Evidence-based answer

Yes, use of preexposure prophylaxis (PrEP) reduces rates and risk of HIV sexual transmission in men who have sex with men (MSM). The risk benefit depends on adherence to daily use and sexual practices (receptive or insertive and HIV status of partner) (SOR: B, RCT).

Evidence summary

An RCT followed 2,499 HIV-negative MSM 18 to 67 years old (mean age 27.5 intervention, 26.8 control), including 29 transgender women, over an average of 1.2 years. Participants were recruited from 11 trial sites in 6 different countries, with 83% of the participants recruited from Central and South America. Participants were assigned either to the intervention group, which took a once-daily tablet of combined 200mg emtricitabine and 300 mg tenofovir disoproxil fumarate (FTC-TDF), or to placebo. Both groups were given HIV testing, risk-reduction counseling, condoms, and treatment of other sexually transmitted infections (STIs). Sexual practices—including number of partners, use of barrier methods, and insertive/receptive behavior—were similar between the groups.

Over a median follow-up period of 1.2 years, 36 patients developed HIV infection in the FTC-TDF group and 64 developed HIV infection in the placebo group, a 44% reduction (95% CI, 15–63). Drug levels were detectable in only 9% (3 of 36) of the FTC-TDF patients who became HIV-positive. In comparison, FTC-TDF patients with detectable levels had a 92% reduction in relative risk of seroconversion compared to those with no detectable levels (P<.001). After discontinuation of administered PrEP, the number of HIV seroconversions in the FTC-TDF group became similar to that in the control group (161 vs 159; P=.42).
A secondary analysis of the results from the above RCT evaluated subpopulations most at risk for sexual transmission of HIV within the MSM population by calculating the NNT for 1 year to prevent 1 infection.\(^2\) The overall NNT was 62 (95% CI, 44–147).

The NNT was lower for MSM reporting receptive anal sex without a condom whether the partner was HIV-negative, -positive, or unknown (NNT=36) and higher for MSM reporting 1 sexual partner (NNT=100) and those engaging in insertive anal sex without a condom (NNT=77). Other subpopulations with low NNTs included those using cocaine (NNT=12) and those with self-reported STIs in the past 6 months (NNT=41).\(^2\)

A cohort study followed 1,603 seronegative MSM, including 175 transgender women (mean age 28), to determine dose-dependent response to PrEP.\(^3\) Of this cohort, 1,225 were given PrEP consisting of a once-daily oral combination tablet of 200 mg FTC and 300 mg TDF. Subsequent stratification of the PrEP group then occurred based on systemic drug levels as measured by dried blood spots.

Drug levels in the dried blood samples correlated with reduction in HIV risk: no infections were present if concentrations were equivalent to 4 to 7 tablets/week; the equivalent of 2 to 3 tablets/week showed a 90% reduction in risk. Only 3.6% (1 of 28) of participants who became HIV-positive had dried blood spots equivalent to 2 to 3 tablets/week, compared to 3.2% (9 of 28) with levels equivalent to ≤2 tablets, and 64.3% (18 of 28) with no detectable drug levels.\(^3\)

After adjusting for baseline sexual practices in the PrEP group, HIV incidence was 49% lower in those taking PrEP than those who did not choose PrEP. In the PrEP group, treatment was interrupted 380 times due to adverse effects such as nausea and abdominal pain, relocation/travel, or suspected HIV infection requiring postexposure prophylaxis, which may have lowered the patients’ blood concentration of PrEP.\(^3\)

After their analysis of the RCT cited above, the CDC released interim guidance on use of PrEP in MSM.\(^4\) The CDC stated that “PrEP has the potential to contribute to effective and safe HIV prevention for MSM” provided it is targeted to the appropriately high-risk population, delivered as part of a comprehensive set of prevention services, and is accompanied by regular monitoring of adherence, side effects, and HIV status.

The CDC commented on limitations of the RCT including nonuniformity in measurement of adherence and difficulties in associating PrEP use with drug levels at the actual time of infection. Additionally, they stressed the importance of adherence to follow-up in assessing appropriate PrEP use, monitoring for side effects, and monitoring for HIV seroconversion for the purposes of patient safety and prevention of the development of drug resistance.\(^4\)

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**REFERENCES**


N of 1

My residency training was at the University of Washington in Seattle. Among the curious things that I was exposed to there (in addition to the virus of the pediatrics rotation) was the concept of the “N of 1” trial. In this type of study, 1 patient takes either a therapy or a placebo in some sequence (unknown to both the patient and the doctor) to see if a benefit or harm results from that therapy. Our residency pharmacist, Allan Ellsworth, coordinated the trials. He seemed to get a real kick out of them.

Our university-based residency clinic was uniquely situated for N of 1 studies. We had a large number of patients who chose academic medical care because of a bewildering array of symptoms that we never quite sorted out. Add on top of that some gargantuan medication list and it is easy to see why neither patients nor providers could track what symptoms came from what medication or disease. Into this morass, Professor Allan Ellsworth, PharmD, would happily stride with specially made lookalike placebos, masked pill bottles, and a random number generator.

Since leaving residency, I have not had much contact with people doing N of 1 studies and the possibility that I might do them in practice seemed rather remote for a very long time. But the concept seems to be gaining some intellectual traction, as evidenced by recent publications by the NIH¹ and AHRQ² that lay out the history, intellectual underpinnings, and appropriate design of N of 1 trials.

At first glance, this may seem remote to our beloved evidence-based medicine, with its familiar reliance on hundred-patient RCTs and thousand-patient meta-analyses. But hold on a minute. Look carefully in the first column of the newest “Levels of Evidence Table” from the Oxford Center. Nestled in there with all those meta-analyses are . . . N of 1 trials!

Maybe one day funders and pharmacies will make it easy for all providers to do formalized N of 1 research in our clinics. It would be a return to my residency roots: finding what works, right at the point of care.

Jon O. Neher, MD

REFERENCES
Diving for PURLs

**Time for new blood pressure goals?**


This RCT compared the effect of a systolic blood pressure target of <120 mmHg with a target of 135 to 139 mmHg in 9,300 patients >50 years of age. Participants had systolic blood pressure between 130 and 180 mmHg and 1 of the following risk factors: cardiovascular disease without known cerebrovascular disease, chronic kidney disease, age >75 years, or a 10-year Framingham risk of ≥15%. Blood pressure was measured with an automated machine, using the mean of 3 readings.

Participants were treated according to a protocol where possible, using chlorthalidone, amlodipine, azilsartan, beta-blockers, and other agents as indicated by blood pressure levels and comorbidities. The primary outcome was a composite of myocardial infarction (MI), acute coronary syndrome without MI, acute heart failure, or death from any cardiovascular cause, and participants were followed for a median 3.26 years.

Overall, 243 of 4,683 (5.2%) patients in the intensive treatment group experienced the primary outcome, compared with 319 of 4,683 (6.8%) in the standard treatment group (ARR 1.6%; NNT=63; P<.001). The intensive treatment group experienced more adverse effects, including acute kidney injury, syncope, and hypotension, but the risk of fall was similar between groups.

In subgroup analysis, the reduction in risk was seen in men, those without previous cardiovascular disease, those >75 years, those without previous kidney disease, nonblack patients, and those with initial systolic pressures <132 mmHg. Other groups did not have a significant benefit.

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**Light therapy helps depression regardless of season**


This double-blind RCT compared bright light monotherapy with fluoxetine, bright light plus fluoxetine, and placebo among 122 adult outpatients who showed at least moderate depression on the Montgomery-Åsberg Depression Rating Scale (MADRS: 10 items, 6 points per item, 0–60 points possible with higher score indicating worse outcome; >34 points indicates severe depression).

Patients self-administered bright light monotherapy (10,000 lux fluorescent white light for 30 minutes per day in the early morning plus placebo pill), antidepressant monotherapy (inactive negative ion generator for 30 minutes daily plus fluoxetine 20 mg per day), combination bright light and fluoxetine, or placebo (inactive ion generator plus placebo pill) and were assessed by board-certified psychiatrists at 0, 1, 2, 4, 6, and 8 weeks. The primary outcome was change score on the MADRS. Secondary outcomes were response (≥50% reduction in MADRS score) and remission (MADRS score ≤10 at endpoint).

Combination therapy (effect size [ES]=1.11; 95% CI, 0.54–1.64) and light monotherapy (ES=0.80; 95% CI, 0.28–1.31) were significantly superior to placebo in the MADRS change score. Combination therapy was superior to placebo in response and remission, with NNTs of 2.4 (95% CI, 1.6–5.8) and 3.5 (95% CI, 2.0–29.9), respectively.

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**Bottom line:** Consider bright light therapy, either alone or in combination with an SSRI, when planning treatment for adult patients with moderate to severe major depressive disorder.

**Review and Summary Author:** Kate Rowland, MD, Rush-Copley FMR, Aurora, IL

**Bottom line:** Adopting a lower target for patients with hypertension at high risk for cardiovascular disease may significantly reduce the risk of cardiovascular events and death.

Reviewer and Summary Author: Kate Rowland, MD, Rush-Copley FMR, Aurora, IL

**Medical care setting** | Yes
| Implementable | Yes
| Clinically meaningful | Yes

**Bottom line:** Consider bright light therapy, either alone or in combination with an SSRI, when planning treatment for adult patients with moderate to severe major depressive disorder.

**Review and Summary Author:** Gene Combs MD, University of Chicago/Northshore University Health System, Chicago, IL
Should timing of induction change according to a woman’s age?

**Bottom line**

No. Evidence clearly shows an increase in stillbirth among women >40 years with advancing gestational age, but no studies have assessed the effect of earlier induction on incidence of stillbirth.

**Evidence summary**

Late-term and postterm pregnancies are associated with an increased risk of perinatal morbidity and mortality. Unexplained stillbirths increase with advancing maternal age and with increasing gestational age in both nulliparous and multiparous women. The mechanism for the increased risk of stillbirth in women of advanced maternal age after exclusion of congenital abnormalities is unknown.¹

A retrospective analysis of >5 million US pregnant women with singleton pregnancies (excluding those with congenital anomalies) showed significant differences in risk of stillbirth based on maternal age.² At 41 weeks of gestation, the risk of stillbirth is 0.75 per 1,000 women aged <35 years and 2.5 per 1,000 women aged ≥40. At 38–39 weeks’ gestation, the risk of stillbirth is 0.98 per 1,000 women aged <35 and 1.99 per 1,000 women aged ≥40. At 37–38 weeks’ gestation, the risk of stillbirth is 0.61 per 1,000 women <35 and 1.12 per 1,000 women ≥40. The effect of maternal age persisted after adjusting for medical disease, parity, race, and ethnicity.

Applying these gestational age–specific stillbirth risks suggest that if all women aged ≥40 with a singleton pregnancy were induced at 39 instead of 41 weeks, 17 stillbirths could be prevented.³ Overall, 550 women would need to be induced to prevent 1 stillbirth. Inducing at 40 instead of 41 weeks would prevent 7 stillbirths and 679 women would need to be induced to prevent 1 stillbirth. This study estimates that women aged ≥40 have a similar stillbirth risk at 39 weeks as women aged 25–29 at 41 weeks, thus suggesting induction of labor earlier in older mothers.

A 2006 review of 22 RCTs (N=9,383 women) compared expectant management with induction of labor.⁴ Induction at 41 weeks resulted in improved perinatal outcomes without increasing cesarean section rate. Induction was associated with a decreased risk of perinatal death (17 trials, N=7,407 women; RR 0.31; 95% CI, 0.12–0.88), cesarean delivery (21 trials, N=8,749 women; RR 0.89; 95% CI, 0.81–0.97), and meconium aspiration syndrome (8 trials, N=2,371 infants; RR 0.50; 95% CI, 0.34–0.73). The number needed to induce to prevent 1 perinatal death was 410 (95% CI, 322–1,492).

A 2009 systematic review of 36 studies found 3 RCTs of women induced at <41 weeks (555 women in the induction group vs 455 in the control group); there was no statistically significant increase in risk of cesarean section (OR 1.73; 95% CI, 0.67–4.5).⁵ This review did not examine the influence of maternal age.

**Recommendations from others**

ACOG recommends induction of labor after 42 weeks regardless of maternal age.⁶ In 2013, RCOG published a recommendation to induce all women >40 years who are between 39 and 40 weeks’ gestation, based on data showing increased risk of stillbirth and the suggestion from other studies that routine induction does not increase cesarean section rates.³ In 2013, SOGC did not identify different induction guidelines based on maternal age.⁷

**Case Wrap-Up**

Jane was assured that it would be reasonably safe to allow her pregnancy to progress into the 39th week. Jane’s pregnancy proceeded uneventfully.

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**REFERENCES**

What laboratory testing can help differentiate a non-envenomed from an envenomed snakebite?

Evidence-Based Answer

The international normalized ratio (INR), activated partial thromboplastin time (aPTT), and creatine kinase (CK) combined with a neurological examination will detect severe envenoming by 12 hours (SOR: B, prospective cohort in Australia). Normal laboratory coagulation testing at 6 hours excludes elapid envenoming in asymptomatic patients (SOR: B, case series in Australia). Bedside coagulation testing (the WBCT20) has low sensitivity (SOR: B, retrospective cohort in Sri Lanka). Limiting coagulation studies to only patients with severe clinical presentations will miss most crotalid bite coagulopathies (SOR: B, case series in the United States).

An Australian multicenter 2010 prospective cohort study (N=478) compared serial (>3 sets) laboratory (INR >1.2, aPTT outside of normal range, and CK >250 U/L) and neurological exam abnormalities over 12 hours in envenomed patients with non-envenomed patients.1 Patients sustained bites from a variety of snakes with neurotoxic and proteolytic venom. Envenomed bites were classified as severe (ie, complete venom-induced consumption coagulopathy [VICC]; myotoxicity with CK >1,000 U/L; neurotoxicity with either 2 nerve groups involved or respiratory paralysis; or thrombotic microangiopathy) or minor (isolated systemic symptoms; anticoagulant coagulopathy; mild VICC, neurotoxicity, or myotoxicity).

In patients with severe envenomation, the median time to abnormal laboratory or neurological findings was 1.75 hours (range, 0.3–33.5 hours) and 99% were identified by 12 hours. In those with minor envenomation, the median time to abnormal laboratory or neurological findings was 2.1 hours (0.3–30.8 hours) and 85% had abnormalities by 12 hours. Patients deemed to have non-envenomed bites (n=163) showed no changes in either laboratory or neurological assessments during the 12-hour time period.1

Limitations of the study include an overrepresentative sample of envenoming, few cases of myotoxicity and isolated neurotoxicity, nonstandardized serial performance of blood tests, and failure to measure venom concentrations in confirmation of clinical envenoming.1

A 2003 retrospective case series (N=276) and prospective cohort (N=84) of patients presenting to a regional hospital in Southeast Queensland, Australia, assessed the period of observation required for laboratory and clinical findings to exclude elapid envenoming in patients with suspected or definite snakebite.2 Laboratory testing for coagulation abnormalities (PT >14 seconds, aPTT >38 seconds, fibrinogen <1.5 g/L, positive D-dimer, CK >500 U/L, hematuria >80 cells/mcL) was performed at presentation, 4 hours, and 10 hours, and time of onset of abnormal clinical features was recorded. Among 34 cases of envenomation, laboratory and clinical abnormalities were detected at the time of presentation (69% and 76% of patients, respectively) and within 6 hours (96% and 95% of patients, respectively). Laboratory abnormalities first detected beyond 6 hours occurred in 1 patient in whom the diagnosis of envenoming had already been established at presentation.

A 2013 prospective, observational cohort study of patients presenting at a hospital in central western Sri Lanka assessed the sensitivity of admission testing with WBCT20.3 The WBCT20 is used as an indicator of envenoming in resource-poor settings. A few milliliters of blood are placed in a small glass tube, and clotting after 20 minutes indicates envenomation. Here the WBCT20 was used to evaluate for coagulopathy in Russell’s viper-envenomed adults (n=140, confirmed with venom-specific enzyme immunosassay [EIA] >2.5 ng/mL and INR >1.5), and specificity of negative WBCT20 in non-envenomed patients (n=9). WBCT20 and INR were collected on admission, and EIA and coagulation studies were done at initial assessment, 1, 4, and 12 hours, then daily until discharge in patients given antivenom.

WBCT20 was positive in 56 of 140 viper bites with coagulopathy, negative in 9 of 9 non-envenomed bites, and negative in 48 of 48 nonvenomous snake bites (sensitivity 40%; specificity 100%; positive likelihood ratio [LR+] 46; negative likelihood ratio [LR−] 0.6). In 221 paired tests with INR >1.5, the WBCT20 was positive in 91 (41%).3

A 2012 retrospective chart review of adults who presented to a university medical center emergency department in Jackson, Mississippi with crotalid snakebite (N=131) was conducted to determine if coagulation studies could be limited to patients with severe and/or rattlesnake envenomation.4 Snakes
Evidence-Based Practice / Vol. 19, No. 3

Is fidaxomicin better than vancomycin for treating *Clostridium difficile* colitis?

Evidence-Based Answer

Fidaxomicin is noninferior to vancomycin for clinical resolution of diarrhea from *C difficile* colitis, and is superior for prevention of recurrence and global cure (SOR: B, meta-analyses).

A 2012 meta-analysis (N=1,164) evaluated fidaxomicin compared with vancomycin for treatment of *C difficile* infection (CDI). Researchers combined data from 2 prospective, multicenter, double-blind, randomized, parallel-group trials. In both trials, patients were eligible if they were 16 years of age or older with CDI defined as >3 unformed stools in the 24 hours prior to randomization and *C difficile* toxin A, B, or both detected in the stool.

Patients were randomized to either fidaxomicin 200 mg by mouth twice daily or vancomycin 125 mg by mouth 4 times daily, both for 10 days. The primary efficacy endpoint was clinical cure, with secondary endpoints of recurrence (defined as a return of >3 episodes of diarrhea in any 24-hour period and presence of *C difficile* toxin A, B, or both during the 28-day follow-up) and global cure.

Investigators defined clinical cure as resolution of persistent diarrhea, while they defined global cure as the resolution of symptoms during initial treatment and no further recurrence during the 28-day follow-up period. In order to clarify their data, the study reported clinical cure and global cure results as the converse “No Clinical Cure” or “No Global Cure”; thus, a relative risk value of <1 would indicate a reduced risk for poor outcomes with fidaxomicin versus vancomycin.

Rates of “No Clinical Cure” were lower with fidaxomicin versus vancomycin (12% vs 14%; RR 0.88; 95% CI, 0.64–1.19), showing noninferiority of fidaxomicin versus vancomycin. Fidaxomycin was superior for avoiding “No Global Cure” as well (24% vs 36%; RR 0.68; 95% CI, 0.56–0.81). Fidaxomicin was also found superior for recurrence (14% vs 26%; RR 0.54; 95% CI, 0.42–0.71). The study did not include information on adverse events with either antibiotic.

A second 2012 meta-analysis, a phase 2 subgroup analysis of the above meta-analysis, focused on patients who were experiencing a first recurrence of a recent CDI episode and evaluated efficacy differences between fidaxomicin and vancomycin (n=66 fidaxomicin, n=62 vancomycin). The primary endpoint was clinical cure of CDI at end of treatment, and a secondary endpoint was recurrence during the 28 days after clinical cure.

At the end of the 10-day treatment, fidaxomycin and vancomycin had similar clinical cure rates (93.7% and 91.6%, respectively). Fidaxomicin was superior to vancomycin in preventing a second recurrence within 28 days (19.7% vs 35.5%; *P*=.045; NNT=7). Although event rates were not provided, the authors stated there were similar adverse events between the antibiotics, with the most common being gastrointestinal and infectious conditions (not defined).

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What is the best treatment for nocturnal enuresis in children?

**Evidence-Based Answer**

The enuresis alarm reduces nighttime bed-wetting in about two-thirds of children during treatment; half of children will remain dry after the alarm is discontinued. Desmopressin results in fewer wet nights while on treatment; however, almost all children start bed-wetting again when treatment is stopped. Combining desmopressin and alarm use does not result in better cure rates after the end of treatment (SOR: A, systematic reviews).

A 2009 systematic review of 56 randomized or quasirandomized trials, involving 3,257 children 5 to 16 years old, examined the effectiveness of alarms for nocturnal enuresis. Compared with no treatment, about two-thirds of children became dry during alarm use (14 trials, n=576; RR for failure 0.38; 95% CI, 0.33–0.45). Nearly half who persisted with alarm use for 2 to 20 weeks remained dry after a 2- to 24-month follow-up after treatment finished, compared with almost none after no treatment (5 trials, n=162; failure plus relapse 55% vs 99%; RR 0.56; 95% CI, 0.46–0.68). Evidence was insufficient to draw conclusions about different types of alarms, or about how alarms compare with other behavioral interventions.

Another 2009 systematic review of 47 RCTs involving 3,448 children 5 to 17 years old examined the effectiveness of desmopressin for nocturnal enuresis. Desmopressin 20 mcg intranasal at bedtime reduced bed-wetting during treatment compared with placebo (12 trials, n=813; 1.3 fewer wet nights per week; 95% CI, 1.1–1.6). The RR for failure to achieve 14 dry nights with desmopressin was 0.84 (95% CI 0.79–0.91). However, no difference was noted between the 2 patient groups after treatment was finished. Desmopressin produced few adverse effects, with nasal irritation and nosebleeds being the most common.

The same 2009 systematic review compared desmopressin with alarm interventions. No significant differences were noted between desmopressin and alarms during treatment when these were used separately, but the chance of failure or relapse after treatment stopped was lower after an alarm (2 trials, n=119; 65% vs 46%; RR 1.4; 95% CI, 1.1–1.9). Although children had fewer wet nights during treatment (2 weeks to 3 months) when they used desmopressin (10–40 mcg intranasally) combined with alarm treatment versus alarms alone (4 trials, n=380; weighted mean difference [WMD] –0.83; 95% CI, –1.1 to –0.55), no significant differences were noted either in failure rates during treatment (5 trials, n=486; RR 0.88; 95% CI, 0.73–1.1) or for relapse 0 to 6 months after treatment stopped (4 trials, n=427; RR 0.91; 95% CI, 0.76–1.1).

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In children with strep pharyngitis, does treating with broader spectrum antibiotics instead of penicillin reduce recurrence or complications?

**Evidence-Based Answer**

A short term (3–6 day) course of oral antibiotics including azithromycin 20 mg/kg, clarithromycin, cefuroxime, and others (erythromycin, cefixime, amoxicillin, amoxicillin/clavulanate, penicillin V, cefprozil, cefpodoxime, josamycin, cefdinir, ceftibuten, loracarbef) has comparable efficacy to a 10-day standard course of oral penicillin in treating children with acute group A beta-hemolytic streptococcal (GABHS) pharyngitis. Short-term late-generation antibiotics have better compliance but more mild-to-moderate, primarily gastrointestinal, adverse effects (SOR: A, systematic review of RCTs). Penicillin remains the recommended treatment (SOR: C, expert opinion).

A 2012 Cochrane review of 20 RCTs compared oral short-term (3–6 day) late-generation antibiotics with longer-term (10-day) standard duration oral penicillin in 13,102 children 1 to 18 years old with acute GABHS pharyngitis by a positive rapid antigen test or throat swab culture. The short-term late-generation antibiotics were divided into 5 subgroups: azithromycin 10 mg/kg, azithromycin 20 mg/kg, clarithromycin, cefuroxime, and others (erythromycin, cefixime, amoxicillin, amoxicillin/clavulanate, penicillin V, cefprozil, cefpodoxime, josamycin, cefdinir, ceftibuten, loracarbef) (doses not provided). Trials on GABHS carriers were excluded.

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Compared with standard-duration treatment, the short-duration treatment trials had shorter periods of fever (2 trials, n=348; 2.6 vs 2.9 days; mean difference [MD] –0.30 days; 95% CI, –0.45 to –0.14) and throat soreness (1 trial, n=188; 2.2 vs 2.7 days; MD –0.50 days; 95% CI, –0.78 to –0.22), lower risk of early clinical treatment failure (23 comparisons within the 20 trials, n=11,713; 5% vs 6%; OR 0.80; 95% CI, 0.67–0.94), and no increase in early bacteriological treatment failure (23 comparisons, n=11,555; 17% vs 16%; OR 1.1; 95% CI, 0.97–1.2) or late clinical recurrence (17 trials, n=8,068; 15% vs 14%; OR 0.95; 95% CI, 0.83–1.1).¹

The overall risk of late bacteriological recurrence was worse with low-dose (10 mg/kg) azithromycin than standard-duration treatment (6 trials, n=1,085; 38% vs 16%; OR 3.6; 95% CI, 2.7–4.9; NNH=5). No significant difference was found when azithromycin was removed from the other 4 subgroups of short-term late-generation antibiotics (18 trials, n=9,164; 11% vs 12%; OR 1.1; 95% CI, 0.92–1.2).¹

All but 3 trials reported adverse effects. More adverse effects were seen in the short-duration treatment group (21 trials, n=7,997; 10% vs 5%; OR 1.9; 95% CI, 1.6–2.2; NNH=20). Adverse effects were most commonly mild to moderate diarrhea, vomiting, and abdominal pain and were self-limiting in both treatment groups. Noncompliance, measured as failure to complete treatment as recommended, was reduced in the short-duration treatment group (6 trials, n=1,909; 6% vs 24%; OR 0.21; 95% CI, 0.16–0.29, NNT=6). Six cases in the short-duration treatment versus 8 in the standard-duration treatment developed long-term complications in the form of glomerulonephritis and acute rheumatic fever, with no statistically significant difference (3 trials, n=8,135; 0.12% vs 0.27%; OR 0.53; 95% CI, 0.17–1.6). However, the studies may have been underpowered to detect a difference.¹

The Infectious Diseases Society of America recommends treating GABHS pharyngitis with penicillin for narrow spectrum of activity, infrequency of adverse reactions, and modest cost.²

Evidence-Based Answer

No, increasing the dose of inhaled corticosteroid (ICS) for asthma exacerbations does not reduce the need for rescue systemic corticosteroids compared with maintaining the usual dose (SOR: A, meta-analysis of RCTs).

A systematic review of 5 RCTs (N=1,250) in 2010 compared the effectiveness of increasing the dose of ICS versus maintaining the usual dose as part of a patient-initiated home treatment plan at the onset of an asthma exacerbation in patients on daily ICS.³ Of the 5 studies, 3 included only adults (n=932), 1 included teenagers and adults (n=290), and 1 included only children (n=28, average age 8.2 years). Three of the 5 studies allowed use of long-acting beta agonists (LABA) at stable doses while the other 2 studies (that included children) excluded patients on LABA. Asthma exacerbations were predefined based as a combination of decrease in peak flow, increase in asthma symptoms, and increase in rescue bronchodilator use relative to baseline. ICS doses were converted to a beclomethasone dipropionate dose equivalent and the mean baseline daily dose was 555 mcg (range, 200–795 mcg/d). The mean increase was 3-fold (range, 2- to 5-fold) for an average of 7 days (range, 3–14 days).

Increasing ICS at onset of asthma exacerbation did not decrease the need for rescue systemic corticosteroids compared with maintaining the usual dose in adults and teenagers (3 trials, n=1,080; OR 0.85; 95% CI, 0.58–1.3). The results of the single small study in children alone showed no difference in outcomes (systemic corticosteroid use) for different ICS regimens. No significant difference was noted between groups in nonserious adverse events such as glossitis or pharyngitis (2 studies, n=142; OR 2.2; 95% CI, 0.58–6.7) and no serious adverse events (fatality, hospitalization) or study withdrawal were reported.¹

A subsequent double-blind RCT involving 197 children (average age 5.8 years) with asthma investigated the benefit of increasing ICS up to 4- or 8-fold at the onset of an asthma exacerbation compared with doubling the ICS dose.² Patients were on ICS for

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at least 3 months prior to enrolling. Over 95% used fluticasone, with most daily doses falling between 176 and 440 mcg/d (range, 80–880 mcg/d).

Patients were randomized to receive 2, 4, or 8 times their current daily dose of ICS at the onset of an asthma exacerbation, which was based on parent-reported symptoms and peak flow measurements. At the time of study, the investigators’ standard treatment for an exacerbation was doubling the dose of ICS, based on 1997 guidelines from the National Institutes of Health (NIH), so the group receiving twice their current daily dose of ICS was used as the control group. Outcomes were total symptom score at 3, 7, and 14 days, and need for systemic steroids. Symptom scores measured the presence and severity of daytime cough and wheeze, nighttime cough and wheeze, and shortness of breath on a 0 to 3 scale, with a maximum possible score of 15 indicating severe symptoms.

During the study, 82 patients had an asthma exacerbation, but only 4 required systemic corticosteroids with no significant difference between the groups (2 in the 2-fold group, 2 in the 4-fold group, and 0 in the 8-fold group, P = .451 for 3-way comparison). The 3 groups had similar average baseline symptom scores at onset of exacerbation of approximately 6. No significant differences were noted among groups in total symptom score improvement at 14 days (average decrease 5.1 points; P = .422 for 3-way comparison). The authors noted that the subsequent 2007 NIH guidelines no longer recommended increasing ICS at the onset of exacerbation.

**Is hoodia helpful in treating patients with obesity?**

**Evidence-Based Answer**

Not really. While hoodia supplementation may be helpful for reducing weight, any change is small (about 1 pound or less) (SOR: B, 2 small inconsistent RCTs).

A 2015, single-blind, placebo-controlled RCT (N=103) assessed efficacy (weight loss, waist circumference, and BMI) of hoodia compared with placebo. Patients were given either a frozen 3-g cube containing 95% fresh ground *Hoodia parviflora* aerial parts, natural lemon juice concentrate, steviol glycosides and conditioners (n=78) or placebo, which contained a lemon-flavored 3-g frozen cube (n=25). The population included volunteers aged 18 to 64 years and measurements were completed at day 1, 10, and 40.

A significant difference was noted in the treatment group compared with the placebo group for mean change of body weight (–0.58 vs +0.2 kg; P = .046), waist circumference (–2.3 vs −0.47 cm; P = .03), and BMI (–0.21 vs +0.06 kg/m²; P = .043). The researchers noted that the product was not efficacious for participants who were defined as morbidly obese, with a baseline BMI ≥35 kg/m². No significant difference was noted between groups for adverse events, which included headache, stomach cramps, indigestion/heartburn, nausea, change in bowel function, and flu symptoms.

A 2011, double-blind, placebo-controlled, parallel-group RCT (N=41) assessed the safety and efficacy of a 79.3% *H gordoni* steroid glycoside extract (HgPE) within a yogurt drink base. Patients were healthy, overweight (body fat 25%–45%) women 18 to 50 years old who were admitted to a nutrition clinic. During the 19-day study period, they consumed only food and beverages provided to them. All patients had a 4-day run-in period (study days –4 through –1), which consisted of no study product on day –4 and a placebo during days –3 to –1. Patients were then randomized to either receive the treatment (1,110 mg HgPE in yogurt drink) or placebo yogurt twice a day for 15 days. Patients were assessed prior to trial initiation at day –4, throughout the study, and at follow-up on days 16, 17, 22, and 37.

The mean body weight at the end of treatment was not clinically different between treatment and placebo groups (absolute difference 0.08 kg; P < .001),

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with significant body weight reduction in both groups. Self-reported adverse events were substantially greater in the treatment group and included skin sensation, headache, dizziness, feeling giddy, and nausea. The authors noted that steroid glycosides from *H. gordonii* are likely extracted with additional uncharacterized substances, which may have had some (negative) clinical effect.²

**Evidence-Based Answer**

Parental education is associated with a reduction in nicotine exposure in high-risk asthmatic children (SOR: C, RCT using biochemical outcomes). It is unclear if parental education is an effective mode of reducing smoke exposure in all children with asthma (no SOR given, conflicting RCTs).

**Does parental education help decrease smoke exposure in children with asthma?**

A 2011 RCT (with 352 pediatric patients 3–12 years old) evaluated the efficacy of a behaviorally based cotinine feedback and monitoring intervention to reduce tobacco smoke exposure in children with asthma over a 12-month period.¹ Smoke exposure was documented by parent-reported exposure of the child to secondhand tobacco smoke and with confirmation of child exposure using a urinary cotinine level ≥10 ng/mL above baseline. Asthma was defined as medication use and/or physician diagnosis suggesting persistent asthma or more than 1 asthma-related visit.

Children were considered as having high-risk asthma if 1 or more of the following events occurred during the preceding 6 months: an asthma-related hospitalization or emergency department visit, receiving ≥6 units of short-acting beta-agonist medication, or asthma medication prescribed by ≥3 physicians. All children received a prerandomization visit for asthma education provided by a respiratory therapist and medication adjustments as required per current treatment guidelines.

Cohort 1 (n=178) included children whose parents received the Lowering Environmental Tobacco Smoke (LETS) Intervention consisting of 3 in-person cotinine feedback and behavioral counseling visits over 6 weeks. This intervention was to formalize strategies to reduce smoke exposure and caregivers’ readiness to make necessary changes, and create a written smoke-exposure-reduction plan. Three follow-up telephone calls at 2, 4 and 6 weeks after visit 3 provided additional counseling. Cohort 2 (n=174) received usual care, which was undefined. Patient follow-up took place at 6 and 12 months. The primary outcome of secondhand smoke exposure was assessed using natural logarithms of cotinine-to-creatinine ratio (lnCCR). Absolute cotinine-to-creatinine ratio values were not reported.

At the end of 12 months, children in the LETS intervention cohort had lower lnCCR values compared with children in the usual care group, but the group difference was not significant (beta coefficient –0.307; 95% CI, –0.633 to 0.018; *P*=.064). Children defined as high-risk asthma in the LETS group had significantly lower follow-up lnCCR values compared to children with usual care (beta coefficient –1.068; 95% CI, –1.816 to –0.319; *P*=.006). A beta coefficient of zero indicates no relationship between education and smoke exposure. A negative beta coefficient indicates that education reduced smoke exposure.¹

A 2010 RCT (N=133) evaluated the effectiveness of 2 smoking cessation interventions for Latino parents of asthmatic children (<18 years old) over 3 months.² Parents received either the precaution adoption model or the behavioral action model. The precaution adoption model intervention used motivational interviewing, which included instruction about the effects of smoke exposure on the child, the smokers’ carbon monoxide levels, and the child’s nicotine exposure levels. The behavioral action model intervention used social cognitive theory and followed clinical guidelines for smoking cessation. Health educators provided these interventions.

Secondhand smoke exposure was measured using 1 nicotine monitor worn by the child and 1 monitor in the room where the child spent the most time. Nicotine collected in the monitors was analyzed by gas chromatography and this method has been validated demonstrating accurate detection of nicotine. Child’s compliance with wearing the nicotine monitor was not addressed.²
Changes in secondhand smoke exposure per the child’s nicotine monitor were reported as not statistically significant (no values provided).²

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Does use of compression stockings after deep vein thrombosis (DVT) improve outcomes?

Evidence-Based Answer
It is unclear if elastic compression stockings (ECS) reduce the risk of postthrombotic syndrome (PTS) (no SOR given, inconsistent results from a systematic review and large RCT). ECS do not reduce the risk of ipsilateral recurrent DVT after a proximal DVT (SOR: A, systematic review and RCT). ECS do not reduce acute leg pain within the first 2 months after symptomatic proximal DVT (SOR: B, RCT).

After acute DVT, the outcomes of primary concern are PTS and recurrent DVT. PTS consists of some combination of leg pain, edema, heaviness, fatigue, pruritus, paresthesias, erythema, hyperpigmentation, induration, telangiectasias, varicosities, lipodermatosclerosis, and venous ulcers.³ PTS occurs in 12% to 54% of patients after DVT, 1–3 usually within 2 years.²³ Severe PTS develops in 3% to 11% of patients.²³

A 2006 systematic review that included 4 RCTs (N=537, range 47–194 patients, mean ages 40–63 years), 1 of which was blinded, evaluated use of ECS after DVT.¹ Follow-up ranged from 36 to 76 months.

Three of the studies (n=421) evaluated ECS after DVT for PTS prevention and found a reduction in PTS from 54% to 25.2% (RR 0.47; 95% CI, 0.36–0.61; NNT=4). Three RCTs (n=490) evaluated ECS to prevent recurrent symptomatic DVT and found no significant reduction in recurrence (RR 0.79; 95% CI, 0.50–1.26). Heterogeneity evaluated by the Cochrane Q statistic was not significant; inconsistency was moderate.¹

A 2014, multicenter, double-blinded RCT assigned patients (N=806, mean age 55 years) with a first symptomatic proximal DVT to below-knee ECS with pressures of 30 to 40 mmHg at the ankle (active ECS) or placebo ECS with pressures <5 mmHg.³ Stockings were applied within 2 weeks of DVT diagnosis and worn for 2 years. Patients wearing their stockings at least 3 days weekly comprised 86% of the study population at 1 month and 57% at 2 years.

By Ginsberg’s criteria (see TABLE), cumulative incidence of PTS from 6 to 24 months of follow-up was 14.2% in the active ECS group versus 12.7% in the placebo ECS group (HR 1.13; 95% CI, 0.73–1.76). The cumulative incidence of PTS using the more inclusive Villalta scale was 52.6% in the active ECS group and 52.3% in the placebo group (HR 1.00; 95% CI, 0.81–1.24). Recurrent ipsilateral DVT occurred within 2 years in 3.9% of patients using active ECS and 4.3% of controls (RR 0.91; 95% CI, 0.47–1.78). In a secondary analysis, no statistically significant difference was noted in leg pain scale between active ECS and placebo groups at 14, 30, or 60 days.⁴ Both groups’ pain scores declined to <1.5 on a 0 to 10 scale by 60 days.

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### TABLE  
**Diagnostic criteria for postthrombotic syndrome**

<table>
<thead>
<tr>
<th>Ginsberg criteria¹</th>
<th>Villalta scale²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ipsilateral leg pain and swelling for ≥1 month that worsens at the end of the day or with prolonged sitting or standing and improves after a night’s rest or leg elevation</strong></td>
<td><strong>Symptoms:</strong> Heaviness, pain, cramps, pruritus, paresthesias in limb</td>
</tr>
</tbody>
</table>
| **Signs:** Pretibial edema, induration, hyperpigmentation, new venous ectasia, redness, pain upon calf compression | **Scoring:** Each sign and symptom listed above is scored from 0 (absent) to 3 (severe). Rating based on total score:  
Mild: 5–9  
Moderate: 10–14  
Severe: ≥15 or lower limb venous ulcer |

¹.  
².  
³.  
⁴.  
⁵.  

Diagnostic criteria for postthrombotic syndrome

- **Ipsilateral leg pain and swelling for ≥1 month that worsens at the end of the day or with prolonged sitting or standing and improves after a night’s rest or leg elevation**
- **Signs:** Pretibial edema, induration, hyperpigmentation, new venous ectasia, redness, pain upon calf compression
- **Scoring:** Each sign and symptom listed above is scored from 0 (absent) to 3 (severe). Rating based on total score: 
  - Mild: 5–9 
  - Moderate: 10–14 
  - Severe: ≥15 or lower limb venous ulcer
What is the role of pulmonary artery pressure (PAP) estimation by Doppler echocardiography (DE) in the diagnosis of pulmonary hypertension (PHTN)?

Evidence-Based Answer

DE is accurate at the population level but lacks precision in individual patients. DE estimation of a tricuspid gradient (TG) >45 mmHg has a sensitivity of 47% and specificity of 97% for the diagnosis of PHTN (SOR: B, cross-sectional studies). DE remains the primary noninvasive tool for detection of PHTN (SOR: C, expert consensus).

A 2013 cross-sectional study (N=152) evaluated the accuracy of PAP measured by DE versus right heart catheterization (RHC) in consecutive patients referred to an Italian PHTN unit for diagnostic RHC. The patients had a mean age of 56 years and 62% of them were women. RHC and DE were performed within 1 hour to minimize error from spontaneous PAP variability. Comparisons of study accuracy were performed using a Bland-Altman analysis (see TABLE 1). The authors concluded that DE was accurate at the population level but lacked precision in individual patients. This study was limited by verification bias because patients were excluded from RHC if their PAP by DE was <37 mmHg.

A 2009 cross-sectional study (N=65) evaluated the accuracy of PAP measurement by DE (performed within 1 hour of clinically indicated RHC) in patients with pulmonary arterial hypertension or PHTN related to interstitial lung disease, pulmonary venous hypertension, or obstructive sleep apnea. The patients had a mean age of 54 years and 84% of them were women. After excluding 6 patients with no measurable tricuspid regurgitation, a Bland-Altman analysis was used (see TABLE 1). In the 59 patients who underwent both DE and RHC, the values were highly correlated ($r^2=0.45$; $P<.005$) with 48% (28 of 59) differing by <10 mmHg and 22% (13 of 59) differing by 11–19 mmHg. Of the 30% (18 of 59) of readings that differed by >20 mmHg, 6 were overestimates and 12 were underestimates.

A 2004 cross-sectional study (N=137) evaluated the accuracy of DE for the diagnosis of PHTN compared with the gold standard of mean systolic PAP on RHC >30 mmHg in patients with systemic sclerosis. Patients had a mean age of 63 years with a broad range of pulmonary fibrosis on high-resolution CT scan and 72% (99 of 137) were diagnosed with PHTN based on RHC. TG estimates PAP by adding the Doppler flow measurements of tricuspid regurgitation to an estimate of right atrial pressure (based on the appearance of inferior vena cava). TG correlates with mean PAP on RHC ($r^2=0.45$; $P<.005$) and, as the TG cutoff was increased from 30 to 45 mmHg, the sensitivity decreased and specificity increased (see TABLE 2). Multiple operators in 2 institutions performed DE, which could have introduced interobserver variability.

A 2009 opinion-based guideline from the American College of Cardiology Foundation and the American Heart Association concluded that patients suspected of PHTN based on history, risk factors, and physical exam should always undergo DE because it may demonstrate several findings that correlate with right heart hemodynamics (right atrial enlargement, right ventricular enlargement, and flattening curvature of the intraventricular septum). These findings may identify coexisting abnormalities that do not cause

### TABLE 1

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Patients, n</th>
<th>Accuracy (average of all differences, in mmHg)</th>
<th>Precision (95% inclusion range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013$^1$</td>
<td>152</td>
<td>−0.05</td>
<td>18 −19</td>
</tr>
<tr>
<td>2009$^2$</td>
<td>59</td>
<td>−0.06</td>
<td>39 −40</td>
</tr>
</tbody>
</table>

### TABLE 2

<table>
<thead>
<tr>
<th>DE TG thresholds (mmHg)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
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</thead>
<tbody>
<tr>
<td>&lt;30 vs ≥30</td>
<td>88</td>
<td>42</td>
<td>1.5</td>
<td>0.29</td>
</tr>
<tr>
<td>&lt;35 vs ≥35</td>
<td>75</td>
<td>66</td>
<td>2.2</td>
<td>0.38</td>
</tr>
<tr>
<td>&lt;40 vs ≥40</td>
<td>58</td>
<td>87</td>
<td>4.5</td>
<td>0.48</td>
</tr>
<tr>
<td>&lt;45 vs ≥45</td>
<td>47</td>
<td>97</td>
<td>16</td>
<td>0.55</td>
</tr>
</tbody>
</table>

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PHTN but support a specific alternate diagnosis. In patients with suspected PHTN based on DE, RHC confirms the presence of PHTN, establishes the specific diagnosis, and determines the severity of PHTN.

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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.


What is the most effective treatment for a patient with symptoms of chronic mucocutaneous candidiasis (CMC)?

Evidence-Based Answer
For patients with CMC, 6-month therapy with a systemic azole may be effective (SOR: B, single RCT). Daily oral fluconazole has been recommended as first-line treatment (SOR: C, expert opinion). Should resistance develop, treatment should be individualized based on Candida albicans culture susceptibility and clinical response; options include posaconazole, echinocandins, and amphotericin B, with the need for maintenance antifungal therapy likely (SOR: C, case reports and expert opinion).

A 1980 double-blinded RCT of 12 patients (age range, 7–31) with CMC compared ketoconazole 100–200 mg daily versus placebo for 6 months for the treatment of CMC.1 Treatment was scored as failure or nonfailure by 2 independent observers; no objective criteria were described.

More patients in the ketoconazole group had resolution of oral lesions (6 vs 2 with placebo; no P value provided) and improvement of involved skin (6 vs 0; no P value provided) at 6 months. One patient in the ketoconazole group developed hepatotoxicity. Notably, this RCT predates the approval of several azoles with less risk of hepatotoxicity.1

A 2011 case report reviewed the medical course of a female with CMC diagnosed at 2 years old.2 The patient had been treated for recurrent infections throughout her life with long-term courses of multiple systemic azole antifungals. At age 39, C albicans cultures at presentation showed multidrug resistance but susceptibility to posaconazole, flucytosine, amphotericin B, and echinocandins. The patient was treated with intravenous amphotericin B 50 mg/d for 2 weeks, followed by oral posaconazole 400 mg twice daily for 2 months and 200 mg daily for an additional 3 months. Relapse occurred after discontinuation. The patient was maintained on a cycle of oral posaconazole: 200 mg 3 times daily for 1 month, followed by 15 days without antifungal therapy.

A 2006 case report discussed the treatment of an 18-year-old German woman with diagnosed CMC, a family history of CMC, and no history of immunological disease.3 The patient received long-term systemic fluconazole therapy as a child and was later dosed at 100–200 mg fluconazole daily dependent on symptoms. Her C albicans cultures grew azole-resistant strains after several years of management. The patient received 70 mg intravenous caspofungin on day 1 of therapy followed by 50 mg 4–7 times per week for almost 12 months, which resolved clinical symptoms.

A 2001 case report discussed the treatment of an 18-year-old German woman with diagnosed CMC, a family history of CMC, and no history of immunological disease. The patient received long-term systemic fluconazole therapy as a child and was later dosed at 100–200 mg fluconazole daily dependent on symptoms. Her C albicans cultures grew azole-resistant strains after several years of management. The patient received 70 mg intravenous caspofungin on day 1 of therapy followed by 50 mg 4–7 times per week for almost 12 months, which resolved clinical symptoms.

A 2010 narrative review recommended fluconazole 100–200 mg daily as the first-line agent for CMC, with up to 800 mg daily appropriate for systemic infections.4 Other azoles were recommended as potential substitutes in cases with decreased fluconazole sensitivity. Echinocandins were recommended first-line for life-threatening systemic candidiasis. Topical amphotericin B was recommended as an option for local infections, with intravenous administration reserved for severe infection.

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Is “morning after” oral ulipristal acetate superior to oral levonorgestrel at preventing unintended pregnancy?

Bottom line
Oral ulipristal acetate (UPA) is superior to oral levonorgestrel (LNG) at preventing pregnancy if administered within 120 hours of a single episode of unprotected intercourse (number needed to treat to prevent one additional pregnancy=110) (SOR: A, meta-analysis of RCTs).

Evidence summary
A 2012 systematic review examined 2 RCTs (N=3,448) of women younger than 35 years with normal menstrual cycles, no use of hormonal contraception or IUD, and no breastfeeding or pregnancy within 1 month. These women had 1 episode of unprotected intercourse within 120 hours. The analysis compared pregnancy rates in groups receiving a single oral dose of UPA 30 or 50 mg versus one oral dose of LNG 1.5 mg or 2 oral doses of LNG 0.75 mg given 12 hours apart. The primary outcome of pregnancy was measured with serial urine pregnancy tests at 5 to 7 days after expected menses and continued serial pregnancy testing until return to menses or until hCG values confirmed pregnancy.

Meta-analysis of these 2 RCTs demonstrated a statistically significant lower pregnancy rate in the group receiving UPA compared with LNG (1.28% vs 2.19%; risk ratio 0.59; 95% CI, 0.35–0.99; NNT=110). A side effect of UPA was later return of menses by a mean of 2.8 days. The primary adverse effects of both interventions included headache (20%–29%) and nausea (12%–29%), with no significant difference between treatments. The studies were rated as good quality and were adequately powered for the clinically significant endpoint of pregnancy. The studies also had adequate allocation concealment and used intention to treat analysis.

A 2013 meta-analysis of 3 crossover studies (N=50) of women younger than 40, with normal menstrual cycles, no hormonal contraception, and no breastfeeding or pregnancy examined the effects of LNG (2 oral 0.75-mg doses 12 hours apart) and UPA (a single oral 30-mg dose) compared with placebo. The primary outcome was ovulation as measured by follicular rupture with serial ultrasounds. The patients were randomized to treatment or placebo at a follicular diameter of more than 18 mm, and monitored with serial ultrasounds through menses.

In patients taking UPA, follicle rupture was delayed for at least 5 days in 58.8% of cycles compared with 14.6% of cycles for women taking LNG and 4% of cycles for those taking placebo ($P=.0001$ for both comparisons to UPA). UPA was more likely than LNG to delay ovulation when given in the late follicular phase, with an NNT of 3.

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REFERENCES

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Are powered or manual toothbrushes better for removing dental plaque and treating gingivitis?

Evidence-Based Answer

Powered toothbrushes, especially the rotation oscillation type, reduce plaque and gingivitis scores in both short- and long-term studies more than manual toothbrushes. The magnitude of effect is greater with longer use (SOR: C, meta-analysis of RCTs and individual RCTs, all with disease-oriented results).

A Cochrane systematic review of 51 RCTs (N=4,624) compared the efficacy of powered versus manual toothbrushes in reducing dental plaque and gingivitis, as measured by a standardized score.¹ Selection criteria included RCTs ≥4 weeks, with unsupervised brushing using either manual or powered toothbrushes. The reviewers identified 7 different types of powered toothbrushes as follows (number of trials in parentheses): side to side (10), counter oscillation (5), rotation oscillation (27), circular (2), ultrasonic (7), ionic (4), and unknown (5). Results were categorized by duration as either short term (1–3 months; 45 trials) or long term (>3 months; 16 trials).

Compared with manual toothbrushes, powered toothbrushes improved plaque scores 11% in the short term (40 trials, n=2,871; P<.0001), and 21% in the long term (14 trials, n=978; P=.01). For gingivitis, both short- and long-term results favored powered toothbrushes with a 6% (44 trials, n=3,345; P<.0001) and 11% (16 trials, n=1,645; P=.0002) reduction in scores, respectively.¹

Regarding the type of powered toothbrush used, only the rotation oscillation brush showed consistent improvement in both plaque and gingivitis scores over both periods. One weakness of the review was a high degree of unexplainable study heterogeneity (I² ranged from 51% to 86%). Overall quality of the studies was poor, with only 5 studies considered low risk of bias. Many studies had declared financial support from the manufacturer or had unclear financial support.¹

Two additional studies have been published since the Cochrane review. A single-blinded RCT assessed plaque reduction and changes in 2 separate gingival inflammation scores in 120 adult patients (aged 18–64 years) assigned to brush with either a power (rotation oscillation) or a manual (soft bristle American Dental Association reference) toothbrush for 4 weeks.² Mean plaque index levels were measured at baseline, 1 week, and 4 weeks. Gingival inflammation in the whole mouth was evaluated at 4 weeks only, using standardized indices for gingival inflammation and gingival bleeding.

Powered toothbrushes showed a greater reduction in plaque at 1 week (percent change from baseline 39.9% vs 17.0%, P<.001) and 4 weeks (percent change from baseline 55.7% vs 26.0%, P<.001). Powered toothbrushes also had greater reductions in the 4-week gingival inflammation score (percent change from baseline 18.6% vs 6.1%, P<.001) and gingival bleeding score (percent change from baseline 61.1% vs 43.5%, P<.001). Weaknesses included single blinding and industry sponsorship.²

A second RCT evaluated plaque reduction and gingivitis scores at 1, 2, and 6 weeks for a power (rotation oscillation) toothbrush versus a manual medium bristle toothbrush in 60 dental students 18 to 28 years old.³ Mean plaque scores dropped 4% more with powered than manual brushing at 1 week (no P value provided), 16% more at 2 weeks (P=.0014), and 23% more at 6 weeks (P<.0001). Standardized gingival index scores showed a nonsignificant difference of 0% at 1 week, 1% at 2 weeks, and 1% at 6 weeks. Weaknesses in this study include questionable generalizability of the results from a study population of dental students who also had high baseline rates of gingivitis.

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What is the effect of diet and dietary supplements on vulvovaginal candidiasis (VVC)?

**Evidence-Based Answer**

Probiotic therapy may help to prevent VVC, although the probiotic, dose, and delivery system are not well defined (SOR: C, systematic review of low-quality trials). There is an association between the presence of some urinary sugars and VVC (SOR: C, disease-oriented cohort study). No evidence supports the use of oral garlic tablets in reducing VVC (SOR: C, disease-oriented RCT).

A 2006 systematic review of microbiological studies and clinical trials (6 RCTs and 2 prospective cohort studies, N=665) evaluated the efficacy of probiotics to colonize the vagina and reduce VVC occurrence as measured by vaginal swab cultures.\(^1\) Five of the trials (n=195) evaluated oral probiotics, but pooling of data was not possible due to heterogeneity and most studies did not use clinical outcomes.

Two RCTs evaluated the effect of yogurt on positive cultures for *Lactobacillus acidophilus* and *Candida*. One randomized crossover trial (n=33) evaluated the consumption of 8 ounces yogurt with *L. acidophilus* for 6 months followed by no yogurt for 6 months (or vice versa) and found the mean number of candidal infections and colonizations per woman were less during yogurt consumption (0.38 vs 2.54, \(P=.001\) and 0.84 vs 3.23, \(P=.001\), respectively). However, an RCT (n=46) comparing 150 mL/d of yogurt with *L. acidophilus* for 2 months followed by no yogurt for 2 months, to pasteurized yogurt for 2 months followed by no yogurt for 2 months, found no differences in positive *Candida* cultures between the groups after 1 and 2 months (56\% vs 62\%, and 44\% vs 37\%, \(P=.05\), respectively).\(^1\)

The review authors concluded that probiotics may be beneficial, but additional studies are needed due to small sample sizes, lack of placebo controlled trials, and differences among the trials regarding strain, dosage, and duration of treatment.\(^1\)

A 1984 cohort study (N=100) examined the relationship among nutritional data, the presence of urinary sugars (glucose, lactose, arabinose, ribose, galactose, fructose), and recurrent VVC in women with complaints of vaginal itching, burning, discharge, or irritation.\(^2\) Patients with recurrent candidal infections (>3 positive cultures in previous 2 years) were identified via chart review (n=46) and 51 women were labelled as controls. Patients with recurrent VVC submitted a dietary history, underwent 2-hour postprandial serum glucose and urine chromatography testing, and vaginal swab testing for presence of *Candida*.

Reduction of milk product and artificial sweetener intake resulted in negative chromatography for urinary sugars in 80\% of patients and 92\% of those patients were free of yeast infection for 1 year. Sucrose restriction resulted in negative chromatography for urinary sugars in 72\% of patients and 90\% did not report a yeast infection for over 1 year. Wine cessation had no effect. The urinary presence of ribose, which is found in dairy products (RR 3.0; 95\% CI, 1.5–6.0); arabinose, an ingredient to produce flavoring in foods (RR 2.5; 95\% CI, 1.3–5.0); and glucose (RR 1.4; 95\% CI, 1.0–2.0) in the urine correlated with an increase in VVC incidence.\(^2\)

A 2014 RCT assessed the effects of oral garlic tablets on vulvovaginal *Candida* colony counts in asymptomatic women (N=59) 18 to 50 years old who reported 1 or more episodes of VVC in the previous 12 months and had *Candida* present at screening with self-collected vaginal swab cultures.\(^3\) Patients took garlic tablets (n=29) or placebo (n=30) for the 2 weeks prior to menses, obtained daily vaginal swabs at home, and recorded symptoms of vaginal itch, discharge and side effects in a daily diary.

No difference was noted in vaginal symptoms (moderate to severe itching or abnormal discharge) during the 2 weeks of treatment (RR 1.03; 95\% CI, 0.67–1.58). No difference was noted in heavy colonization (ie, colony counts of *Candida* >100 CFU/mL any day of the week before menstruation) between garlic and placebo groups (76\% vs 90\%; RR 0.85; 95\% CI, 0.67–1.08). A significant difference was found between the proportion of women in the garlic group who reported at least 1 adverse effect (gastrointestinal symptoms, frequent urination, nightmares/insomnia, rash) compared with the placebo group (83\% vs 43\%; difference in proportion 39\%; 95\% CI, 17–97).\(^3\)

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Emily Cooper, MD  
Karen Sanders, MS, RN  
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Which hospitalized medical patients need deep vein thrombosis (DVT) prophylaxis?

Evidence-Based Answer
Hospitalized medical patients may be assessed for risk of venous thromboembolism (VTE) using criteria-based tools to determine if prophylaxis would be beneficial. Some of these risk factors include active cancer, previous VTE, reduced mobility, older age, and thrombophilia (SOR: B, based on 2 cohort studies).

A 2011 prospective cohort study investigated the incidence of VTE in 15,156 acutely ill hospitalized medical patients for 3 months after hospital admission. Inclusion criteria included age ≥18 years, admission for acute illnesses, and at ≥3 days’ admission. Patients were excluded if they were enrolled in a therapeutic clinical trial, if anticoagulation or thrombolytic medication were used at or within 48 hours of admission, if major surgery or trauma occurred within 3 months before admission, if patients were admitted for DVT or pulmonary embolism (PE), or if follow-up was not possible.

A total of 184 patients developed VTE (76 had PE and 67 had lower-extremity DVT) at 3 months, diagnosed by imaging studies. Patient records were reviewed to determine patient characteristics associated with VTE risk and each factor was assigned a risk score via a Cox regression model (see TABLE 1). Researchers also calculated the 3-month expected VTE risk based on the cumulative scores (see TABLE 2). A key weakness of this study was the lack of evaluation of whether any prophylaxis was used during admission. Also patients were not screened for VTE routinely; testing was based on clinical signs and symptoms, which likely underestimated the VTE incidence.

A 2010 prospective cohort study analyzed 1,180 consecutive hospitalized medical patients over 2 years for VTE risk. Patients were excluded for ongoing anticoagulation, contraindications to pharmacological prophylaxis, pregnancy, creatinine clearance <30 mL/min, age ≥18, and failure to give informed consent. Patients in the study were classified by a study operator as being at high risk for VTE (score >4) or low risk of VTE (score <4) based on a predefined risk assessment model (RAM) (see TABLE 3). The attending physicians were not informed of the RAM score and gave VTE prophylaxis at their discretion. A screener then reviewed the physicians’ orders for which patients received prophylaxis.

Patients were divided into 3 groups: high-risk untreated (if patients were inadequately treated such that prophylaxis was not started within 48 hours of admission or if prophylaxis did not cover ≥80% of hospital stay), high-risk treated, or low-risk untreated. Adjusted hazard ratios for VTE were then assessed after 90 days.

### TABLE 1
Determining risk score for venous thromboembolic disease (VTE) in hospitalized patients

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Hazard ratio (95% CI)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>4.7 (3.0–7.2)</td>
<td>3</td>
</tr>
<tr>
<td>Known thrombophilia</td>
<td>3.5 (1.1–11)</td>
<td>2</td>
</tr>
<tr>
<td>Current lower-limb paralysis</td>
<td>3.0 (1.6–5.7)</td>
<td>2</td>
</tr>
<tr>
<td>Current cancer</td>
<td>2.8 (1.9–4.2)</td>
<td>2</td>
</tr>
<tr>
<td>Immobilized ≥7 days</td>
<td>1.9 (1.3–2.9)</td>
<td>1</td>
</tr>
<tr>
<td>ICU/CCU stay</td>
<td>1.8 (1.1–2.9)</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>1.7 (1.1–2.6)</td>
<td>1</td>
</tr>
</tbody>
</table>

### TABLE 2
3-month expected venous thromboembolic disease (VTE) risk by cumulative score

<table>
<thead>
<tr>
<th>Cumulative score</th>
<th>3-month expected VTE risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.4%</td>
</tr>
<tr>
<td>1</td>
<td>0.6%</td>
</tr>
<tr>
<td>2</td>
<td>1.0%</td>
</tr>
<tr>
<td>3</td>
<td>1.7%</td>
</tr>
<tr>
<td>4</td>
<td>2.9%</td>
</tr>
<tr>
<td>5–10</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

### TABLE 3
A risk assessment model, where scores ≥4 indicated medical inpatients who were likely to derive benefit from DVT prophylaxis

<table>
<thead>
<tr>
<th>Baseline features</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>3</td>
</tr>
<tr>
<td>Previous VTE (excluding superficial VTE)</td>
<td>3</td>
</tr>
<tr>
<td>Reduced mobility</td>
<td>3</td>
</tr>
<tr>
<td>Known thrombophilia</td>
<td>3</td>
</tr>
<tr>
<td>Recent (≤1 month) trauma and/or surgery</td>
<td>2</td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td>1</td>
</tr>
<tr>
<td>Heart/respiratory failure</td>
<td>1</td>
</tr>
<tr>
<td>Acute MI or ischemic stroke</td>
<td>1</td>
</tr>
<tr>
<td>Acute infection/rheumatologic disorder</td>
<td>1</td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m²)</td>
<td>1</td>
</tr>
<tr>
<td>Ongoing hormonal treatment</td>
<td>1</td>
</tr>
</tbody>
</table>

CONTINUED
VTE developed in 11% of high-risk untreated patients, 2.2% of high-risk treated patients, and 0.3% of low-risk untreated patients. There was a statistically significant reduction in VTE in the high-risk treated group compared with the high-risk untreated group (HR 0.13; 95% CI, 0.04–0.40). There was a statistically significant increase in VTE in the high-risk untreated group compared with the low-risk untreated group (HR 32; 95% CI, 4.1–251). Of the 469 patients at high risk of VTE, gastrointestinal, intramuscular, or cerebral bleed occurred in 1.6% (3 of 186) of the treated high-risk patients. Bleeding occurred in 0.4% (1 of 711) of the low-risk patients. Limitations of this study included no formal statistical evaluation to derive the clinical prediction rule used for RAM generation and lack of randomization (although randomization would have been unethical); additionally, testing for VTE was not routinely performed unless there were signs or symptoms of VTE.

In 2011, the American College of Physicians (ACP) issued evidence-based clinical guidelines to guide VTE prophylaxis in hospitalized medical patients. The ACP recommended assessment of medical patients for VTE risk and bleeding risk prior to VTE prophylaxis, but did not endorse a specific risk assessment tool, citing insufficient evidence. The ACP recommended pharmacological VTE prophylaxis for medical patients, including patients with stroke, unless bleeding risk outweighed the benefits.

The ACP concluded that VTE prophylaxis did not decrease total mortality, but did decrease the risk of PE (RR 0.69; 95% CI, 0.52–0.90) and increase the risk of bleeding events (RR 1.34; 95% CI, 1.08–1.66). All recommendations were graded as strong (benefits clearly outweigh the risks and burden, supported by moderate-quality evidence).

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**Evidence-Based Answer**

**How prevalent is intimate partner violence among women presenting in orthopedic clinics?**

A 2013 cross-sectional multinational study of 2,945 women presenting to 12 orthopedic fracture clinics in 5 countries examined the prevalence of IPV. IPV was defined as physical, emotional, or sexual abuse by an intimate partner. Participants were asked direct questions about physical, emotional, and sexual IPV and completed 2 validated questionnaires (Women Abuse Screening Tool and the Partner Violence Screen).

About 16% reported a history of IPV within the past year (95% CI, 14.7–17.4). About 35% had experienced IPV in their lifetime (95% CI, 32.8–36.5). Only 1.7% presented to the clinics as a direct consequence of IPV (95% CI, 1.3–2.2). The 12-month prevalence of IPV was higher in the Canadian, US, and Indian centers than in the Dutch and Danish centers (18% vs 12%; P<.001). The lifetime prevalence of IPV was significantly higher in Canada and the United States (40%) than in other countries.

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the Netherlands and Denmark (24%; \( P=.001 \) vs US) and India (18%; \( P<.016 \) vs US). Only 6% of women reported being asked previously about IPV by another healthcare professional.\(^1\)

The same investigators previously studied the prevalence of IPV in 2011 among 282 women presenting in 2 orthopedic fracture clinics in Canada.\(^2\) The reported prevalence of IPV within the prior year was 32% (95% CI, 26.5–37.2). Only 2.4% presented to the clinic as a direct consequence of IPV. Overall, 24 (8.5%) women reported physical abuse in the prior year. Only 4 of these women had been asked about IPV by a physician.

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### Does daily use of fish oil by pregnant women affect the newborn?

**Evidence-Based Answer**

Supplementation with daily fish oil or other long-chain polyunsaturated fatty acids (LCPUFA) during pregnancy reduces early preterm birth (<34 weeks) in high-risk pregnancies and slightly increases birth weight (SOR: \( A \), meta-analysis of RCT). Infants born to mothers who are supplemented with fish oil have fewer illness symptoms including upper respiratory and gastrointestinal symptoms (SOR: \( B \), low-quality RCT) and may have less atopic disease (SOR: \( B \), underpowered RCTs).

A 2012 meta-analysis of 15 RCTs (N=8,474) compared n-3 LCPUFA supplementation with a range of placebos (10–23 weeks of treatment duration) across all trimesters.\(^1\) The study included 6,530 uncomplicated and 1,944 high-risk (eg, previous pregnancy complicated by preterm birth, intrauterine growth restriction, pregnancy-induced hypertension, stillbirth, or current twin pregnancy, current preeclampsia, or abnormal umbilical artery Doppler) pregnant patients living in predominantly high-income countries. Twelve of 15 included studies started supplementation in the second trimester. LCPUFA included docosahexanoic acid (DHA) and/or eicosapentaenoic acid (EPA) found in fish oils. The daily dose of DHA ranged from 80 mg to 2.2 g in various forms (fish oil tablet, foods, beverages), and placebo delivery mimicked the intervention in each study. Infant outcomes included birth weight, length and head circumference, NICU admissions, stillbirth, infant death, and preterm birth.

In a subgroup of 4,343 patients from 5 studies, the intervention significantly decreased the risk of early preterm (<34 weeks) birth (RR 0.74; 95% CI, 0.58–0.94; NNT=68). There was a higher mean birth weight in the intervention group in the subset of 6,020 patients in the 9 studies that examined birth weight (mean difference [MD] 42.22 g; 95% CI, 14.76–69.69), although the clinical significance is uncertain. Heterogeneity among trials and patients’ high socioeconomic status may limit generalizability.\(^1\)

A 2011, double-blinded RCT examined infant morbidity after 400 mg daily oral DHA supplementation or placebo given to 1,094 low-risk, Mexican pregnant women (age range, 18–35 years) between 18 and 22 weeks’ gestation through delivery.\(^2\) Parents reported occurrence and duration of illness symptoms in their infants at 1, 3, and 6 months of age via a self-report questionnaire.

With few exceptions, significant differences in symptom duration favored the intervention group (see **TABLE**). However, results were inconsistent across ages, and researchers did not statistically correct for the risk of multiple comparison bias.\(^2\)

A 2003, double-blinded RCT evaluated 98 pregnant Australian women with atopy who were given oral

### Illness symptoms in infants of mothers supplemented with DHA versus control\(^2\)

<table>
<thead>
<tr>
<th>Infant age</th>
<th>Decreased</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cold, 0.76(^a)</td>
<td>• Rash, 1.22</td>
<td></td>
</tr>
<tr>
<td>• Cough, 0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Phlegm, 0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Wheeze, 0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Total days ill, 0.86</td>
<td>• Nasal secretions, 1.15</td>
<td></td>
</tr>
<tr>
<td>• Other illnesses, 0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fever, 0.80</td>
<td>• Vomiting, 1.74</td>
<td></td>
</tr>
<tr>
<td>• Nasal secretions, 0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Difficulty breathing, 0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Other illness, 0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rash, 0.77</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Only RR ratios in which 95% confidence intervals did not include 1 are listed in the table.

DHA=docosahexanoic acid.
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Fish oil 3.7 g daily versus olive oil from 20 weeks’ gestation to delivery. Clinical outcomes among infants included incidence of asthma, atopic dermatitis, and food allergies assessed with skin prick testing (SPT). A pediatrician blinded to therapy evaluated 72 infants and performed SPT (the standard and most sensitive clinical test for detecting IgE-mediated food allergy) for allergies at 1 year of age; 11 other infants who did not present for the clinical exam were assessed by parental telephone interview.

Among infants with atopic dermatitis (n=31), those in the intervention group were less likely to have severe dermatitis based on a score of >25 on the modified objective SCORAD (an accepted dermatological indexing tool, which classifies cases of dermatitis as <15=mild; 15–40=moderate; >40=severe) (OR 0.09; 95% CI, 0.01–0.94). No other clinical outcomes were statistically significant.

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