups; however, significantly more patients used chlorpromazine in the “no pharmacologic treatment” group.

By the end of 5 weeks, headache frequency was significantly reduced in all groups from baseline; however, there were no differences between groups in headache frequency or intensity in this
small study. Of note, there were statistically fewer withdrawal symptoms and less use of rescue medications among patients who received the initial prophylactic treatments. The indomethacin rescue use was 24%, 18%, and 14% of patients for the no prophylactic treatment, prednisone, and naratriptan groups respectively, while chlorpromazine rescue use was 14%, 0%, and 0%, respectively. The number of patients needed to treat to prevent any withdrawal symptoms (nausea, vomiting, nervousness, dizziness, etc.) was 1 for every 3.5 for naratriptan, and 6.4 for prednisone.

RECOMMENDATIONS FROM OTHERS

The American Council for Headache Education recommends discontinuing all analgesics. It notes some patients may need prophylactic medication (although no specific agent is recommended), and hospitalization may be indicated for withdrawal for patients who have abused narcotics.

A headache textbook recommends 1 of 2 approaches for patients undergoing outpatient treatment: (1) gradual tapering of the offending medication with substitution of a long-acting nonsteroidal anti-inflammatory drug (NSAID) and initiation of preventive therapy, or (2) abrupt discontinuation of the offending medication and initiation followed by gradual tapering of a “transitional” medication such as NSAIDs, DHE, corticosteroids, or triptans. The authors recommend an intravenous DHE protocol for treatment failures and patients requiring inpatient treatment.

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REFERENCES


CLINICAL COMMENTARY

Consider anxiety, depression, substance abuse, psychosocial stressors as triggers

Analgesic rebound headaches are clinically challenging. Patients are reluctant to believe that analgesic use is the cause, and good evidence for pharmacologic treatment of the problem is limited. Therefore, the family physician’s unique skills in patient-centered treatment of the problem is limited. Therefore, the family physician’s unique skills in patient-centered care are invaluable for helping patients comply with the only proven remedy: long-term analgesic abstinence. Even with intense education and support, abstinence rates are low and headache improvement for abstinent patients is relatively slow and not universal.

In discussing options for assisting with detoxification, we must be honest about the limits of our knowledge and clarify that improvement, rather than cure, is the goal. Identification and treatment of concurrent anxiety, depression and substance use is important, as well as identification of psychosocial stressors that may have triggered increased headache frequency. As even moderate amounts of regular analgesic use can cause this difficult to treat syndrome, preventive counseling with migraine patients, particularly those with increasing headache frequency, is essential.

Lisa Erlanger, MD, Swedish at Providence Family Medicine Residency, Seattle, Wash
Is sputum evaluation useful for patients with community-acquired pneumonia?

■ EVIDENCE-BASED ANSWER
No high-quality studies specifically address the utility of sputum Gram stain or culture in the assessment or treatment of community-acquired pneumonia (CAP) or nursing home–acquired pneumonia (NHAP). The available evidence suggests that analysis of the sputum adds little to the care or outcomes of patients with CAP (strength of recommendation [SOR]: B, inconsistent results from non-randomized case control, case series, and a systematic review of disease-oriented evidence).

■ EVIDENCE SUMMARY
Studies investigating the role of sputum Gram stain and culture are both difficult to interpret and compare. The difficulty in obtaining an adequate sputum sample, variation in preparation, levels of skill in interpretation, and the lack of a gold standard for the microbiologic diagnosis of pneumonia all contribute to these difficulties.

The sole meta-analysis identified 12 studies that met 17 specified study criteria regarding the use of sputum Gram stain for patients with community-acquired pneumococcal pneumonia. Sample sizes ranged from 16 to 404; reference standards were most frequently sputum culture but also included culture of transtracheal and bronchial aspirates. Results revealed that patients with community-acquired pneumococcal pneumonia were able to produce a valid sputum sample (>20 neutrophils, <10 squamous epithelial cells per low-power field) 70% of the time; the sensitivity of sputum Gram stain ranged from 15% to 69% (when reviewed by a lab technician); and specificity ranged from 11% to 100%.

Because of the heterogeneity of test characteristics, interpreter skill levels, study populations, and reference standards among the studies in this meta-analysis, no single estimate of Gram stain sensitivity or specificity could be reached. Similarly, information regarding the sensitivity and specificity of sputum culture is lacking. Small studies (n=13–85) using blood culture, transthoracic aspirate, or transtracheal aspirate as reference standards in untreated cases of definite pneumococcal pneumonia demonstrate sensitivities ranging from 36% to 100%. There are no reliable data regarding the specificity of sputum culture.

Recent nonrandomized studies and case series have called into question the role of sputum analysis in CAP. In a case-control study of 605 patients hospitalized with CAP diagnosed by chest x-ray and either cough, chest pain, auscultatory findings, or leukocytosis, establishing an etiologic diagnosis did not influence the choice of antibiotic therapy, length of hospital stay, or mortality. Of the 482 patients who had microbiological diagnostics performed (Mycoplasma pneumoniae serology, respiratory virus serology, blood culture, or sputum culture), only 132 (27%) had a presumptive etiologic diagnosis made. Therapy was narrowed or focused in 49 of the 132 (37%) patients who had a presumptive etiologic diagnosis, while 84 of the 350 (24%) without a presumptive diagnosis had their therapy narrowed (P > .05). There was no difference in in-hospital changes of therapy, the proportion of new regimens having a narrower antimicrobial spectrum than the initial one, length of hospital stay, death in hospital, or death within 3 months after admission.

A prospective study of 74 patients suggested sputum studies had little use in a highly selected population aged <65 years with nonsevere, uncomplicated CAP and no comorbidities. In the 74 patients who produced a valid sputum sample, Gram stain failed to identify the causative agent in any patient (sensitivity 0%), and sputum cultures identified a pathogen in only 4 patients (sensitivity 5%). All patients responded similarly and, even with the identification of a pathogen in 4 patients, there were no changes in initial empiric antibiotics. In a retrospective case series, 19 of 54 (35%) patients with SCAP did not respond to initial empiric antibiotics and had a change in their
antibiotic regimen. There was no difference in mortality between the group that had empiric antibiotic change (11 patients) and the group that had a change based on sputum culture results (3 patients) (relative risk reduction = –0.14; 95% confidence interval, –0.47 to 0.12). While these studies suggest the need for re-evaluation of routine sputum analysis, the strength of their conclusions are weakened by lack of randomization, small sample size, inadequate blinding, and lack of control group comparison.

Demographic evidence and nonrandomized trials suggest that patients with CAP who have increased risk of infection from multiple-resistant bacteria, such as patients from long-term care facilities, are a unique population that might need to be evaluated differently. However, the only evidence available regarding the utility of either sputum Gram stain or culture for patients with NHAP derives from expert opinion. These authors suggest that determining a causative diagnosis of pneumonia in this population is desirable and postulate that sputum examination would permit recognition of multiply resistant organisms that are being isolated with increasing frequency in long-term care facilities. However, the same authors acknowledge that the elderly are often too weak or too confused to provide adequate sputum specimens, resulting in a low diagnostic yield, and no data demonstrate that sputum evaluation favorably influences the outcome of pneumonia in these patient populations.

**RECOMMENDATIONS FROM OTHERS**

The Infectious Disease Society of America (IDSA) and the Canadian Infectious Disease Society/Canadian Thoracic Society (CIDS/CTS) recommend routine sputum analysis for all patients with CAP or NHAP, while the American Thoracic Society (ATS) recommends performing sputum analysis only if a drug-resistant pathogen or an organism not covered by usual empiric therapy is suspected. For those with CAP or NHAP treated as outpatients, the ATS, the IDSA, and the CIDS/CTS recommend microbiological testing only if drug-resistant bacteria or an organism not covered by usual empiric therapy is suspected.

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What is the best regimen for newly diagnosed hypertension?

**EVIDENCE-BASED ANSWER**

Low-dose thiazide diuretics (eg, hydrochlorothiazide 12.5 to 25 mg/d) are the best first-line pharmacotherapy for treating uncomplicated hypertension (strength of recommendation [SOR]: A, based on randomized trials [RCTs] and 1 meta-analysis). Alternate first-line agents include angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and calcium channel blockers (SOR: A, based on RCTs).

**EVIDENCE SUMMARY**

Three landmark placebo-controlled studies have established that thiazide diuretic–based treatment reduces morbidity and mortality among patients with hypertension. Based on these data, thiazide diuretic therapy is considered the gold-standard treatment for uncomplicated hypertension.

Several other clinical trials have subsequently compared the effect of thiazide diuretics with that of other antihypertensive agents (beta-blockers, calcium channel blockers, and alpha-blockers) on patient-oriented outcomes. These were analyzed in a recent meta-analysis of 42 clinical trials that included 192,478 patients randomized to 7 treatment strategies including placebo. Results from the largest antihypertensive clinical trial, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), were included in this meta-analysis. Comparative results are depicted in the Table. Although these data showed no differences between drug therapies in total and cardiovascular disease mortality, low-dose diuretics reduced certain cardio-vascular endpoints (ie, heart failure, stroke, cardiovascular disease events) more than other drug therapies.

Angiotensin receptor blockers (ARBs) have not been compared with thiazide diuretics in a trial. Two long-term trials have compared an ARB to other types of drug therapy: losartan vs atenolol in the Losartan Intervention for Endpoint Reduction (LIFE) trial, and valsartan vs amlodipine in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial. In the LIFE trial, the primary composite endpoint of cardiovascular death, myocardial infarction, and stroke was less with losartan than atenolol (23.8 vs 27.9 events per 1000 patient-years, losartan and atenolol, respectively; number needed to treat=243 people-years, \( P=.021 \)). However, in the VALUE trial, the primary endpoint of time to cardiac event was not different between valsartan and amlodipine (25.5 vs 24.7 events per 1000 patient-years, valsartan and amlodipine, respectively; \( P=.49 \)).

**RECOMMENDATIONS FROM OTHERS**

The Seventh Report of the Joint National Committee (JNC7) recommended thiazide diuretics as preferred initial agents in uncomplicated hypertension. The European Society of Hypertension/European Society Cardiology recommended either a diuretic, beta-blocker, calcium channel blocker, ACE inhibitor, or ARB for initial therapy stating that blood pressure control to recommended values via any agent is more important than the type of agent used. Both guidelines identified other antihypertensives that may be used in addition to or in place of thiazide diuretics for compelling indications, such as heart failure, diabetes, high-risk cardiovascular disease, chronic kidney disease, post-myocardial infarction, and secondary stroke prevention.

CONTINUED
First-line treatments for hypertension

<table>
<thead>
<tr>
<th>Low-dose diuretic vs</th>
<th>Relative risk (95% CI) of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHD</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0.87 (0.74–1.03)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>1.00 (0.88–1.14)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>0.89 (0.76–1.01)</td>
</tr>
<tr>
<td>Alpha-blocker</td>
<td>0.99 (0.75–1.31)</td>
</tr>
</tbody>
</table>

*Denotes statistically significant difference favoring low-dose diuretics (*P <.05).

CI, confidence interval; CHD, congestive heart disease; CVD, cardiovascular disease; ACE, angiotensin-converting enzyme.


### CLINICAL COMMENTARY

Thiazide diuretics: first or second agent for patients with hypertension

Skeptics argue that other antihypertensives are equal to thiazides. However, thiazides are the least expensive agents (1-year hydrochlorothiazide 25 mg/d is <$25.00). This aspect of therapy supports thiazides as first-line pharmacotherapy. The debate of which agent to use first may be moot considering most hypertensive patients require 2 or more drugs to achieve a systolic blood pressure goal of <140 mm Hg. In addition, the JNC7 recommended starting with 2 agents for patients far from their blood pressure goal (eg, systolic blood pressure ≥160 mm Hg). Therefore, even if a thiazide is not the initial agent (because of preference or other compelling indications) it should be the second agent for most patients.

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### REFERENCES


