What is the risk of restenosis after drug-eluting stent placement?

**Evidence-based answer**

The rates of restenosis requiring revascularization for drug-eluting stents are 4% to 6% at 6 months and 7% to 10% at 3 years (SOR: A, systematic review of RCTs). Newer generation drug-eluting stents with everolimus and zotarolimus provide better results, with revascularization rates of 3% at 2 years (SOR: B, retrospective cohort study).

**Evidence summary**

A 2010 systematic review of 47 RCTs compared drug-eluting stents and bare metal (non-eluting) stents in 14,891 patients with stable angina or acute coronary syndrome who underwent percutaneous transluminal coronary angioplasty. Patients were followed for up to 5 years after stent placement. Antiproliferative agents studied in some of these RCTs included the 3 drugs currently approved by the US FDA in drug-eluting stents: everolimus, paclitaxel, and zotarolimus. This systematic review examined 3 RCTs containing 76 patients treated with everolimus-eluting stents, 16 RCTs containing 3,514 patients treated with paclitaxel-eluting stents, and 1 RCT containing 598 patients treated with zotarolimus-eluting stents.

Restenosis, defined as narrowing of a previously stented coronary vascular lesion, can occur after treatment with drug-eluting stents. Target lesion revascularization (TLR) rate is a measure of clinically significant restenosis requiring repeat revascularization. The TLR rates for coronary stents with the 3 FDA-approved antiproliferative agents are provided below (see TABLE), but were not compared statistically.

A 2012 retrospective cohort study in Sweden compared “new-generation” drug-eluting stents (n-DES), “old-generation” drug-eluting stents (o-DES), and bare metal stents (BMS) in all patients with coronary stent placement from November 2006...
**TABLE**

Target lesion revascularization rates in drug-eluting stents with 3 FDA-approved antiproliferative agents

<table>
<thead>
<tr>
<th>Time since stent placement</th>
<th>Everolimus (data set)</th>
<th>Paclitaxel (data set)</th>
<th>Zotarolimus (data set)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>3.8% (2 trials, n=53)</td>
<td>5.5% (10 trials, n=1,994)</td>
<td>4.6% (1 trial, n=592)</td>
</tr>
<tr>
<td>1 year</td>
<td>No data</td>
<td>4.7% (6 trials, n=1,406)</td>
<td>No data</td>
</tr>
<tr>
<td>2 years</td>
<td>No data</td>
<td>8.4% (6 trials, n=1,912)</td>
<td>No data</td>
</tr>
<tr>
<td>3 years</td>
<td>7.1% (1 trial, n=28)</td>
<td>10.3% (2 trials, n=243)</td>
<td>7.3% (1 trial, n=577)</td>
</tr>
<tr>
<td>4 years</td>
<td>No data</td>
<td>6.9% (3 trials, n=928)</td>
<td>No data</td>
</tr>
<tr>
<td>5 years</td>
<td>No data</td>
<td>14.3% (1 trial, n=217)</td>
<td>No data</td>
</tr>
</tbody>
</table>

Stents were not compared head-to-head.

through October 2010 at 29 sites across the country. The n-DES were classified as containing everolimus or zotarolimus. The o-DES were classified as older stent designs containing zotarolimus or stents containing either paclitaxel or sirolimus.

After 2 years, the TLR rates were 3.1%, 4.9%, and 5.5%, respectively, in n-DES (n=10,551), o-DES (n=19,202), and BMS (n=64,631). The adjusted hazard ratio for TLR in n-DES versus o-DES was 0.60 (95% CI, 0.51–0.70), and the hazard ratio for TLR in n-DES versus BMS was 0.32 (95% CI, 0.28–0.38).

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**REFERENCES**


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**GLOSSARY**

- **ARR**=absolute risk reduction
- **CDC**=Centers for Disease Control and Prevention
- **CI**=confidence interval
- **CT**=computed tomography
- **FDA**=US Food and Drug Administration
- **HR**=hazard ratio
- **LOE**=level of evidence
- **MRI**=magnetic resonance imaging
- **NNH**=number needed to harm
- **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
- **WHO**=World Health Organization

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A world of opportunity

If your patient panel is anything like mine, you’ve noticed that at least half of the adults are overweight, about a third have high blood pressure, and a smaller, but frequently seen, fraction has diabetes. Yet, with motivational interviewing, lifestyle modification, pills, and injections, bad outcomes like amputations, strokes, and heart attacks before age 60 are thankfully rare.

I was contemplating this the other day when I picked up a copy of a Scientific American monograph, “Promoting Cardiovascular Health Worldwide.” The data inside were jaw-dropping. It turns out that developing nations (where most people live) are rapidly surpassing the United States in the incidence of illnesses we family physicians manage every day. The following data are not for the United States—they are for the whole world:

- 35% of adults (1.4 billion people) are overweight or obese and 10% have diabetes
- The diabetes rate is expected to hit 20% by 2030
- More people now die from the complications of obesity than from malnutrition
- 30% of adults get <150 minutes a week of moderate exercise
- Excessive salt intake is thought to be responsible for 2.3 million deaths a year
- Hypertension is present in 30% of people older than 25 and in 40% older than 45
- 15% of people smoke. Residents of developing nations smoke at 4 times the rate of developed nations. India alone suffers 1 million tobacco-related deaths a year
- Unfortunately, cardiovascular disease, hypertension, and diabetes mellitus received just 3% of global health aid from 2001 through 2007

The same monograph, thankfully, highlighted some good news:

- Turkey cut hospital admissions from smoking-related illnesses 24% in 1 year
- Finland decreased myocardial infarction and stroke deaths by 85% over 30 years
- Some international food companies are reformulating products with less sugar, fat, and salt
- Tobacco reduction policies in 41 countries likely prevented 7.5 million deaths over 3 years

So, my fellow family physicians, it appears our humble skills are urgently needed around the world. Let’s go to work.
Diving for PURLs

Rule out MI faster with high-sensitivity troponin


This large prospective trial of patients presenting to the emergency room (ER) with chest pain and suspected acute coronary syndrome (ACS) evaluated the high-sensitivity troponin (hs-troponin) threshold for predicting low risk of a cardiac event, using a derivation cohort as well as an internal and external validation cohort. Primary outcomes were type I myocardial infarction (MI) at presentation (index MI) and 30 days, and cardiac death at 30 days. Secondary outcomes were MI or cardiac death within 1 year after ER presentation.

In the derivation cohort (n=4,780), 16% had an index MI; at 30 days 1% had an MI and 2% had cardiac death. Overall, 61% with standard troponin levels <99% in the ER had an hs-troponin level <5 ng/L, with a negative predictive value (NPV) of 99.6% (95% CI, 99.3–99.8) for type I MI or cardiac death within 30 days.

The validation cohorts (n=1,434) showed similar results, with an NPV of 99.3% (95% CI, 98.5–99.9) in the internal validation cohort and 99.8% (95% CI, 98.0–100.0) in the external validation cohort.

No significant difference was noted in the NPV for hs-troponin <5 ng/L when stratified by sex, age, or cardiovascular risk factors. Only 0.6% (n=12) of patients with hs-troponin <5 ng/L had MI or cardiac death at 1 year versus 3.3% (n=48) of patients with hs-troponin >5 ng/L, with an adjusted HR of 0.41 (95% CI, 0.21–0.80; P<.0001).

Note, although hs-troponin tests are available in many hospitals in the United States, the test used here is even more sensitive and is not yet widely available.

Bottom line: Discharging ER patients with suspected ACS may be reasonable if their hs-troponin is <5 ng/L, but check your lab first to see what kind of troponin assay was used.

Popeye’s new spinach: IV iron for heart failure patients with iron deficiency


This double-blind RCT compared IV iron (ferric carboxymaltose, FCM) with placebo in 304 ambulatory, symptomatic (NYHA class II–III) heart failure (HF) patients with iron deficiency, defined as ferritin <100 ng/mL or 100–300 ng/mL if transferrin saturation <20%. Patients received either weight-based dosing of FCM IV at baseline and at 6 weeks (correction phase) and FCM 500 mg IV doses at weeks 12, 24, and 36 (maintenance phase) if iron deficiency was still present or placebo.

The primary outcome was the change in 6-minute walk test (6MWT) from baseline to 24 weeks. Secondary outcomes included changes in NYHA stage, patient global assessment (PGA), and rates of hospitalization, death, and adverse events from weeks 6 through 52.

At baseline, the FMC IV group had a mean 6MWT of 288±98 m; in the placebo group the mean was 302±97 m. At week 24, the 6MWT increased for FCM patients (18±8 m) and decreased for placebo patients (–16±8 m), resulting in a significant difference of 33±11 m (P=.002).

There was significant benefit for the FCM group compared with placebo in PGA from week 12 onward (P<.05) and NYHA class from week 24 onward (P<.05). Overall, there was no difference in death or hospitalization. However, subgroup analysis showed a decrease in hospitalization due to worsening HF (HR 0.39; 95% CI, 0.19–0.82). No differences were noted between the 2 groups for adverse events.

Bottom line: IV iron therapy increased 6MWT times and decreased hospitalizations due to worsening HF in patients with iron deficiencies. However, these results are tempered by lack of information on oral iron therapy failure, and significant pharmaceutical company oversight of the study.

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What is the likelihood that snoring predicts obstructive sleep apnea or other significant pathology in the preschool-aged child?

Evidence-based answer
Snoring, alone, does not predict obstructive sleep apnea in children.

Case
You are seeing a healthy 4-year-old boy for a well-child visit when his parents mention that he snores “a lot” most nights. They are concerned that this may mean he has sleep apnea and ask for your opinion.

Evidence summary
“Primary snoring,” which is snoring without sleep apnea, has a prevalence of 3% to 12% in children. Parents are often concerned that snoring means sleep apnea is present, but the prevalence of pediatric obstructive sleep apnea is just 2%. According to the 2012 American Academy of Pediatrics (AAP) clinical guidelines, clinicians should inquire whether a child snores at routine health maintenance visits. If a child does, a focused evaluation should be done before deciding on a referral for a polysomnogram (grade A recommendation).

The AAP recommendation is based on 350 articles, very few of which were large RCTs. The variation in how pediatric obstructive sleep apnea is defined and measured also makes it difficult to interpret this data set. Overall, studies revealed poor sensitivity and specificity of snoring history alone.

A 2012 meta-analysis of 10 studies and 1,525 patients, which assessed the accuracy of clinical symptoms and signs in predicting pediatric obstructive sleep apnea, concluded that neither single nor combined signs and symptoms have satisfactory performance in predicting pediatric obstructive sleep apnea. Excessive daytime sleepiness, witnessed apneas, and difficulty breathing during sleep had high specificity but low sensitivity, with 7 models of combinations of symptoms and signs having sensitivities ranging between 0.04 and 0.94 and specificities of 0.28 to 0.99. Use of these signs and symptoms may lead to a higher than desired number of false-positive diagnoses of obstructive sleep apnea.

An analysis of the Childhood Adenotonsillectomy (CHAT) study data, which was a single-blinded RCT including 453 children 5 to 9 years old, found that questionnaires were poor predictors of obstructive sleep apnea severity. African American race and obesity (defined by body mass index z score >2) were associated with higher apnea-hypopnea and oxygen-desaturation indices.

Case Wrap-Up
You share with the family that snoring alone is not predictive of sleep apnea in the preschool-aged child. As this child is otherwise completely well, you recommend no other workup at this time.

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REFERENCES
In the third stage of labor, is delayed cord clamping beneficial compared with early cord clamping for term neonates?

Evidence-Based Answer

Delayed cord clamping (compared with early cord clamping) is associated with a decreased risk of iron deficiency at 3 to 6 months of age but an increased risk of hyperbilirubinemia requiring phototherapy (SOR: A, meta-analysis). By 12 months the hematologic differences disappear (SOR: C, meta-analysis of RCTs of disease-oriented outcomes). The effect on reducing infant anemia may be more pronounced if the mother is anemic (SOR: C, single cohort study of disease-oriented outcomes).

A Cochrane review of 15 RCTs in term infants (N=3,911) examined effects of early (<1 minute) versus delayed cord clamping on hemoglobin (Hgb), iron deficiency, and hyperbilirubinemia. “Delayed” was defined as 10 seconds after infant breathing, cessation of cord pulsations, or 5 minutes after delivery.

Early cord clamp groups compared with delayed groups had lower 24- to 48-hour Hgb levels (4 trials, n=884; mean difference [MD] –1.5 g/dL; 95% CI, –1.8 to –1.2), increased iron deficiency at 3 to 6 months of age (5 trials, n=1,152; risk ratio [RR] 2.7; CI 1.0–6.7), and decreased hyperbilirubinemia requiring phototherapy (7 trials, n=2,324; RR 0.62; 95% CI, 0.41–0.96).

A 2014 RCT of 347 term infants compared the effect of delayed (>179 seconds) versus early (<11 seconds) cord clamping on iron status and neurodevelopment at age 12 months. There were no differences at 12 months between the infants in the delayed and early groups in iron status (n=337, ferritin MD 2.3 ng/mL; 95% CI, –3.0 to 7.5; transferrin saturation MD –0.1%; 95% CI, –1.6 to 1.5; soluble transferrin receptor MD –0.08 mg/L; 95% CI, –0.29 to 0.13), hemoglobin (n=337, MD –1.4 g/dL; 95% CI, –3.3 to 0.5), or neurodevelopment evaluated by Ages and Stages Questionnaire scores (n=340, MD –3.4; 95% CI, –11.9 to 5.0). Breast milk, formula, and solid food intake in both groups were similar.

In 2013, with a cohort of 207 pairs of mothers and infants, researchers examined the effects of cord clamp timing on infant anemia (Hgb <11 g/dL) at 4- and 8-month follow-up visits in mothers with and without anemia (Hgb <11 g/dL) at delivery. For each minute clamping was delayed (range 0.19–6.6 minutes), there was an approximate 40% risk reduction for anemia in infants born to anemic mothers at 4 months of age (n=45, adjusted odds ratio [aOR] 0.59; 95% CI, 0.31–0.98) and a 60% reduction at 8 months of age (n=40, aOR 0.38; 95% CI, 0.19–0.76). The time of cord clamping had no significant effect on the odds of developing anemia at 4 or 8 months of age in infants of mothers not anemic at delivery.

The World Health Organization makes the recommendation to delay cord clamping 1 to 3 minutes after delivery.

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What is the best treatment for hairy leukoplakia?

Evidence-Based Answer

Topical podophyllin 25% resin alone, podophyllin with acyclovir 5% cream, and podophyllin with penciclovir 1% cream are all effective in treating oral hairy leukoplakia (OHL). Podophyllin with acyclovir may have a better resolution rate than podophyllin alone. No significant differences have been noted in rates of recurrence (SOR: B, 2 small RCTs).

A 2010 double-blind RCT evaluated the number of applications for clinical resolution and rate of recurrence of OHL using podophyllin 25%, podophyllin 25% with a 5% acyclovir cream, or podophyllin 25% with a 1% penciclovir cream. The study consisted of 42 patients with a total of 69 OHL lesions.

The podophyllin-acyclovir treatment led to clinical healing after only 18 applications (23 lesions) compared with 23 applications for the podophyllin-penciclovir treatment (22 lesions) and 25 applications for the podophyllin treatment (24 lesions). However, this difference was not significant (podophyllin-
The Pediatric Appendicitis Score (PAS) is not sufficiently accurate to rule out or rule in acute appendicitis in children with abdominal pain (SOR: B, systematic reviews of prospective cohort trials).

The PAS is an 8-item, 10-point clinical decision rule to aid in the diagnosis of acute appendicitis in children. A systematic review of 6 moderate- to high-quality prospective cohort studies (N=2,170) assessed the accuracy of the PAS in children (age range 1–21 years) presenting to the emergency department with acute abdominal pain. Surgery and clinical follow-up were used as the reference standard in all studies. The review attempted to identify if the PAS had optimal cutoffs for low- and high-risk patients. Low risk was defined as a PAS score of <4, moderate risk as a score of 4 to 7, and high risk as a score of ≥8.

The low-risk group was found to have a pooled positive likelihood ratio (LR+) of 0.13 (95% CI, 0.04–0.40), the moderate-risk group a pooled LR+ of 0.7 (95% CI, 0.45–1.1), and the high-risk group a pooled LR+ of 8.1 (95% CI, 4.1–16).

The LR+ of 0.13 corresponds to a posttest probability of at least 6% for any pretest probability of ≥20%, which was higher than the target cutoff of 5% cited by the authors. At the same pretest probability, the LR+ of 8.1 corresponds to a posttest probability of 80%, which was below the author’s accepted high-risk posttest probability of 85%. The authors concluded that the PAS was not clinically useful to identify children at low or high risk for appendicitis.

A 2013 systematic review of clinical prediction rules for children with suspected appendicitis included 5 prospective cohort studies of the PAS (N=2,953). Four of 5 demonstrated high methodological quality, although the largest (n=1,170) had the lowest quality. The studies included children aged 1 to 21 years who presented to the emergency department with acute abdominal pain, using a reference standard of pathology and clinical follow-up. Due to the heterogeneity of the patient populations included, pooling of results was not possible.

The specificity of the PAS ranged from 65% to 95%. The sensitivity of the PAS ranged between 82% and 100% (median 93%) and the negative likelihood ratio (LR–) between 0 and 0.27 (median 0.1). The rule predicted appendicitis in 43% to 98% of patients (median 52%), representing an overdiagnosis rate of 35%. The study authors concluded that the PAS did not meet the performance benchmarks of sensitivity >95%, LR– <0.1, or an acceptably low negative appendectomy rate.
Are conservative treatment options effective for pelvic floor dysfunction due to pelvic organ prolapse?

Evidence-Based Answer
Pelvic floor muscle training (PFMT) decreases symptoms of pelvic floor dysfunction among women with varying degrees of pelvic organ prolapse (POP) (SOR: A, consistent RCTS), although the amount of improvement is unclear. A pessary may be about as effective as PFMT, while combining the 2 modalities provides no additional benefit over PMFT alone (SOR: B, RCTs).

A Cochrane review examined 3 RCTs of 203 women with varying degrees of POP, comparing PFMT for 5 to 24 sessions over 3 to 6 months to usual care with or without lifestyle advice.1 PFMT was more effective than usual care for reducing POP symptoms from baseline, but results could not be combined across studies because different outcome measures were used.

One RCT (n=109; mean age 49 years) reported reduced frequency of prolapse symptoms of vaginal bulging and/or heaviness with 18 PFMT sessions versus usual care after 6 months (31% vs 74%; RR 0.37; 95% CI, 0.21–0.65) and reduced bother from vaginal bulging and/or heaviness (42% vs 67%; RR=0.56; 95% CI, 0.33–0.97). However, nonequivalent groups at baseline may have biased results. A second RCT (n=47; mean age 53 years) reported less pelvic heaviness with 24 PFMT sessions versus usual care after 3 months (19% vs 70%; RR 0.26; 95% CI, 0.11–0.61). A third RCT (n=47; mean age 56 years) reported greater reduction from baseline in prolapse symptom scores (range 0–28) with 5 PFMT sessions compared with usual care after 26 weeks (mean difference [MD] −3.4; 95% CI, −6.2 to −0.5).1

An RCT of 287 women (mean age 64 years) with mild POP compared individualized PFMT with no treatment or general recommendations for 3 months (5–7 sessions) for bladder, bowel, and pelvic symptoms.2 The PFMT group had significantly fewer symptoms (urinary symptoms, POP distress, and colorectal-anal distress) than controls at follow-up compared with baseline (0–300 range, MD −11; 95% CI, −16.6 to −5.4). Reductions were mainly in urinary symptoms (0–100 range, MD −6.0; 95% CI, −9.1 to −2.9) with some reduction in POP distress (0–100 range, MD −2.6; 95% CI, −4.9 to −0.4), but not in colorectal-anal distress (0–100 range, MD −1.4; 95% CI, −3.7 to 0.8). Groups did not differ in quality of life or sexual symptoms. An individualized rather than uniform protocol may have biased results.

Another RCT of 446 women with urinary stress incontinence were evaluated with a POP distress index (POPDI, range 0–300) and POP impact questionnaire (POPIQ, range 0–300) after treatment with PFMT or a pessary.3 After 3 months, no significant differences were noted for change from baseline in the pessary group versus the PFMT group (POPDI −14 vs −15; P=.24; POPIQ −7.2 vs −5.3; P=.26).

Does cessation of the use of tobacco products affect the INR in patients receiving warfarin?

Evidence-Based Answer
Smoking cessation is associated with higher plasma warfarin levels (SOR: C, bench research) and perhaps a 12% decreased warfarin dosing requirement (SOR: C, conflicting cross-sectional studies).

A 1979 small, prospective crossover study (N=12) examined the effect of smoking cessation on plasma warfarin levels and prothrombin time in healthy...
smoking volunteers.\(^1\) Patients 19 to 60 years of age who smoked at least 1 pack per day were given 1.5 to 3.0 mg warfarin daily for 14 days. After a 1-month washout of not smoking, patients took the same warfarin dose for 14 days. Three patients dropped out because they returned to smoking. Steady-state warfarin levels measured on days 11 to 14 of each phase were averaged for each subject.

The steady-state warfarin level in the nonsmoking phase was 0.45 mg/L compared with 0.40 mg/L in the smoking phase (\(P<.01\)). Prothrombin times were not measurably different between groups.\(^1\)

A 2011 systematic review (N=3,386) examined 12 cross-sectional studies (7 prospective, 5 retrospective) and the crossover study above investigating the interactions between tobacco use and warfarin therapies.\(^2\) Three studies (n=1,783) that reported the outcome as percent difference in warfarin dosing showed smokers required 12% higher warfarin doses (95% CI, 7.0–17) than nonsmokers. The mean age in these 3 studies ranged from 58 to 65 years. There was no heterogeneity among these studies. Three other studies (n=544), with significant heterogeneity, reported the outcome as absolute difference in warfarin dosage. They showed smokers required a nonstatistically significant 2.3 mg per week higher dose of warfarin compared with nonsmokers (95% CI, –2.5 to 7.0). The mean age in these 3 studies ranged from 59 to 69 years.

A 2001 case report describes an 80-year-old man who had been taking 5 mg warfarin daily for stroke and had INR values in the 2.0 to 3.0 range for 10 months.\(^3\) He had a 50 pack-year history of smoking. INR values steadily increased the 3 months after smoking cessation to a peak of 3.7. His warfarin dose was reduced from 35 to 30 mg weekly. INR was stable on the new dose for 9 months. No changes in prescription medications, over-the-counter medications, herbal medications, or alcohol were reported.

A 2005 case report describes a 58-year-old man with a history of deep vein thrombosis who was admitted with bacterial meningitis.\(^4\) Prior to admission he took 58.75 mg per week of warfarin and had stable INR values for 6 months. He received multiple antibiotics during the admission. On discharge, he resumed his usual 3 to 5 glasses of wine each day, but not tobacco (39 pack-years). Two months after the antibiotics were discontinued, elevated INRs of 3.4 then 5.5 were reported on his previous warfarin dose. His dose was ultimately reduced to 43.75 mg per week, which resulted in stabilized INRs at or near the target range.

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Does manual extraction of the placenta or manual exploration of the uterus increase the risk of endometritis?

Evidence-Based Answer

Manual extraction of the placenta appears to increase the risk of endometritis after vaginal or cesarean delivery (SOR: B, cohort study and RCT).

In 1995, a retrospective cohort study of more than 25,000 deliveries compared manual removal of the placenta with spontaneous delivery of the placenta after vaginal delivery.\(^1\) A total of 1,421 deliveries had manual removal of the placenta and 24,266 deliveries involved spontaneous delivery of the placenta of which, 1,227 and 1,278, respectively, were randomly selected. After exclusion criteria (postpartum antibiotics and neonates weighing <550 g or <20 weeks’ gestation), records were available for 1,052 deliveries with manual extraction of the placenta and 1,085 with spontaneous delivery of the placenta. Endometritis was defined as temperature >38°C and physician impression, or any patients treated for endometritis postpartum regardless of temperature.

Manual removal of the placenta was associated with an increased risk of endometritis (OR 2.9; 95% CI, 1.7–4.9; NNH=20).\(^1\)

In 2005, a prospective RCT of 840 cesarean deliveries evaluated the incidence of endometritis after manual extraction of the placenta compared with spontaneous delivery of the placenta.\(^2\) All women with an indication for cesarean section were randomized into 2 subgroups: manual placental delivery (n=420) and spontaneous placental delivery (n=420). Exclusion criteria included intrapartum antibiotics, chorioamnionitis, emergency cesarean hysterectomy, rupture of membranes for
>12 hours, bleeding diathesis, abnormal placentation, and prior postpartum hemorrhage. All patients received 1 g cefazolin after clamping of the umbilical cord. Endometritis was defined as temperature of ≥38°C on 2 occasions 6 hours apart after the first postoperative day and 2 of the following signs or symptoms: foul-smelling lochia, leukocytosis (white blood cell count >15,000/mL), or uterine tenderness.

The incidence of postoperative endometritis was significantly higher with manual removal of the placenta than with spontaneous delivery of the placenta (15% vs 5.7%; OR 3.0; 95% CI, 1.8–4.9; NNH=10).

Does an increased rate of IV fluids shorten the labor course of low risk nulliparous women?

Evidence-Based Answer

The answer is unclear. In nulliparous women with singleton pregnancies presenting in spontaneous active labor, there is conflicting evidence that IV fluids at more than the standard rate of 125 mL/h shorten labor (no SOR given).

A 2012 RCT evaluated the rate of IV fluid administration on the duration of labor in 293 nulliparous women. Low-risk nulliparous women in active labor received oral hydration alone, lactated Ringer’s at 125 mL/h, or lactated Ringer’s at 250 mL/h.

The duration of labor among the 3 groups was not significantly different: 391 minutes in the oral fluid group, 363 minutes in the 125 mL/h group, and 343 minutes in the 250 mL/h group (P=.20 for 3-way comparison). Labor lasting longer than 12 hours occurred in 7.1%, 4.1%, and 3.1%, respectively (P=.42 for 3-way comparison). Need for oxytocin administration was 37%, 32%, and 33%, respectively (P=.68 for 3-way comparison).

A 2006 RCT evaluated the effect of IV fluid rates on labor length in 300 low-risk nulliparous women with singleton pregnancies over 37 weeks’ gestation in spontaneous active labor. Mean length of labor was decreased in the 250 mL/h group compared with the 125 mL/h group (253 vs 386 minutes; P=.0001). Labor lasting longer than 10 and 15 hours was less common in the 250 mL/h group (13.8% vs 8.1%; P=.001; 4.5% vs 0%; P=.02). Need for oxytocin administration was significantly less in the high rate group (20.4% vs 8.1%; P=.001).

A 2000 RCT evaluated the effects of IV fluid rates on the length of labor in 195 nulliparous women. Patients at more than 36 weeks’ gestation in active labor received lactated Ringer’s or isotonic sodium chloride solution at a rate of 125 or 250 mL/h. Labor lasting longer than 12 hours occurred more frequently in the 125-mL group (26% vs 13%; P=.047). Need for oxytocin administration was no different between the 125-mL group and the 250-mL group (65% vs 49%; P=.06). Rate of cesarean deliveries between the 2 groups was no different (17% vs 10%; P=.22).

Can wearing high heels every day have detrimental effects?

Evidence-Based Answer

Wearing high heels (HH) habitually leads to multiple changes in a person’s biometrics, including increased lower extremity tendon stiffness, increased lumbar lordosis, and a more retroflexed pelvis, but inconsistent changes in muscle fascicle shortening (SOR: C, disease-oriented evidence from small cohort trials). Whether these changes cause symptoms is not known.

A cohort study done in 2012 examined muscle fascicle length and strain markers in the lower extremity of habitual HH users versus nonusers during barefoot standing and walking. The sample group included 9 women who had worn heels 5 cm high for at least 40 hours a week for at least the past 2 years. The control group consisted of 10 women who did not regularly wear heels. The study does not state how participants were recruited. Measurements were taken using a mixture of surface electromyography and ultrasound.
Mean resting gastrocnemius fascicle length was reported to be significantly shortened in HH wearers versus nonwearers, but actual measurements were not given. However, mean peak fascicle strain (the maximum amount of stress an average fascicle of the gastrocnemius muscle was under during barefoot walking) was not significantly different between groups (3.8 for HH users and 3.6 for controls; $P=.85$, units of measure not reported).\(^1\)

Another cohort study in 2011 examined lumbar and pelvic mechanics in adolescent HH users versus nonusers.\(^2\) The sample group included 50 teenagers who had worn HH of an unspecified height for at least 4 consecutive hours at a time, at least 4 times per week over the past year. The control group included 50 teenagers who did not habitually wear HH. All participants were volunteers from a private school in Brazil. Measurements were taken using postural analysis software on sagittal photographs.

The mean barefoot lumbar lordosis angle was 62° in HH users and 40° in non-HH users, a difference of 22° (95% CI, 20.1–24.0). The mean barefoot pelvic horizontal alignment in HH wearers was −9.5° and in those who did not normally wear HH, it was −14.5°, a mean difference of 5° (95% CI, 2.8–7.3). The study authors theorized that increased lumbar lordosis and a more retroflexed pelvis among the HH user group may contribute to the participants’ stated complaints of back fatigue and pain.\(^2\)

A third cohort study performed in 2010 looked at multiple biomechanical markers among habitual HH users and nonusers.\(^3\) The sample group included 11 women who had worn shoes with at least a 5-cm heel for at least 2 hours per day, 5 times per week, for at least the past 2 years. The control group comprised 9 women who did not habitually wear heels. The volunteers were recruited through local advertisements. Outcome measurements were taken using ultrasound at the time the participants entered the study.

Mean Achilles tendon stiffness during isometric contraction was 111 N/mm in the control group and 136 N/mm in the habitual HH users, a mean difference of 25 N/mm (95% CI, 2.3–48). The mean resting gastrocnemius muscle fascicle length was 56 mm in the control group and 50 mm in the sample group (mean difference [MD] 6 mm; 95% CI, –1.0 to 13). The authors posited that this stiffer muscle-tendon unit represented a set of compensatory mechanisms for those who wear HH frequently and might be one explanation for the “muscular discomfort” that many habitual HH users experience.\(^3\)

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with sleep apnea comparing a MAD with a placebo device. No difference was noted in AHI events per hour in the MAD group compared with the placebo group after 3.8 to 6.5 months of device use. Limitations of this RCT were small samples size and lack of patient-centered outcomes.

The 2006 American Academy of Sleep Medicine evidence-based guidelines stated that MADs were a reasonable alternative to continuous positive airway pressure (CPAP) for patients with mild to moderate OSA who prefer oral appliances to CPAP, do not respond to CPAP, are not appropriate candidates for CPAP, or fail treatment attempts with CPAP or treatment with behavioral measures such as weight loss or sleep position change (level II evidence, based on 14 RCTs and 16 lower quality studies).

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What is the most effective way to ablate the nail matrix during surgical treatment of an ingrown toenail?

Evidence-Based Answer
The answer is unclear. The addition of topical phenol to standard partial nail avulsion (PNA) appears to reduce the recurrence of ingrown toenail over PNA with surgical matrix excision (SOR: B, single RCT). The addition of phenol to PNA is also associated with faster healing times than either surgical matrix excision or electrocautery (SOR: B, RCTs). Electrocautery and cryotherapy are equivalent in preventing recurrence (SOR: B, RCT).

In a 2012 Cochrane review (24 RCTs, N=2,826), 25 different interventions (5 nonsurgical, 16 surgical, and 4 postoperative) for ingrown toenails were examined. Of the 16 surgical trials reviewed, only 1 RCT (n=117) specifically addressed nail ablation recurrence as a primary outcome.

PNA with phenol was more effective in preventing recurrence (determined at 12-month follow-up by observers blinded to initial treatment) than PNA with surgical matrix excision alone (RR 0.34; 95% CI, 0.17–0.69). In regard to secondary outcomes (single RCT, n=249), the addition of phenol ablation to PNA was associated with a reduction in postoperative analgesic use compared with wedge resection and surgical matrix excision (RR 0.36; 95% CI, 0.25–0.54).

A 2014 RCT (N=60; mean age 41 years) compared recurrence rates and healing times in patients with pain, swelling, and discharge from an ingrown nail plus either granulation tissue or deformity of the nail who underwent partial matrixectomy. Patients were randomized into 2 groups, receiving either phenolization (88% phenol applied to the nail matrix for 60 seconds using a cotton-tipped applicator, then washed with 70% alcohol) or electrocautery (using monopolar diathermy at medium level of total energy for 60 seconds). Follow-up exams occurred on days 7, 14, 30, 60, and 90.

Healing times (defined as complete re-epithelization of nail bed, resolution of edema, and discharge) in the phenolization group were statistically shorter than in the electrocautery group (healing ≤10 days versus >10 days; OR 4.5; 95% CI, 1.1–19).

A 2013 RCT (N=53; mean age 32 years; with 3–12 months of follow-up) compared ingrown nail recurrence rates in patients with erythema and pain at the nail margin plus evidence of infection or formation of granulation tissue who underwent partial nail extraction before partial matrixectomy with either electrocautery (a monopolar tip with a 50-V power and supply applied for 10 seconds) or cryotherapy (2 applications of liquid nitrogen for 20-second freezing-melting cycles). The outcomes measured were relapse after a follow-up period of 3 to 12 months and matrixectomy success.

No difference in relapse was noted between the electrocautery and cryotherapy groups (7% vs 0%; P=.49). In addition, no difference was noted in successful matrixectomy (not defined in the study) between the electrocautery and cryotherapy groups (62% vs 83%; P=.09).
Is hypnotherapy effective for reduction of irritable bowel syndrome symptoms?

Evidence-Based Answer
Some evidence suggests that abdominal hypnotherapy is effective at reducing pain and bloating in patients with irritable bowel syndrome (IBS) (SOR: C, inconsistent findings from small and lower quality RCTs).

A Cochrane review of 4 RCTs (N=147) evaluated hypnotherapy efficacy for the treatment of IBS. A meta-analysis could not be completed due to differences in outcomes and study design, but all 4 studies did show a positive effect with hypnotherapy compared with usual management, primarily for abdominal pain and composite primary IBS symptoms (a means for describing clinically significant symptom improvement), in the short term for patients who failed standard medical therapy.

A potential for performance bias was noted, due to inability to blind patients; additionally, in 2 studies the therapist also assessed outcome variables and analyzed data. Due to poor methodological quality and small size, the authors stated that the data were inadequate to allow for any evidence-based conclusion.

In 2011, an RCT examined symptom and quality-of-life improvement with gut-directed hypnotherapy consisting of once-weekly sessions lasting 60 minutes, for 12 weeks, in 90 adult patients who met Rome II criteria for IBS. Patients received either gut-directed hypnotherapy or supportive therapy by meeting with a dietician, physiotherapist, or gastroenterologist. The outcome measure for both groups was change in gastrointestinal (GI) symptom severity at the 3-month follow-up using a GI symptoms questionnaire (with score ranging from 7 for no symptoms, to 49 for very severe symptoms), relative to baseline.

Gut-directed hypnotherapy resulted in a total GI symptoms score improvement of 4.5 (P<.05), sensory symptoms (pain, bloating, and gas) score improvement of 2.3 (P<.05), and bowel habits score improvement of 2.2 (P not significant). In comparison, the control group had a total GI symptoms score improvement of 0.8, a sensory symptoms score improvement of 0.1 (P value not provided), and a bowel habits score improvement of 0.6 (P values for change from baseline not provided). With regard to quality of life at the 3-month follow-up, no significant differences were noted between the gut-directed hypnotherapy group and the control group.

A separate RCT discussed in the same report compared symptom improvement in 48 patients with Rome II IBS who received gut-directed hypnotherapy or were wait-listed for 12 weeks. Hypnotherapy sessions were once weekly and lasted 60 minutes.

Compared with baseline, at the 3-month follow-up there was significant reduction in the total GI symptoms severity score for pain and bloating, but no significant reduction seen in the control group (see TABLE 1). However, the change in severity of total GI symptoms between the 2 groups did not reach statistical significance (P=.22).

In 2012, an RCT evaluated the long-term success of treatment for 90 patients with refractory IBS by Rome III criteria; hypnotherapy was compared with medical treatment alone. An IBS impact scale was used, which consisted of 26 questions over 5 domains of fatigue, impact on daily activities, sleep disturbance, emotional distress, and eating habits to determine IBS severity.

### TABLE 1

| Gastrointestinal Symptoms Rating Scale (GSRS) score (out of 7) compared with baseline² |
|---------------------------------|---------------------------------|------------------|
| Gut-directed hypotherapy        | Control                         |
| Baseline, 3 months, 1 year      | Baseline, 3 months              |
| GSRS total                      | 4.0                             | 3.9              |
| Pain                            | 5.1                             | 4.8              |
| Bloating                        | 4.7                             | 4.5              |
| Constipation                    | 2.9                             | 3.2              |
| Diarrhea                        | 4.1                             | 4.0              |
| Satiation                       | 2.5                             | 3.0              |

*P<.05, **P<.01, ***P<.001 vs baseline.

### TABLE 2

| Number (%) of patients with severe IBS who improved to mild or moderate IBS after weekly hypnosis sessions³ |
|-------------------------------------------------|-------------------------------------------------|------------------|
| Hypnotherapy (n=46)                             | Controls (n=44)                                 | P (1-tailed)      |
| At screening                                    | 11 (24%)                                        | .549             |
| First session                                   | 17 (37%)                                        | .542             |
| Fifth session                                   | 33 (72%)                                        | .003             |
| Tenth session                                   | 34 (74%)                                        | .005             |
| 3 months after treatment                        | 35 (76%)                                        | .027             |
| 6 months after treatment                        | 35 (76%)                                        | .005             |
| 12 months after treatment                       | 29 (63%)                                        | .010             |

IBS=irritable bowel syndrome.
Patients were treated with 10 weekly sessions, lasting 45 minutes, over the course of 12 weeks. After 5 weeks of treatment, 72% of the hypnotherapy group and 41% of the control group scored higher than the mean in the IBS impact scale questionnaire, indicating improvement from severe to mild or moderate IBS (see TABLE 2).³

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The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Medical Department of the US Army or the US Army Service at large.

Does folic acid supplementation have a role in the treatment of anemia associated with beta thalassemia?

Evidence-Based Answer
In patients with beta thalassemia major, folic acid supplementation for 1 month does not increase hemoglobin levels or change transfusion intervals. In children with beta thalassemia minor, however, folate supplementation for 3 months appears to increase hemoglobin levels and decrease symptoms of bone pain and myalgia and improve some measures of fatigue (SOR: B, RCT and cohort study).

A randomized, placebo-controlled trial studied folate supplementation in 51 patients with beta thalassemia major.¹ Patients with beta thalassemia major were ranked according to their folic acid levels, paired up by levels, and randomly assigned to treatment with 1 mg/d folic acid or placebo. Overall, 68% of the patients had folic acid deficiency, defined by serum levels <3 ng/mL.

At 1 month, mean serum folic acid levels improved in the treatment group (from 3.4 to 9 ng/mL; P<.0001), but not the control group (from 4 to 3.1 ng/mL; P=.3). Folic acid treatment did not result in significant changes in mean hemoglobin levels (from 8.9 to 9.3 g/dL; P<.1) or red blood cell indices. The mean blood transfusion interval did not change either (from 20.2 to 20.4 days; P=-.8). The study might have been limited by folic acid administration for only 1 month and the times were unclear between folic acid administrations and transfusion intervals.¹

A prospective cohort study of 73 children with beta thalassemia minor (average age of 8.5 years, range 2–18 years) assessed hemoglobin levels, pain from myalgias and arthralgias, and fatigue in response to combinations of folic acid and carnitine.² Results were compared with 23 healthy controls.

Children with beta thalassemia minor were allocated to 3 groups matched for sex and age, hemoglobin levels, and clinical characteristics and given 3 months of 1 mg/d folic acid, 50 mg/kg per day carnitine, or 50 mg/kg per day carnitine plus 1 mg/d folic acid. Hemoglobin levels, symptom questionnaires, and measures of fatigue (number of stairs climbed per day and amount of time spent studying) were assessed before and after 3 months. The questionnaires asked about the frequency and duration of myalgia, arthralgia, and fatigue over 1 day and 1 week, but the specific wording and scoring of the symptom questionnaires and the time period used to measure number of stairs climbed were not detailed.²

Folate supplementation alone increased hemoglobin concentration from 11.6 to 11.9 g/dL (P=.047), as did the combination of folate and carnitine (from 11.3 to 11.6 g/dL; P=.0001), but not carnitine only (unchanged at 12.1 g/dL). Because healthy controls did not receive any supplementation, no comparison was made for hemoglobin concentration. Treatment (beta thalassemia minor) groups had more complaints of pain than the control group at baseline, but the control group results were not reported. All 3 treatment groups had less pain complaints and climbed more stairs with supplementation. Folate supplementation decreased pain complaints per day from 3.7 to 1.4 (P=.0001) and increased the number of stairs climbed per day from 3.0 to 5.9 (P=.016). Amount of time spent studying did not change in any of the treatment groups.²

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REFERENCES
Do inhaled levalbuterol and racemic albuterol have different cardiac effects?

**Bottom line**

No. There are inconsistent differences in heart rates between inhaled levalbuterol and racemic albuterol at equivalent doses that are not clinically meaningful (no SOR given).

**Evidence summary**

A randomized, single-blind crossover study examined heart rate response in adults (N=70) requiring bronchodilators in the intensive care unit.\(^1\) Group A received 2.5 mg albuterol alternating with 0.63 mg levalbuterol every 4 to 6 hours and group B received 2.5 mg albuterol alternating with 1.25 mg levalbuterol every 4 to 6 hours.

Group A mean heart rate change was +0.89 beats per minute (bpm) after albuterol versus +0.85 bpm after levalbuterol \((P=.89)\). Group B mean heart rate change was −0.16 bpm after albuterol versus +1.4 bpm after levalbuterol \((P=.03)\). No significant tachycardia or tachyarrhythmias necessitating discontinuation of treatment occurred in the 70 patients receiving a combined total of 836 treatments of albuterol or levalbuterol.\(^1\)

A double-blind RCT of children aged 6 to 17 years (N=99) presenting to the emergency department with moderate to severe asthma exacerbation evaluated change in heart rate after nebulizer treatments of either albuterol or levalbuterol.\(^2\) Investigators measured heart rate change after 1 or 2 continuous, hour-long nebulizer treatments of 7.5 mg albuterol or an equivalent 3.75 mg levalbuterol.

After 1 treatment, albuterol increased mean heart rate by 7.6 bpm versus 12.1 bpm with levalbuterol \((P=.22)\). After 2 treatments, the increases were 13.2 bpm for albuterol versus 13.0 bpm for levalbuterol \((P=.61)\). These differences were not statistically significant.\(^2\)

A multicenter, randomized, double-blind, 2-way crossover study in patients older than 12 years with asthma (N=49) compared inhaled albuterol HFA (90 mcg) and an equivalent dose of levalbuterol HFA (45 mcg).\(^3\) Treatment consisted of 1 puff at 0 and 30 minutes, 2 puffs at 60 minutes, 4 puffs at 90 minutes, and 8 puffs at 120 minutes, for a total of 16 doses. Heart rate was measured prior to dosing, 15 minutes after each dose, and every 30 minutes for 8 hours after final treatment. After a 7-day washout period, patients were crossed over to the other treatment arm. Results were reported as least squares mean (LSM) difference to better account for the multiple measurements in multiple patients after multiple treatments.

Albuterol increased heart rate slightly more than levalbuterol after 8 doses (LSM difference +2.8 bpm; 95% CI, 0.3–5.3) and 16 doses (LSM difference +3.5 bpm; 95% CI, 0.6–6.4). The researchers did not consider this difference to be clinically meaningful. No statistically significant differences were noted at 2 or 4 consecutive treatments (no statistics given).\(^3\)

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