What is the best treatment for cradle cap?

Evidence-based answer
Gentle washing or emollient use with brushing to remove scale is considered first-line treatment of infantile seborrheic dermatitis, or cradle cap (SOR: C, expert opinion). Ketoconazole 2% shampoo and 1% hydrocortisone cream, while equally effective (SOR: C, case series), may be no better than placebo (SOR: C, consensus opinion). Ketoconazole shampoo for 10 to 30 days does not produce measurable serum levels or raise liver enzymes (SOR: C, case series). Potent topical steroids are associated with acute reductions in serum cortisol levels, but low-potency steroids are not (SOR: C, case series).

Evidence summary
General measures
Experts recommend applying emollient to the infant’s scalp, followed by gentle brushing, with or without mild shampoo, to remove scale.¹ No clinical trials have evaluated these recommendations.

Ketoconazole therapy
A case series with 60 infants with infantile seborrheic dermatitis identified 12 infants with Malassezia furfur and 3 infants with Candida.² Nevertheless, another case series with 48 infants with infantile seborrheic dermatitis found no benefit from ketoconazole versus hydrocortisone cream. Investigators applied ketoconazole 2% cream to half of the scalp and hydrocortisone 1% cream to the other half each day. Both sides resolved equally (40% resolution at 1 week and 100% at 2 weeks).³ There was no placebo group.

Topical hydrocortisone therapy
A randomized, double-blind, split-side comparison trial in infants aged 2 weeks to 1 year (N=75) compared hydrocortisone 1% versus a moisturizer containing licochalcone (a natural phenol) and found...
Evidence-Based Practice / April 2014

no difference. Both products produced equal resolution at 1 and 2 weeks (90% vs 92% at 1 week; P=.45).⁴

Safety
A case series (N=13) found no measurable ketoconazole serum levels or elevation of liver enzymes when ketoconazole shampoo was applied twice weekly for 1 month to infants younger than 1 year.⁵ A second case series (N=19) of children younger than 1 year also found no measurable ketoconazole serum levels after 10 days of daily ketoconazole application.⁶

One small case series assessed systemic effects of topical steroids in infants with atopic dermatitis using plasma cortisol as a marker of adrenal suppression. Twenty-six infants with severe atopic dermatitis were randomized to use topical steroids at 6 levels of potency for 1 week. More potent steroids were associated with lower cortisol levels (eg, betamethasone propionate 0.05% was associated with a 35% decrease in day 2 adrenal function vs baseline). Low-potency steroid (desonide) did not suppress adrenal function in 4 of the 5 infants. Hydrocortisone cream 1% was not tested. No other side effects were noted.⁷

Recommendations
The American Academy of Pediatrics supports a stepwise approach beginning with reassurance and watchful waiting, before proceeding with petroleum jelly emollients, topical antifungals, and steroids.⁸

REFERENCES
This study was brought to you by...

I’ve been running the journal club at my residency program for well over a decade. Through trial and error, I’ve gradually developed a system that gets my learners thinking critically about the medical literature. One of my primary goals is to help residents identify sources of bias in research design. However, I usually don’t have to make the case that industry sponsorship might create bias. Residents seem to come preloaded with the belief that the slightest industry connection completely nullifies any outcome.

That attitude is probably a bit harsh, but until very recently I had no idea of how to quantify sponsorship bias. So I was happy to see a recent Cochrane review that attempted to do just that.

The authors collected 48 reports that included cross-sectional studies, cohort studies, systematic reviews, and meta-analyses that compared primary research studies sponsored by industry with studies funded in other ways.1 As expected, industry-sponsored studies had a higher favorable result rate than alternatively funded studies of the exact same drugs or devices (risk ratio [RR] 1.2; 95% CI, 1.1–1.4) and studied interventions were more likely to be harm free (RR 1.8; 95% CI, 1.5–2.3). In industry-sponsored studies, there was also less agreement between the authors’ stated conclusions and numerical results given in the same report (RR 0.84; 95% CI 0.70–1.01). Fortunately for the rules of logic, this did not reach statistical significance. Industry-sponsored studies did tend to have better blinding than nonindustry-sponsored studies (RR 1.3; 95% CI, 1.1–1.7).

Personally, I was a bit surprised that the effect of industry sponsorship on reported efficacy was so modest. I expected something more outrageous, perhaps a RR in the 2–10 range. As it turns out, underreporting of adverse effects is the more dramatic effect of industry sponsorship.

So my messages to those worried about sponsorship bias are now evidence-based: (1) the magnitude of effect may be modestly inflated, (2) worry about harms that are not divulged, and (3) be happy that the blinding is good. Journal club is now dismissed.

Jon O. Neher, MD

This systemic review and meta-analysis evaluated the efficacy and safety of intravenous (IV) iron for iron deficiency anemia in patients not receiving dialysis. Trials conducted between 1966–2013 were included (72 RCTs, N=10,605).

IV iron increased hemoglobin by 0.65 g/dL (95% CI, 0.51–0.79) and reduced the need for transfusion (RR 0.74; 95% CI 0.62–0.88). However, there was a significant increase in the risk of infection (RR 1.3; 95% CI, 1.1–1.6).

**Bottom line:** Consider IV iron instead of transfusions in patients with moderate to severe iron deficiency anemia if oral therapy is not tolerated or will not work quickly enough for other treatment needs. The severity, timing, and type of infection risk needs to be more clearly defined.

**Review Author and Summary Author:** Janice L. Benson, MD, NorthShore University, Chicago, IL

---

This study enrolled 5,145 overweight people with type 2 diabetes (average body mass index of 36 kg/m², average age 59 years, average hemoglobin A1c 7.2%) and compared cardiovascular outcomes in those randomized to either an intensive lifestyle modification program that required at least 7% weight loss in the first year and 175 minutes of exercise a week, or a control arm with 3 educational group visits a year in years 1 through 4 and then yearly after that for the duration of the study.

The primary endpoint was the combined outcomes of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina. All-cause mortality was also tracked. Outcomes were assessed by investigators unaware of treatment assignment over a median of 9.8 years.

No difference was noted in the primary endpoint (HR 0.95; 95% CI, 0.83–1.09; P=.51) or in mortality (HR 0.85; 95% CI, 0.69–1.04, P=.11) between groups. The intervention group did have sustained, significant improvements in weight, waist circumference, physical fitness as assessed by metabolic equivalents, and hemoglobin A1c.

**Bottom line:** For people with well-controlled diabetes, we may not need to emphasize the cardiovascular benefits of weight loss and exercise.

**Review Author and Summary Author:** Niladri Das, MD, U of Pittsburgh Medical Center, St. Margaret FMRP, Pittsburgh, PA

---

**IV iron can prevent transfusion but may increase infection rate**


---

**Weight loss and exercise do not improve cardiovascular morbidity in patients with well-controlled diabetes**

D-dimer testing has excellent sensitivity for detecting venous thromboembolism (VTE), so it is useful for ruling out VTE in low-risk patients. However, in patients older than 50 years, the low specificity of D-dimer (0%-18%) results in the unnecessary imaging.

This meta-analysis explored how the use of age-specific cutoff values changed the specificity and sensitivity of D-dimer testing compared with a conventional cutoff of 500 mcg/L for all ages. The D-dimer cut-off was increased by 100 mcg/L for each decade of life above 50 years (ie, age ≤50 years: cutoff 500 mcg/L; age 51–60 years: 600 mcg/L, etc). The analysis included 13 diagnostic cohorts comprising more than 12,000 patients with suspected pulmonary embolism (PE) or deep venous thrombosis (DVT) but with a low clinical risk of VTE as determined by a Wells or Geneva score. Pooled sensitivities and specificities were calculated using random effects regression models.

The age-specific cutoffs increased the specificity of D-dimer for all age groups older than 50 years without sacrificing significant sensitivity. In the oldest subgroup (>80 years), the age-specific cutoff resulted in a specificity of 35% versus 15% using the conventional cutoff ($P<.001$). Using the age-specific cutoff would result in the avoidance of 175 unnecessary imaging examinations in a population of 1,000 individuals with a low risk of VTE, while missing an additional 4 cases of VTE in that group. Additional analyses controlling for the type of D-dimer assay and whether the patient had a suspected DVT or PE did not significantly influence the results.

**Bottom line:** The use of age-specific cutoff values substantially improves the utility of D-dimer for ruling out VTE in elderly patients without significantly increasing the number of missed cases.

**Review Author and Summary Author:** Kate Kirley, MD, The University of Chicago Department of Family Medicine, Chicago IL

---

This RCT compared fluid intake restricted to 800 mL daily and sodium intake restricted to 800 mg daily (intervention) with liberal fluid intake of 2.5 L daily and sodium intake of approximately 3 to 5 g daily (control) on weight loss and clinical stability in hospitalized patients with acute decompensated heart failure. Patients followed these regimens for 7 days or until discharge.

The primary outcomes were weight loss and clinical stability at 3 days. Clinical stability was assessed by a 22-point validated scale, with higher scores indicating worse congestion. Secondary outcomes included daily perception of thirst and readmissions within 30 days.

No significant between-group differences were noted in weight loss from baseline to day 3 (intervention group $–4.4$ kg vs control group $–4.7$ kg; mean difference $0.25$ kg; 95% CI, $–1.9$ to $2.5$; $P=.82$), or change in clinical congestion score from baseline to day 3 (intervention group $–4.0$ vs $–3.4$ points; mean difference $0.59$; 95% CI, $–2.21$ to $1.03$; $P=.47$).

Thirst (measured on a 10-point visual analog scale) was worse in the intervention group than in the control group ($5.1$ vs $3.4$; $P=.01$) at the end of the study period. There was no significant between-group difference in the readmission rate at 30 days (29% intervention group vs 19% control group; $P=.41$).

**Bottom line:** Aggressive fluid and sodium restrictions are not necessary in patients with an ejection fraction of less than 45% admitted for acute decompensated heart failure.

**Review Author and Summary Author:** Kortnee Robertson, MD, The University of Chicago Department of Family Medicine, Chicago IL

---

Additional information can be found at: [www.fpin.org/purlsoverview](www.fpin.org/purlsoverview)
Systemic corticosteroids for acute low back pain: Do we treat because we are expected to?

Trigger Case
An elderly patient came to see me because her “regular doctor” was away on vacation. Two days earlier she had developed severe 10/10 low back pain. “Dr. Regular gives me steroid pills for back pain,” she explained. As we proceeded through a medical history, physical examination, and a review of her x-rays, there was nothing to suggest she had cord impingement, cauda equina syndrome, infection, neoplasm, or fracture.

Background
Systemic corticosteroids have myriad adverse effects that range from relatively mild (eg, fluid retention, headache, insomnia, mood lability, and poor glycemic control) to severe (eg, tendon rupture, heart failure, adrenal insufficiency, and immunosuppression). These effects are mostly time- and dose-dependent. Nevertheless, oral steroid therapy such as prednisone bursts, prednisone tapers, and Medrol Dosepaks are often used for a variety of ailments, including acute low back pain.

Review of the evidence
After a thorough literature review and “consensus discussion,” the American College of Physicians and the American Pain Society in 2007 concluded, “Systemic corticosteroids are not recommended for treatment of low back pain ... because they have not been shown to be more effective than placebo.”

Since that time, 2 placebo-controlled RCTs have assessed the effectiveness of systemic steroids. The first (in 2008) enrolled patients within 7 days of developing low back pain with sciatic symptoms and administered either a single IM dose of 160 mg methylprednisolone acetate (37 patients) or placebo (41 patients). All participants received oral NSAIDs and oral narcotics. Using a 0–10 step visual analog scale (VAS), pain symptoms improved in both groups over time, although neither group improved significantly more than the other. At 1 week the mean VAS difference = 1.1 (95% CI, −0.5 to 2.8), and at 1 month the mean VAS difference = 1.3 (95% CI, −0.5 to 2.7). Furthermore, although a series of secondary outcomes including rate of analgesic use and level of functional disability were also compared, the 2 groups had no significant differences at the completion of the 1-month study.

That same year, 1 of the only studies to evaluate the use of oral systemic corticosteroids for low-back–related symptoms was published. In this RCT, patients within 7 days of developing low back pain with sciatic symptoms were administered either a 9-day tapering course of oral prednisone (13 patients) or placebo (14 patients). All participants received oral NSAIDs, oral narcotics, and formal physical therapy. Throughout 6 months of follow-up, no statistical differences were noted in physical examination findings, use of NSAIDs, use of narcotics, or rates of return to work between the 2 groups.

More recent reports reached the same conclusion as the 2007 guidelines: it is impossible to recommend systemic corticosteroids for acute low back pain based on current evidence. Notably, the presence or absence of sciatic nerve irritation does not alter the recommendation.

Conclusion
Evidence-based medicine shows systemic corticosteroids to be ineffective for relief from acute low back pain.

Case Wrap-Up
I did not write a prescription for oral steroids that afternoon. We discussed acetaminophen and ibuprofen dosing, and a script for a couple of pills of low-dose opiate analgesic as back-up. She and I touched base several times over the next few weeks, gradually adding in physical therapy exercises. Although skeptical at first, she did very well and was happy with the service and treatment she received from this new doctor.

Andrew W. Gottschalk, MD
Cleveland Clinic
Cleveland, OH

REFERENCES
What treatments are effective for eustachian tube dysfunction after viral upper respiratory infections?

Evidence-Based Answer
The evidence is insufficient to recommend any specific treatment for eustachian tube dysfunction (SOR: C, heterogeneous low-quality trials with non-patient-oriented outcomes). Intranasal corticosteroids do not appear to be effective (SOR: B, single small RCT).

A 2002 systematic review of 34 trials—including 13 animal trials, 6 human adult trials, and 15 human child trials—focused on general therapeutic improvement of eustachian tube function. The human adult trials were all small RCTs; of the human child trials, there were only 2 RCTs, with the remainder being small, nonrandomized prospective trials. The review did not consistently state the number of subjects or the study design of the studies reviewed.

Pharmacologic interventions included surfactant (instillation or nebulization; animal trials only), beta-adrenoceptor agonists (intravenous or subcutaneous injection; 1 human adult trial, N=10), decongestants or antihistamines (intra-arterial injection, oral, or topically applied to the pharyngeal eustachian tube opening; 4 human child trials and 5 human adult trials, total N=338), the macrolide antibiotic roxithromycin (oral; single animal trial), and the herbal medicine saireito (oral; single animal trial). Surgical interventions included adenoidectomy and ventilation tube placement (all human children with otitis media with effusion, 1 RCT with N=132, the remainder nonrandomized prospective trials with unstated numbers of subjects). There was significant heterogeneity among the reviewed studies with most studies not using placebo controls or randomization.

While some interventions were shown to modify physiologic factors such as opening and closing pressure of the eustachian tube and clearance capacity, there were no patient-oriented outcomes such as symptom severity, length of illness, or prevention of complications such as otitis media.

A subsequent 2011 randomized, placebo-controlled, double-blind prospective clinical trial compared the effectiveness of intranasal steroid spray (triamcinolone acetonide) with placebo in treating eustachian tube function in adults and children (N=91) who presented with otitis media with effusion or negative middle ear pressure, or both. Primary outcome measures were resolution of abnormal tympanometry as well as change in frequency and severity of 5 symptoms (ear fullness or pressure, ear pain, plugged sensation, popping sensation, and dampened hearing) using 10 five-point scales. There was no statistically significant difference between the 2 arms in either the rate of tympanometric normalization (19% with steroid vs 32% with placebo; P=.18) or overall poststudy symptom score.

Michael D. Geurin, MD
Montana FMR
Billings, MT


Are there any elements of the clinical presentation of gastritis that suggest Helicobacter pylori infection?

Evidence-Based Answer
Among patients undergoing esophagogastroduodenoscopy (EGD) for gastritis, about 80% will be H pylori positive. Proton pump inhibitor use, alcohol consumption, and smoking history do not affect H pylori infection rates. Eructation is more common in patients without H pylori infection (SOR: B, cohort studies).

A prospective cohort trial of 491 adults scheduled for an elective EGD examined the prevalence of H pylori and gastritis. Seven mucosal biopsies from prespecified locations were taken from each of the patients undergoing an EGD (n=458) and also from patients undergoing screening colonoscopy who were also asked to complete an EGD with biopsies (n=33). Within this cohort, 200 patients had gastritis on mucosal biopsy and 159 of those patients tested positive for H pylori (so gastritis was 80% H pylori-positive and 20% H pylori-negative).

There was no difference in proton pump inhibitor (PPI) use between the H pylori-positive group and the H pylori-negative group (OR 1.7; 95% CI, 0.78–3.7), current or former alcohol use (OR 0.76; 95% CI, 0.22–2.5), or current or past tobacco use (OR 1.5; 95% CI, 0.6–3.5).

A retrospective chart review of 94 adult patients seen in a gastroenterology clinic, who each had
endoscopy-confirmed gastritis, examined the clinical features associated with gastritis and presence of *H pylori.* Overall, 57% patients were found to be *H pylori* positive.

Compared with patients who did not have *H pylori*, there was no difference between the groups with symptoms such as nausea (OR 0.57; 95% CI, 0.24–1.4), vomiting (OR 0.56; 95% CI, 0.14–2.2), abdominal pain (OR 0.85; 95% CI, 0.37–2.0), reflux (OR 6.8; 95% CI, 0.81–57), or abdominal distention (OR 2.2; 95% CI, 0.95–5.1). Eructation was less common in the *H pylori* group than the group without *H pylori* (32% vs 60%; OR 0.3; 95% CI, 0.13–0.72).

Sarah Hemeida, MD
Kurt Cook, MD
University of Colorado FMR
Denver, CO


When can sunscreen safely be used on infants?

**Evidence-Based Answer**
Currently no evidence is available regarding when it is safe to use sunscreen on infants. Direct sunlight avoidance is recommended in infants younger than 6 months. However, when sun exposure cannot be prevented with clothing, hats, or shade, sunscreen may be used on small areas of skin on the face and backs of hands (SOR: C, expert opinion).

The outermost layer of the epidermis, the stratum corneum, shows evidence of immaturity until about 1 to 2 years of age. Measurements of skin conductance and water distribution demonstrate higher hydration and more alkaline pH in infants and toddlers. Given their higher body surface-to-mass ratio and immature stratum corneum, it is hypothesized that infants are at greater risk for systemic absorption of organic sunscreens (chemical absorbers of ultraviolet radiation). It has not been well studied how frequently infants experience skin reactions to organic sunscreens, such as irritant dermatitis and allergic contact dermatitis. Due to the lack of adequate research, it is unknown when sunscreen use is safe for infants.

According to consensus recommendations by the American Academy of Pediatrics (AAP) in 2011, direct sun exposure should be avoided with infants younger than 6 months. The AAP recommends keeping infants in shade when possible, avoiding outdoor activities during peak sun intensity between 10:00 am and 4:00 pm, and dressing infants in long sleeves and pants, socks, wide-brimmed hats, and sunglasses. When adequate coverage is not provided by shade or clothing, they advise that sunscreen may be applied to small areas of skin on the face and backs of hands.

Heather Layher, DO
Bethany Teer, MD
Madigan Army Medical Center
Tacoma, WA


What is the most effective lipid-lowering therapy for children with dyslipidemia?

**Evidence-Based Answer**
In children with familial hypercholesterolemia, statins are effective for lowering total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). Diets or dietary supplements do not appear to significantly lower lipid levels. There is limited evidence that ezetimibe is effective and safe in lowering TC, LDL-C, and triglycerides (TG) (SOR: C, disease-oriented evidence).

A 2010 Cochrane review of 8 RCTs (N=897) assessed the effectiveness and safety of statins in children aged 8 to 18 years with familial hypercholesterolemia when compared with placebo or diet alone for a period of 6 months to 1 year. Statins significantly reduced TC (mean difference [MD] at 12 months –27%; 95% CI, –29% to –25%) and LDL-C (MD –33%; 95% CI, –37% to –28%) compared with placebo or diet. The risks of myopathy and clinical adverse events were similar in the statin and control groups. No significant improvement was noted in HDL-C or TG over placebo at 12 months. This review did not provide starting lipid values, and results were reported only as a percentage mean difference.
Evidence-Based Practice / Vol. 17, No. 4

Another 2010 Cochrane review of 11 RCTs (N=331) involving children and adults with familial hypercholesterolemia compared the short-term benefits of lipid-lowering dietary interventions alone and in combination with dietary supplements including omega-3 fatty acids, soy proteins, plant sterols, or plant stanols. Five of the studies were randomized controlled crossover trials of children aged 6 to 19 years (N=102) followed over 4 to 8 weeks of therapy. No significant lipid-lowering effect was noted for lipid-lowering diet alone or combined with dietary supplements.

A 2009 retrospective review (N=36) of children aged 8 to 17 years with either familial hypercholesterolemia or familial combined hyperlipidemia (FCHL) evaluated the effects of standard diet therapy alone for variable lengths of time, followed by diet plus ezetimibe 10 mg daily (mean duration 14 months; range 1–44 months). Compared with diet therapy alone, ezetimibe was effective in lowering TC (MD –23%, P<.02 for familial hypercholesterolemia; MD –18%, P<.01 for FCHL) and LDL-C (MD –30%, P<.02 for familial hypercholesterolemia; MD –23%, P<.01 for FCHL) with no adverse effects attributable to the medication. Ezetimibe was also effective in lowering TG in patients with FCHL (MD –13%; P<.05).

Ricardo E. Castellon-Inestroza, MD
Linda Oberst-Walsh, MD
Ashley Bridges, MD
Rohita Inturi, MD
U of OK School of Community Medicine
Tulsa, OK

Are there safe and effective treatments for patients with stretch marks?

Evidence-Based Answer
The topical agents Verum® and Trofolastin® may reduce the incidence of stretch marks, while treatment with tretinoin or laser therapy may result in overall clinical improvement in appearance of stretch marks (SOR: B, small RCTs and a cohort trial).

A Cochrane review of 2 RCTs (N=130 pregnant women up to 20 weeks’ gestation) examined the effectiveness of topical treatments in preventing the development of stretch marks by comparing active creams with either no treatment or placebo. One trial of 50 women compared massage using an ointment containing tocopherol, panthenol, hyaluronic acid, elastin, and menthol (Verum) with no treatment. Fewer women developed stretch marks with the active ointment (OR 0.26; 95% CI, 0.08–0.84). A second RCT of 80 women compared a cream containing Centella asiatica extract, alpha tocopherol, and collagen-elastin hydrolysates (Trofolastin) with placebo. Women using the active agent were less likely to develop stretch marks than women using placebo (OR 0.41; 95% CI, 0.17–0.99).

A randomized, double-blind, vehicle-controlled study examined the effectiveness of daily tretinoin 0.1% cream on existing stretch marks in 22 patients (10 in tretinoin group and 12 in vehicle group) for 6 months. At the end of the study, the severity score in the tretinoin group was 2.7 (down from 5.8 at baseline) while in the vehicle group the score was 5.3 (down from 5.2) (P<.001 for change from baseline between groups).

After 6 months, 80% had marked improvement in the tretinoin group compared with 8% in the vehicle group (P=.002). Targeted stretch marks in the tretinoin group had a decrease in length and width of 14% and 8% respectively, compared with increases of 10% (P<.001) and 24% (P=.008 ), respectively, in the vehicle group.

An observational trial examined using the 308-nm xenon chloride (XeCl) excimer laser to treat mature hypopigmented striae. Seventy-five subjects with hypopigmented striae on the trunk and extremities present for at least 2 years underwent treatment. A total of 615 treatments were done. The results were based on the change in pigment in the treatment area using a 4-point scale: 0=0% (no increase), 1=1%–25% (mild increase), 2=26%–75% (moderate) and 3=76%–100% (substantial increase). All subjects achieved a score of 3 after an average 8.4 treatments. Eighty percent of subjects noted improvement in cosmetic appearance of the striae.

Yuriy Bukavyn, MD
Kim Havard, PhD, GNP-BC
UAMS – South FMRP
El Dorado, AR
What are the health effects of night and alternating shift work?

Evidence-Based Answer
The answer is unclear. Individuals doing shift work have an increased risk of myocardial infarction, coronary events, and ischemic stroke, although a causal link has not been proven (SOR: B, meta-analysis of cohort and case-control trials). There also appears to be an association with the development of the metabolic syndrome in men and breast cancer in women (SOR: B, prospective cohort and single case-control studies).

In a recent meta-analysis, 34 multinational (Austria, Canada, Denmark, Finland, Germany, Iceland, Italy, Japan, Norway, Sweden, Qatar, UK, USA) observational studies (11 prospective cohorts, 13 retrospective cohorts, and 10 case-control analyses; >2 million patients) were reviewed to assess the association of shift work (any work schedule that is not approximately 9:00 am to 5:00 pm) and major vascular events in widely diversified, international populations and work environments.¹

Compared with non-shift work, shift work was associated with an increased risk of myocardial infarction (10 trials, 1.1 million patients; risk ratio [RR] 1.2; 95% CI, 1.2–1.3), ischemic stroke (28 trials, 1.5 million patients; RR 1.1; 95% CI, 1.0–1.1), and coronary events (2 trials; N=81,000; RR 1.2; 95% CI, 1.1–1.4), independent of smoking and socioeconomic status. The key weakness was that the study design did not allow for conclusions regarding causality.¹

A 2008 prospective study of Belgian men (N=1,529 from 6 private companies, 2 public administrations, and 1 bank) over a median observation period of 6.6 years compared the incidence of metabolic syndrome in shift workers (n=309) and day workers (n=1,220).² Risk of metabolic syndrome in shift work was significantly increased (61 per 1,000 person-years in shift workers vs 37 per 1,000 person-years in day workers; OR 1.8; 95% CI, 1.3–2.3).

There were also increases in hypertension (≥130/85 mmHg or need for antihypertensive medications; OR 1.3; 95% CI, 1.0–1.7), low levels of high-density lipoprotein cholesterol (<40 mg/dL; OR 1.4; 95% CI, 1.0–1.9), nonfasting glucose ≥120 mg/dL or type 2 diabetes (OR 1.6; 95% CI, 1.2–2.1), and hypertriglyceridemia (≥220 mg/dL; OR 1.5; 95% CI, 1.2–1.9) when compared with baseline examinations. Limitations of the study included gender bias (small number of women performing shift work) and more homogeneous populations and work environments than in other countries.²

A 2012 Danish military, case-control study compared the night shift work records of 141 women with breast cancer and 551 age-matched controls (<1 year of night work).³ The duration of night shift work exposure was associated with a higher rates of breast cancer. Women with the most exposure to night shift work (≥3 times/wk for ≥15 years) had the greatest risk for breast cancer (OR 2.5; 95% CI, 1.0–6.6) compared with controls (women never exposed to night shift as a preference). Women with moderate exposure had a moderate risk (≥3 times/wk for 6–15 years; OR 2.1; 95% CI, 1.0–4.8) compared with controls. Minimal exposure did not alter risk compared with controls (≥3 times/wk for 1–5.9 years; OR 1.1; 95% CI, 0.5–2.3).

These findings were present even when data were adjusted for age, hormone replacement therapy, number of childbirths, age at menarche, years of education, sunbathing frequency, and tobacco smoking status. Limitations of the study included small study size, case-control design, and homogeneous population.³

David M. Smith, DO
Robert K. Persons, DO, FAAFP
Eglin AFB FMR
Eglin AFB, FL

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the US Air Force at large, or the Department of Defense.

What is the best diagnostic approach to postmenopausal vaginal bleeding in women taking hormonal replacement therapy (HRT)?

**Evidence-Based Answer**

Independent of hormonal therapy, the workup for a postmenopausal woman with vaginal bleeding should be either an endometrial biopsy or transvaginal ultrasound (TVUS) followed by endometrial biopsy or hysteroscopy as indicated (SOR: C, consensus opinion guideline). The incidence of endometrial carcinoma is lower in women with postmenopausal bleeding on HRT compared with those not on HRT (SOR: B, cross-sectional study and a retrospective study).

Vaginal bleeding is the presenting sign in more than 90% of postmenopausal patients with endometrial carcinoma. Bleeding in postmenopausal HRT users can be due to the irregular use of the hormones or to underlying causes such as polyps, leiomyoma, atrophy, or carcinoma.¹

A retrospective medical record review of 326 women with postmenopausal bleeding was conducted from 2005 to 2009.² Of these women, 24% were on topical or systemic HRT and 76% were not on HRT. The diagnostic workup of postmenopausal bleeding independent of the presence or absence of HRT started with TVUS. If endometrial thickness was between 5 and 10 mm, then endometrial biopsy was done. If endometrial thickness was more than 10 mm, then women underwent hysteroscopy with endometrial biopsy or curettage followed by histopathological analysis.

Six percent of the 326 women in this study were diagnosed with endometrial cancer; none were taking HRT. There was a significantly lower risk of endometrial cancer in the HRT group compared with the non-HRT group (OR 0.08; 95% CI, 0.04–0.13).²

A cross-sectional study published in 2012 compared 4,847 postmenopausal women who presented to a gynecology oncology center with postmenopausal bleeding; 15% were on HRT and the remaining 85% were not.³ The diagnostic workup was similar to the protocol in the study above. The HRT group had a significantly thicker endometrium (median 5.2 vs 4.6 mm, respectively; P=.0024).

Endometrial carcinoma was diagnosed in 6.1% of all women with postmenopausal bleeding. Women in the HRT group were less likely to be diagnosed with both type I (estrogen-dependent, low-grade) and type II endometrial cancer (non-estrogen–dependent, high-grade) (OR 0.23; 95% CI, 0.12–0.45) compared with the non-HRT group.³

The American College of Obstetricians and Gynecologists published consensus opinion guidelines for the management of postmenopausal bleeding.⁴ Any episode of vaginal bleeding in postmenopausal women should be investigated to exclude malignancy. They recommend performing either immediate endometrial biopsy or TVUS. If endometrial thickness is more than 4 mm on TVUS, then endometrial biopsy is required. When postmenopausal bleeding persists despite negative or suboptimal evaluation, then additional evaluation with hysteroscopy, sonohysterography, and endometrial biopsy should be pursued.

Anca Sisu, MD
John Woytowicz, MD
Maine Dartmouth FMR
Augusta, ME

What prophylactic treatments are effective for patients with recurrent bacterial vaginosis?

**Evidence-Based Answer**

In patients with recurrent bacterial vaginosis (BV) who have just completed therapy for active disease, intravaginal probiotics for 14 additional days or intravaginal metronidazole gel 0.75% twice a week for 16 weeks decreases the recurrence rate (SOR: B, small RCTs). A 5-day course of intravaginal probiotic followed by a 5-day course of intravaginal metronidazole gel 0.75% after each menses may also lower the recurrence rate (SOR: C, low-quality cohort study).

A 2010 double-blind RCT assessed the efficacy of repopulating the vaginal flora with vaginal probiotic capsules in 120 healthy women of Asian descent with history of recurrent BV (≥2 BV episodes in the previous year).¹ Patients were randomly assigned to receive either daily Probaclac® vaginal probiotic (n=58, or placebo capsule n=62) for two 7-day periods with a 7-day break...
between. The primary endpoint was diagnosis of BV by Amsel criteria at any time during the 2-month follow-up.

The probiotic group had a lower BV recurrence rate through 2 months (16% vs 45%; OR 0.23; 95% CI, 0.10–0.55). At an 11-month follow-up telephone interview, patient-reported BV symptoms remained lower in the intervention group (11% vs 28%; OR 0.31; 95% CI, 0.11–0.93).

A 2006 multicenter, prospective, open-label RCT studied the use of suppressive vaginal metronidazole for the prevention of recurrent BV in 157 women with active BV and a history of at least 2 episodes of BV in the previous year. Patients received treatment with 0.75% metronidazole gel intravaginally at bedtime for 10 days. Ninety-five women who had been successfully treated for BV at 3 to 5 days after completion of the initial therapy were randomly assigned to receive suppressive metronidazole vaginal gel (n=51) or placebo (n=44) twice per week for 16 weeks. The women were evaluated every 4 weeks for recurrence of BV by Amsel criteria. Those who were without recurrence after 16 weeks were followed for an additional 12 weeks without any intervention.

At 16 weeks, fewer women in the metronidazole group had recurrence compared with the placebo group (26% vs 59%; RR 0.43; 95% CI, 0.25–0.73). Recurrences were also lower in the metronidazole group at 28 weeks (51% vs 75%; RR 0.68; 95% CI, 0.49–0.93).

Another prospective study evaluated the efficacy of extended antibiotic treatment with adjuvant lactobacilli in reducing the rate of relapse in 63 women with active BV diagnosed by Amsel criteria and no history of recurrent BV. Patients were treated initially with 2% vaginal clindamycin cream and 300 mg oral clindamycin twice a day for 7 days. After treatment with clindamycin, the women were treated with a 5-day course of intravaginal capsules containing lactobacilli and then 5 more days of metronidazole vaginal gel. This cycle of lactobacillus and metronidazole was repeated after each menstrual cycle for a total of 6 menstrual cycles. The patients sent vaginal samples by mail after each cycle. Follow-up was at 6, 12, and 24 months, unless relapse occurred sooner.

Cure rate (by Amsel criteria) was 75%, 65%, and 56% after 6, 12, and 24 months, respectively. An important weakness on this study was the lack of a comparison with a control group and the possibility of enrollment bias due to the lack of blinding.

Kamini Geer, MD
Temitope Adebisi, MD
Overlook Hospital FPR
Summit, NJ

What is the prevalence of acetabular labral tears in athletes involved in noncontact sports?

**Evidence-Based Answer**
Acetabular labral tears in athletes involved in noncontact sports range in prevalence from 22% to 100%. Labral tears may be found in both symptomatic and asymptomatic hips (SOR: C, case series).

A prospective clinical series of 42 hips from nonsymptomatic active-duty personnel of the US Air Force were assessed by MRI for the prevalence of acetabular labral tears. All patients met the yearly physical fitness standards and were excluded if they had previous hip surgery, previous labral lesions, or ever had sought medical treatment for hip pain. The average age was 34 years (range 27–43 years) with 16 men and 5 women. Between 80% and 85% of participants had labral tears with good inter/intraobserver reliability (90%/95%) between the 2 radiologists. Although there was no history of trauma or hip pain in this active population, there was no comment on patient participation in contact sports.

A prospective observational study of 18 patients (age range 17–48 years) with symptomatic hip/groin pain were assessed for the presence of labral tears with magnetic resonance arthrography. Each patient had onset of pain between 4 and 16 weeks before initial consultation. All patients participated in noncontact sports. With magnetic resonance arthrography, 22% of the hips studied had evidence of labral tears. Patients with labral tears were participants in dancing, badminton, or long distance running.

A retrospective case series studied 8 “high level” long distance runners with unilateral hip pain refractory to conservative measures. These athletes were either Olympic or college runners or had completed at least 100% of their training in noncontact sports.
5 marathons. The average age was 36 years (range 19–45 years) with 2 men and 6 women. There was no history hip trauma or underlying hip pathology in these patients. Hip arthroscopy of these runners showed that 100% had labral tears in the symptomatic hip.

Cory Nelson, DO  
Socorro Shelton, MD  
Southern Illinois University-Carbondale FMR  
Carbondale, IL


How effective is postexposure prophylaxis for varicella?

**Evidence-Based Answer**

The administration of varicella vaccine to children within 3 days of contact with a household member with varicella reduces the rate of infection and the severity of subsequent disease (SOR: A, systematic review). Some protection may be seen with vaccination as late as 5 days after contact (SOR: B, prospective cohort). No RCTs with adolescents or adults were identified.

Varicella (chickenpox) is a highly contagious viral infectious disease caused by the varicella zoster virus. It is usually self-limited in healthy children, manifesting as vesicular rash, fever, and constitutional symptoms. The condition is also associated with morbidity and mortality especially in immunocompromised hosts. Chickenpox can be prevented by vaccination with live-attenuated varicella vaccine.¹

A systematic review of 2 double-blind RCTs and 1 trial (with the method of randomization unclear) assessed the efficacy and safety of varicella vaccine for postexposure prophylaxis given within 3 days of exposure to 110 healthy children who were siblings of household contacts.² The trials varied in quality, study design, vaccine used, and outcomes measured.

When comparing vaccine with no vaccine in the overall analysis, varicella developed in significantly fewer vaccinated patients (23% treated vs 78% for placebo; *P*<.05; NNT=2), and in those patients who did develop varicella, moderate to severe varicella (>50 skin lesions) was much less common (2% vs 76% for placebo; *P*<.05; NNT=1.4). None of the trials reported on adverse events after immunization.²

A prospective cohort trial of 67 pediatric patients evaluated the effectiveness of the varicella vaccines in preventing and attenuating the disease in patients exposed to varicella.³ The patients were older than 1 year in a household with a primary case of chickenpox, and had a negative history of the disease, no evidence of previous vaccination, and varicella vaccination within 5 days after exposure.

The efficacy of the vaccine within 5 days of exposure in preventing any type of disease was 62% (95% CI, 0.48–0.75). The vaccine was 80% (95% CI, 0.66–0.89) effective in preventing moderate to severe disease.³

Lynda E. Mbah, MD  
Alan LeBato, MD  
LSUHSC Lake Charles Memorial FMR  
Lake Charles, LA


**GLOSSARY**

| ARR=absolute risk reduction | HR=hazard ratio |
| CDC=Centers for Disease Control and Prevention | LOE=level of evidence |
| CI=confidence interval | MRI=magnetic resonance imaging |
| CT=computed tomography | NNH=number needed to harm |
| FDA=US Food and Drug Administration | NNT=number needed to treat |
| NSAID=nonsteroidal anti-inflammatory drug | OR=odds ratio |
| RCT=randomized controlled trial | RR=relative risk |
| SOR=strength of recommendation | SSRI=selective serotonin reuptake inhibitor |

Evidence-Based Practice / Vol. 17, No. 4
What is the best pharmacologic therapy for dermatophyte skin infections?

**Bottom line**
Topical allylamines (eg, terbinafine, naftifine) and topical azoles (eg, miconazole, clotrimazole) both effectively treat tinea infections of the skin; however, allylamines cure slightly more infections than azoles (SOR: A, systematic review of RCTs). Tea tree oil is not an effective treatment for tinea (SOR: B, systematic review of 2 inconsistent RCTs).

**Evidence summary**
A 2009 Cochrane review of topical treatments for tinea pedis found 67 RCTs of men and women (N=8,115) with tinea pedis confirmed by fungal culture and KOH microscopy. The primary outcome was treatment failure defined as positive culture or microscopy. Key results are shown in the TABLE.

Allylamines and azoles were more effective than placebo (relative risk of treatment failure of 0.33 and 0.40, respectively). In direct comparison studies, allylamines were more effective than azoles. The review gave the individual outcomes for the 2 allylamines naftifine and terbinafine. Naftifine 1% for 4 weeks had fewer treatment failures than placebo (5 trials, N=607; RR 0.42; 95% CI, 0.30–0.59; NNT=2). Terbinafine 1% for 1, 2, and 4 weeks had fewer treatment failures than placebo as well (6 trials, N=500; RR 0.23; 95% CI, 0.15–0.38; NNT=2).¹

Tea tree oil (10% applied twice daily for 4 weeks) was evaluated in 2 placebo-controlled trials. One study (N=114) demonstrated a lower risk of treatment failure (RR 0.49; 95% CI, 0.42–0.83). However, a meta-analysis of the 2 studies combined (N=185) did not show a statistically significant benefit (RR 0.73; 95% CI, 0.48–1.1).²

A 2012 Brazilian systematic review produced consistent findings and conclusions to the Cochrane review from 2009.²

---

**TABLE**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>No. of subjects</th>
<th>Treatment</th>
<th>Comparison</th>
<th>Treatment duration</th>
<th>Follow-up</th>
<th>Relative risk of treatment failure (95% CI)</th>
<th>Absolute risk reduction (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>1,116</td>
<td>Topical allylaminea</td>
<td>Placebo</td>
<td>1–4 weeks</td>
<td>6 weeks</td>
<td>0.33 (0.24–0.44)</td>
<td>55% (50%–60%)</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>1,235</td>
<td>Topical azolesb</td>
<td>Placebo</td>
<td>4–6 weeks</td>
<td>6 weeks</td>
<td>0.40 (0.35–0.46)</td>
<td>40% (34%–45%)</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>173</td>
<td>Topical allylaminea</td>
<td>Topical azolesc</td>
<td>1–2 weeks</td>
<td>6 weeks</td>
<td>0.34 (0.22–0.52)</td>
<td>36% (21%–47%)</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>1,003</td>
<td>Topical allylaminea</td>
<td>Topical azolesd</td>
<td>4–6 weeks</td>
<td>6 weeks</td>
<td>0.63 (0.42–0.94)</td>
<td>14% (8%–19%)</td>
<td>8</td>
</tr>
</tbody>
</table>

CI=confidence interval; NNT=number needed to treat; RCT=randomized controlled trial.

TaTopical allylamine = naftifine 1% or terbinafine 1%.
²Topical azoles = bifonazole 1%, clotrimazole 1%, miconazole nitrate 2%, oxiconazole nitrate 1%, sulconazole nitrate 1%, or tericonazole 1%.
³Topical azoles = clotrimazole 1% or oxiconazole nitrate 1%.
⁴Topical azoles = bifonazole 1% or clotrimazole 1%.

---

1. How should physicians counsel patients on sun exposure and sunscreen use for infants?
   a. Sunscreen should not be used before 2 years of age because infants and toddlers should not be exposed to ultraviolet radiation within the first 2 years of life.
   b. Sunscreen and sun avoidance are not important for infants because their skin is immature and thus is not susceptible to damage by ultraviolet radiation.
   c. Direct sun exposure should be avoided with infants <6 months of age but when exposure is unavoidable, small amounts of sunscreen can be used on areas of face and hands not covered by clothes or shade.
   d. It is appropriate to use sunscreen on infants regardless of age because their skin is just like adult skin.

2. What history or physical finding is associated with Helicobacter pylori-positive gastritis?
   a. Smoking history
   b. Lack of belching
   c. Abdominal distention
   d. Abdominal pain

3. Which of the following is an effective lipid-lowering therapy for children with familial hypercholesterolemia?
   a. Cholesterol-lowering diet
   b. Plant stanols and sterols
   c. Statin medications
   d. Soy protein

4. What treatments improve the appearance of existing stretch marks?
   a. Laser
   b. Tretinoin
   c. No treatments improve the appearance
   d. A and B

5. What can be said of the prevalence of acetabular labral tears in athletes participating in noncontact sports?
   a. These tears are uniformly symptomatic
   b. These tears do not occur in noncontact sport athletes
   c. They are extremely rare, seen in <5% of symptomatic patients
   d. They are common and occur in patients with and without symptoms

6. Which of the following strategies is an appropriate initial diagnostic test in the workup of postmenopausal bleeding in a woman taking hormone replacement therapy?
   a. Clinical observation for 1 year
   b. Transvaginal ultrasound
   c. Curettage and histopathological analysis
   d. Hysteroscopy with endometrial biopsy

7. Appropriate topical treatment of dermatophyte skin infections includes all but which of the following agents?
   a. Butenafine
   b. Naftifine
   c. Tea tree oil
   d. Terbinafine

8. You are practicing in an urban community with many companies operating around the clock. One of your patients, the matriarch of a family heavily involved with shift work at various facilities, asks if there are any health concerns associated with shift work. You respond:
   a. There are no health risks associated with shift work
   b. A decreased risk of breast cancer has been identified in shift workers
   c. There is a decreased risk of diabetes in shift workers
   d. Shift work is associated with higher rates of myocardial infarction and stroke, although causality has not been proven

For CME credit, return this test to: FPIN, 409 W. Vandiver Drive, Bldg. #4, Ste 202, Columbia, MO 65202 or fax to 573-256-2078. If you have questions, please contact Kerri Reynolds (ebp@fpin.org or call 573-256-2066).

Renew or Subscribe to EBP at www.fpin.org/subscribe or call 573-256-2066
A Sustainable Model With A Global Reach

The NEW CI Series

After publishing more than 700 Clinical Inquiries over the last 10 years in The Journal of Family Practice, American Family Physician and Evidence-Based Practice, we have restructured the process to produce the highest quality product possible and create a rewarding and educational experience for our members. We believe this streamlined editorial approach will sustain the series for decades to come.

Why Are Clinical Inquiries Important for Family Medicine?

- Clinical Inquiries are published in the world medical literature.
- Clinical Inquiries rigorously answer clinical questions relevant to practicing physicians.
- The Clinical Inquiries methodology requires a reproducible literature search.
- The Clinical Inquiries project provides an avenue for faculty promotion and tenure.

Interested in finding out more about the new Clinical Inquiries series? Join us at STFM for our session, Useful Scholarship: Writing Structured Evidence Reviews for Publication with the New Model Clinical Inquiries Series, or contact ci@fpin.org.