What is the most effective treatment for acne rosacea?

Evidence-Based Answer

Topical metronidazole and azelaic acid are equally effective for the papulopustular lesions of acne rosacea, although metronidazole is better tolerated. Oral doxycycline, tetracycline, and metronidazole are also effective, but not enough evidence exists to determine whether one is more effective than another or more effective than topical therapy (SOR: A, systematic review and individual RCTs). Some evidence supports a benefit for topical sodium sulfacetamide with sulfur, and benzoyl peroxide (SOR: B, small single RCTs). Pulsed-light and laser therapy may improve the erythema and telangiectasias associated with acne rosacea (SOR: C, case series). All patients with acne rosacea should use sunscreen and emollients, and avoid skin irritants (SOR: C, expert opinion).

Evidence summary

A Cochrane systematic review found that topical metronidazole and azelaic acid are both more effective than placebo for patients with papulopustular lesions of acne rosacea (TABLE). The authors noted that the studies were generally weak because of poor methodology and reporting, small sample sizes, and lack of quality-of-life measures (only 2 RCTs evaluated patient assessment of treatment effectiveness).¹

Another systematic review reported small case series suggesting possible effectiveness with topical tretinoin (43 cases), oral clindamycin (43 cases), oral erythromycin (13 cases), and topical tacrolimus (3 cases).²

Oral metronidazole and tetracycline also work

The Cochrane systematic review also found that oral metronidazole and tetracycline were more effective than placebo for papulopustular lesions.¹ A subsequent systematic review found that anti-inflammatory doses of oral doxycycline (20–40 mg daily) were effective.³ ⁴

Evidence for other oral drugs is limited or inconclusive

Limited supporting evidence exists for oral macrolides, isotretinoin, and spironolactone.⁵ ⁶ Three small placebo-controlled RCTs found...
insignificant or inconclusive benefits for ampicillin, oral clarithromycin plus omeprazole, and oral rilmenidine (a centrally acting, sympatholytic antihypertensive.)

Many studies, little difference in drug effects
A large number of studies have compared the effectiveness of one treatment against another, but only one comparison demonstrated a statistically significant benefit. Two RCTs enrolling 104 patients found that oral doxycycline (40 mg daily) in combination with topical metronidazole reduced the number of lesions more than topical metronidazole alone (4 and 7 fewer lesions; \( P < .01 \) for both studies). It is unclear whether the reduction is clinically significant.

Not all therapies were equally well tolerated, however. Topical metronidazole produced fewer adverse events than topical azelaic acid (OR 4.56; 95% CI, 2.07–10.03). Doxycycline dosed at 40 mg daily produced fewer gastrointestinal adverse effects than 100 mg daily (5% vs 26%; \( P \) value not given).

Therapy for erythema and telangiectasia
A systematic review described multiple small case series that reported improvements in erythema and telangiectasias with pulsed-light therapy (188 cases) and laser therapy (82 cases). Another case series with 17 patients reported improvements with photodynamic therapy with red light.

General skin care measures
A case series reported improved symptom scores among 20 patients using twice-daily metronidazole gel when they added moisturizing lotion to one side of their face. Expert opinion recommends using sunscreen and protective emollients and avoiding triggers that cause flushing, such as certain foods, beverages, and cosmetics.

Recommendations
The American Acne and Rosacea Society guidelines state that good evidence supports 3 topical treatments—metronidazole, azelaic acid, and sulfacetamide/sulfur—as well as anti-inflammatory doses of oral doxycycline.

The guidelines also list other topical and oral antibiotic treatments, but cite low-quality evidence for their efficacy and concerns about the emergence of antibiotic resistance. They advise appropriate skin care, including gentle cleansers, moisturizers, and sun protection.

REFERENCES
Dear EBP Readers,

Have you ever wondered how long it takes for a new medical discovery to become widely accepted?

Researchers at the School of Medicine of the University of Ioannina decided to look into that very question.1 They used as a proxy for "widely accepted" the point when a study about an intervention received >1,000 citations. They then looked backward and sought the first mention of that intervention. It turns out that about 16 years pass between an effective intervention’s debut in the literature and the time it becomes "widely accepted."4

Now 16 years is rather long. Sixteen years is long enough to go to college, medical school, residency, and spend a few years in practice. Sixteen years is also long enough for someone to stop exercising, develop insulin resistance, then frank diabetes, followed by kidney damage.

One might therefore argue that 16 years is just a bit slow on the uptake. Sixteen years means that new wonders coming out now will not be widely accepted until after I’ve retired. It is also likely that those same new wonders will not be widely accepted until after patients who might benefit have developed irreparable injuries.

But there are some interesting details beneath these statistics. Two drugs made it through the research gauntlet in only 4 years – indinavir and abciximab. Both drugs had strong financial backing from the developers, strong interest in research circles, and strong advocacy in the community. Clearly, concerted determination makes a difference. Conversely, the researchers noted that out of 100 very promising claims of new discoveries between 1979 and 1983, only 5 were eventually licensed for clinical use and only 1 went on to extensive clinical use. Perhaps more sobering, nearly half of all studies that received >1,000 citations were for therapies that were partially or fully refuted within a couple of years.

So this just raises another prickly question. How can we pick up the pace of translational processing without letting even more junk research through the gauntlet? Feel free to call me when you have the answer.

Regards,

Jon O. Neher, MD


From the Editor
Diving for PURLs

**PURLs Criteria**

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

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

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

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

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

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

## Prostate cancer: To screen or not?


This was a meta-analysis of 6 RCTs that compared a policy of screening for prostate cancer with prostate-specific antigen (PSA) with or without digital rectal examination versus a policy of not screening.

Results showed no significant effect of screening on all-cause mortality or death from prostate cancer (RR=0.88; 95% CI, 0.71–1.09; *P*=.25). Screening did increase the probability of being diagnosed with prostate cancer (RR=1.46; 95% CI, 1.21–1.77; *P*<.001).

**Bottom line:** This review would not encourage us to start PSA screening, but does it provide sufficient evidence to stop it altogether? We think rather that it modifies the information we provide as we counsel men about this screening test.

First, there was a decrease in death from prostate cancer in patients who were screened, although the decrease did not achieve statistical significance; it is still possible that future RCTs will demonstrate decreased mortality. Second, while the meta-analysis itself was well done, the included RCTs were of moderate to low quality. Finally, no quality-of-life measures were included.

Based on the results of this study, we would inform patients that currently, the best evidence shows that screening with PSA does not reduce the risk of dying from prostate cancer.

**Article Reviewer:** Sue Slatkoff, MD

**Summary Author:** Anne L. Mounsey, MD

This RCT enrolled 76,639 men aged 55–74 years to compare the mortality impact of annual prostate cancer screening with prostate-specific antigen (PSA) and digital rectal exam (annually screened group) versus a usual-care group. A subgroup analysis was also conducted of men with comorbidities (including hypertension, diabetes, stroke, COPD, or BMI >30 kg/m²) and without comorbidities (healthy men). Men randomized to usual care received a wide range of PSA testing and examination; 52% received at least 1 PSA during the study.

Healthy men in the annually screened group experienced lower prostate cancer-specific mortality than healthy men in the usual-care group (adjusted hazard ratio [AHR] 0.56; 95% CI, 0.33–0.95; *P*=.03) after an average of 10 years of follow-up.

Deaths from prostate cancer were infrequent in both groups, occurring in 0.22% (164/73,378) of all patients. The absolute risk reduction for men without comorbidities who received yearly screening versus usual care was 0.11% (0.29% vs 0.18%). The number needed to screen (NNS) to prevent 1 death from prostate cancer was therefore 909.

**Bottom line:** To our knowledge, this is the first convincing evidence that a subgroup of men may experience decreased mortality from prostate cancer screening. However, all-cause mortality rates were similar in both groups, regardless of comorbidities.

This study does not address the downsides of screening, such as unnecessary biopsies, unnecessary treatments for prostate cancer, or side effects of treatment such as incontinence and impotence. Such potential unintended consequences and the presence of comorbidities should be taken into account when advising men about annual prostate cancer screening.

**Article Reviewer:** Kohar Jones, MD

**Summary Author:** Kate Rowland, MD

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**Prostate cancer: To screen or not?**

**Relevant** | Yes
---|---
**Medical care setting** | Yes
**Valid** | Yes
**Implementable** | Yes
**Clinically meaningful** | Yes

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**Comorbidities should guide conversations about prostate cancer screening**


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**Comorbidities should guide conversations about prostate cancer screening**


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**Article Reviewer:** Kohar Jones, MD

**Summary Author:** Kate Rowland, MD
Blood pressure management after acute ischemic stroke

**Bottom line**

Current consensus guidelines recommend that if a patient is not eligible for thrombolytic therapy, blood pressure (BP) should not be treated until it is >220/120 mmHg. If the patient is otherwise eligible to receive thrombolytic therapy, the maximum permitted BP is 185/110 mmHg, because of an increased risk of hemorrhage above this value. Some evidence suggests that actively lowering BP within 36 hours of acute stroke does not worsen outcomes and decreases all-cause mortality at 3 months.

**Review of the evidence**

A 2008 Cochrane review of 12 RCTs involving 1,153 patients evaluated the effect of BP management regimens after an acute CVA. Eleven trials lowered BP with various agents, including calcium channel blockers, ACE inhibitors, angiotensin II receptor inhibitors, thiazide diuretics, clonidine, or a combination thereof. The authors concluded that evidence is insufficient to suggest that altering BP immediately after a stroke alters outcome. Data seem to suggest that very high or very low BPs may be harmful.

A 2009 randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of early BP reduction (within 36 h) in 126 adult patients with an acute cerebral infarction. Patients were randomized to receive labetalol 50 mg PO (or IV in patients with dysphagia), lisinopril 5 mg PO (sublingual in patients with dysphagia), or matching placebo if hypertensive (defined as systolic BP >160 mmHg) and to treat to a goal of systolic BP 145–155 mmHg and to treat to a goal of systolic BP 145–155 mmHg or a 15-mmHg reduction. The treatment was repeated at 4 and 8 hours if not at goal and then continued for up to 14 days.

The primary outcome was death or dependency at 2 weeks (dependency defined as a modified Rankin scale [mRS] score of >3 points), which occurred in 61% in the combined active treatment group versus 59% in the placebo group (RR=1.03; 95% CI, 0.80–1.3; P=.82). No difference was noted in early neurological deterioration (<72 h) in the active group (6%) compared with the placebo group (5%) (RR=1.2; 95% CI, 0.32–4.5; P=.76). There was no increase in serious adverse events reported with active BP treatment compared with placebo (RR=0.91; 95% CI, 0.69–1.1; P=.50). However, all-cause mortality at 3 months was cut in half in the active treatment group (9.7% vs 20%; HR 0.40; 95% CI, 0.2–1.0, P=.05).

**Recommendation**

A 2007 evidence-based guideline from the American Heart Association/American Stroke Association (AHA/ASA) states if the arterial BP needs to be lowered, a reasonable goal would be to lower the pressure by approximately 15% during the first 24 hours, but that the exact BP that would mandate lowering after ischemic stroke is unknown.

Expert consensus opinion holds that medications should be withheld unless systolic BP is >220 mmHg or diastolic BP is >120 mmHg, as long as there are no signs of end-organ involvement (TABLE). If the patient is eligible to receive thrombolytic therapy, goal BP is <185 mmHg systolic and <110 mmHg diastolic prior to treatment and <180 mmHg systolic and <105 mmHg diastolic during and after thrombolytic administration.

**TABLE**

| Guidelines for management of BP after acute ischemic stroke
| Not eligible for thrombolytic therapy | Treatment |
| Systolic <220 mmHg or diastolic <120 mmHg | • Observe, unless signs of end-organ involvement, ie, aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy |
| Systolic >220 mmHg or diastolic >120 mmHg | • Aim to reduce BP by 10%–15% • Treat with IV antihypertensives, nitroprusside, labetalol, or nicardipine |

**Eligible for thrombolytic therapy**

| Pretreatment | Systolic <185 mmHg or diastolic <110 mmHg | • Observe |
| Posttreatment | Systolic >180 mmHg or nicardipine diastolic >105 mmHg | • Treat with IV antihypertensives, nitroprusside, labetalol, or nicardipine |

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**REFERENCES**

What is the prognostic implication of right bundle branch block in asymptomatic coronary artery disease patients?

Evidence-Based Answer
In patients with asymptomatic coronary artery disease (CAD), complete right bundle branch block (RBBB) likely increases mortality risk compared with similar patients without complete RBBB. (SOR: B, based on 3 cohort studies with heterogeneous results.) Incomplete RBBB in patients with CAD does not affect mortality risk. (SOR: B, based on 1 cohort study.)

In 1 prospective cohort study, 7,073 patients with known or suspected CAD were referred for exercise treadmill stress testing with thallium imaging. These patients were evaluated for the presence or absence of bundle branch block (BBB), and followed for a mean of 6.7±1.6 years. The primary endpoint was all-cause mortality. Patients were excluded if they had valvular or congenital heart disease, congestive heart failure, pre-excitation syndrome, or a pacemaker. The mean age of patients without RBBB was 60±11 years, and of those with RBBB was 66±9 years. One hundred ninety patients (3%) had complete RBBB and 305 (4%) had incomplete RBBB.

The overall mortality of patients without complete RBBB or left bundle branch block (LBBB) was 11%. For patients with incomplete RBBB, mortality was 10%. Complete RBBB was associated with a 24% mortality rate (HR 1.5; 95% CI, 1.1–2.1; \( P = .007 \)), and was as strong a predictor of mortality as complete LBBB (24% mortality; HR 1.5; 95% CI, 1.1–2.0; \( P = .017 \)).

Another cohort study of 15,609 patients with known CAD undergoing coronary and left ventricular angiography identified 272 (1.7%) with RBBB. The aim of this study was to determine if BBB was an independent risk factor for mortality. Exclusion criteria included valvular heart disease, nonischemic cardiomyopathy, or congenital heart disease, and the average age of all patients was 54±9 years. Those who qualified were followed for a mean of 4.9±1.3 years, with the endpoint being all-cause mortality.

The presence of RBBB in a patient with known CAD increased the mortality rate above that of patients with CAD but without BBB (26% vs 15%, respectively; \( P < .0001 \)). Unlike the aforementioned cohort study, the mortality increase with LBBB was larger than that associated with complete RBBB (58% vs 26%; \( P < .0001 \)).

In a third prospective cohort study, 9,541 patients who had known asymptomatic CAD were evaluated for the presence or absence of BBB, then followed for a median of 4.5 years. The primary endpoint of the study was major cardiovascular events, but patients were also evaluated for all-cause mortality. Exclusion criteria included heart failure or known left ventricular dysfunction, uncontrolled hypertension, significant valvular disease, renal disease, and major noncardiac illness. The mean age of patients was 65.9±7 years, for both those with and without RBBB.

Mortality rates were higher in patients with RBBB versus those without, but unlike the other 2 studies, the difference was small and not statistically significant (13.8% vs 11.1%; 95% CI, 0.80–1.35).

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GLOSSARY

<table>
<thead>
<tr>
<th>ARR=absolute risk reduction</th>
<th>HR=hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC=Centers for Disease Control and Prevention</td>
<td>LOE=level of evidence</td>
</tr>
<tr>
<td>CI=confidence interval</td>
<td>MRI=magnetic resonance imaging</td>
</tr>
<tr>
<td>CT=computed tomography</td>
<td>NNH=number needed to harm</td>
</tr>
<tr>
<td>FDA=US Food and Drug Administration</td>
<td>NNT=number needed to treat</td>
</tr>
<tr>
<td>OR=odds ratio</td>
<td>RCT=randomized controlled trial</td>
</tr>
<tr>
<td>RR=relative risk</td>
<td>SOR=strength of recommendation</td>
</tr>
</tbody>
</table>
What cold sore medication is most effective at speeding resolution?

Evidence-Based Answer
Of the oral antiviral medications, famciclovir showed the quickest time to healing (2 days sooner than placebo). Among topical treatments available in the United States, zinc oxide cream showed the quickest time to healing (1.5 days sooner than placebo), although the studies for 1% penciclovir cream and 10% docosanol cream (each 0.7 days sooner than placebo) are of higher quality. (SOR: B, based on a comparison of placebo-controlled trials.)

A cold sore (herpes labialis) is a self-limiting, painful, blistering lip and perioral rash typically caused by herpes simplex virus type 1. Healing occurs in 7 to 10 days without treatment. Multiple potential treatments (oral and topical) for shortening duration of lesions and symptoms have been studied, and the **TABLE** provides a brief summary of trial results. Not included in the Table was one article discussing 4 case reports of topical herbal preparations (not FDA approved), each of which had reported healing times of 3 to 4 days.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Participants (Adults)</th>
<th>Dosing</th>
<th>Mean difference from placebo (significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral antiviral agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acyclovir&lt;sup&gt;2&lt;/sup&gt;</td>
<td>673</td>
<td>400 mg 5x/d × 5 days</td>
<td>–0.6 day (P=.007)</td>
</tr>
<tr>
<td>Famciclovir&lt;sup&gt;2&lt;/sup&gt;</td>
<td>701</td>
<td>500 mg × 1 dose</td>
<td>–2.1 days&lt;sup&gt;a&lt;/sup&gt; (P=.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg BID × 1 day</td>
<td>–2.5 days&lt;sup&gt;a&lt;/sup&gt; (P=.01)</td>
</tr>
<tr>
<td>Valacyclovir&lt;sup&gt;2&lt;/sup&gt;</td>
<td>954 participants aged ≥12 y</td>
<td>2 g BID × 1 day</td>
<td>–1 day (P&lt;.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>603</td>
<td>2 g BID × 1 day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>902</td>
<td>2 g BID × 1 day then 1 g BID × 1 day</td>
</tr>
<tr>
<td><strong>Topical agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1% Penciclovir cream&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2,209</td>
<td>Every 2 h when awake × 4 days</td>
<td>–0.7 day (P&lt;.001)</td>
</tr>
<tr>
<td>Acyclovir 5%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>689</td>
<td>5x/d × 4 days</td>
<td>–0.5 day (HR 1.23; 95% CI, 1.06–1.44)</td>
</tr>
<tr>
<td>Acyclovir 5% + hydrocortisone 1%&lt;sup&gt;3&lt;/sup&gt;</td>
<td>833</td>
<td>5x/d × 5 days</td>
<td>–0.8 day (P=.008)</td>
</tr>
<tr>
<td>Zinc oxide&lt;sup&gt;2&lt;/sup&gt; (available over the counter)</td>
<td>46</td>
<td>2x/h during waking hours</td>
<td>–1.5 days (P=.018)</td>
</tr>
<tr>
<td>1.8% Tetracaine cream&lt;sup&gt;2&lt;/sup&gt; (not available in U.S.)</td>
<td>72</td>
<td>6x/day</td>
<td>–2.1 days (P=.002)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1,5-Pentanediol gel&lt;sup&gt;4&lt;/sup&gt; (not FDA approved)</td>
<td>102</td>
<td>8x/d × 5 days</td>
<td>–2 days (P&lt;.001)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Docosanol 10% cream&lt;sup&gt;5&lt;/sup&gt; (available over the counter)</td>
<td>737</td>
<td>5x/d</td>
<td>–0.7 day (95% CI, 0.08–0.92)</td>
</tr>
</tbody>
</table>

Adults= immunocompetent and aged ≥18 years; CI=confidence interval, HR=hazard ratio.
<sup>a</sup>Study only reported median number of days, not mean.
<sup>b</sup>Outcome measure for this study was scab loss. Outcome used was a combined symptom score (pain, blistering, or swelling).

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2. Worrall G. Herpes labialis. *Clin Evid (Online)*. 2009; (9):1704–1716. ([LOE 2b](#))
3. Hull CM, Brunton S. The role of topical 5% acyclovir and 1% hydrocortisone cream (Xerese<sup>™</sup>) in the treatment of recurrent herpes simplex labialis. *Postgrad Med*. 2010; 122(5):1–6. ([LOE 2b](#))
What is the best use of serum markers in the evaluation of threatened miscarriage?

Evidence-Based Answer
Ultrasound is the most definitive test to determine pregnancy location and viability. (SOR: C, based on expert opinion.) Serial human chorionic gonadotropin (hCG) levels are useful when ultrasound is nondiagnostic or initial hCG levels are less than 1,500–2,000 IU/L; failure to attain at least a 53% increase in 2 days indicates abnormal gestation. (SOR: B, based on a cohort study.) A low progesterone level can signify nonviability, but cannot locate a pregnancy. A combination of hCG and progesterone may be more useful than either serum marker alone. (SOR: B, based on a cohort study.)

Threatened abortion is defined as bleeding before 20 weeks’ gestation, and occurs in around 20% of recognized pregnancies.1 Consensus guidelines from the American College of Obstetricians and Gynecologists (ACOG) recommend transvaginal ultrasonography for the evaluation of early pregnancy pathology, including bleeding. When diagnostic, ultrasound can locate pregnancy as definitely intra- or extraterine. If ultrasound is equivocal, ACOG guidelines suggest the use of serum markers to aid in diagnosis.2

In a retrospective cohort study of 287 women who presented to an emergency department with first trimester bleeding, researchers followed serial serum hCG measurements until definitive ultrasound diagnosis of intrauterine pregnancy. Ninety-nine percent of viable singleton pregnancies between 4 and 10 weeks’ gestation had at least a 53% increase in hCG over 2 days. Pregnancies not attaining this increase in hCG could be more reliably diagnosed as abnormal. This study did not address the hCG patterns of ectopic pregnancies.3

A systematic review of 18 cohort studies (6,801 patients) examined the usefulness of a single progesterone level for the diagnosis of ectopic pregnancy in patients between 4 and 20 weeks’ gestation. Included studies had significant heterogeneity and different progesterone thresholds, preventing calculation of summary sensitivity or specificity.4

In a subset of studies reporting cutoff at 5 ng/mL, only 5 of 1,615 (0.3%) patients with viable pregnancy had levels <5 ng/mL. However, progesterone could not differentiate ectopic from intrauterine location. There is no evidence to support serial progesterone measurement.4

A single-site retrospective cohort study of 245 women with naturally conceived pregnancies measured serum hCG and progesterone levels between 4 and 5 weeks' gestation. A total of 175 women who presented with threatened abortion (108 with ongoing pregnancies and 67 with eventual abortions) were compared with 70 controls without bleeding.5

Using a receiver operating characteristic curve, researchers found the combination of hCG and progesterone (cutoff values 7,236 mIU/mL and 16 ng/mL, respectively) had 88% sensitivity and 84% specificity for a continuing pregnancy (positive likelihood ratio [LR+] 5.6; negative likelihood ratio [LR–] 0.14). Serum hCG alone had 64% sensitivity and 81% specificity (LR+ 3.5; LR– 0.44) and progesterone alone had 76% sensitivity and 70% specificity (LR+ 2.57; LR– 0.34).1 These cutoff values have not been validated in a prospective trial.

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In evaluating hyponatremia in a patient who is taking a diuretic, is there any value to checking uric acid level?

Evidence-Based Answer

Measuring uric acid (either as a simple serum level or as a fractional excretion) may be beneficial in evaluating hyponatremia in patients taking diuretics because it helps differentiate between the syndrome of inappropriate antidiuresis (SIAD) and extracellular volume depletion. (SOR: B, based on diagnostic cohort studies.)

Correctly identifying the cause of hyponatremia in a patient taking a diuretic is difficult because the enhanced sodium excretion alters results of the clinical tests usually used for evaluation. Serum uric acid (S-UA) concentration and the fractional excretion of uric acid (FE-UA) have been proposed as alternative tests to evaluate hyponatremia in these patients.

One cohort study evaluated 57 hyponatremic patients using diuretics. Eligible patients (aged >18 years) had serum sodium <130 mmol/L and serum osmolality <280 mOsm/L on hospital admission. Utilizing a standardized method to assess volume status, which included careful measurement of orthostatic changes in heart rate and blood pressure, 15 patients were classified as having SIAD and 42 as non-SIAD.¹

FE-UA was more accurate than urinary sodium, fractional excretion of sodium, fractional excretion of urea, and S-UA in differentiating SIAD versus non-SIAD. A normal FE-UA is approximately 10%. A FE-UA >12% was 100% specific for SIAD (ruling in the syndrome), while FE-UA <8% excluded SIAD (sensitivity=86%). The study authors identified limitations of using FE-UA for patients with cirrhosis, cerebral salt wasting syndrome, or those taking uricosuric medications, all of which produce an elevated FE-UA.¹ (Sensitivity and specificity for S-UA derived from this study are shown in the table.)

Another inpatient-based prospective study examined S-UA values in 40 adult patients with hyponatremia who were taking diuretics. The cause of hyponatremia was determined after a detailed history, physical examination, and review of laboratory data.²

Compared with other biochemical markers, S-UA values of 4 mg/dL effectively discriminated between SIAD and extracellular volume depletion states with a sensitivity of 90% and a specificity of 75% (table). The receiver operating characteristic curve showed a discriminative value for S-UA to be 0.865. S-UA levels <4 mg/dL were consistent with SIAD, whereas S-UA levels ≥4 mg/dL indicated extracellular volume depletion.²

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What is the best screening test for past tuberculosis infection?

Evidence-Based Answer

Interferon-γ release assays (IGRAs) are at least as sensitive as and more specific than the tuberculin skin test (TST) in diagnosing latent *Mycobacterium tuberculosis* infection (LTBI). When screening for LTBI, it is acceptable to use an IGRA in the place of TST. (SOR: A, based on consistent findings from 2 systematic reviews.) In patients with Bacillus Calmette-Guérin (BCG) vaccination, an IGRA is preferred over the TST. (SOR: A, based on consistent findings from 2 systematic reviews.)

The 2 most commonly used IGRA tests are the QuantiFERON-TB Gold In-Tube test (QFT-GIT) and T-Spot.TB test (T-Spot). An inherent challenge of screening for LTBI is the lack of a gold standard to confirm latent infection; in most studies a clinical diagnosis of an active TB infection is used as a surrogate standard.

In 2010, the Centers for Disease Control (CDC) performed a systematic review of 96 studies comparing sensitivity, specificity, and agreement between TST and IGRAs. The pooled results are shown in **TABLE 1**. The sensitivity was highest for T-Spot at 90% and the specificity was highest for the QFT-GIT at 99%. Limitations to this review included variable TST cutoffs and small sample sizes in the T-Spot studies.

Another systematic review, from 2008, included 38 studies looking at sensitivity and specificity of IGRAs and TST (**TABLE 2**). This study had similar limitations as the CDC systematic review. The highest pooled sensitivity was seen in the T-Spot at 90% (95% CI, 86–93). The sensitivities of the QFT-GIT and TST were roughly equivalent. Specificity was highest with QFT-GIT at 98% (95% CI, 96–99). With regard to BCG-vaccinated populations, QFT-GIT had a much higher specificity at 96% compared with TST at 59% (which varied from 35% to 79% across studies).

A prospective study looked at the agreement between different IGRAs and the sensitivity of TST.

This was the only study to use positive QFT-GIT and T-Spot concordance to define cases of LTBI. Using this definition, the sensitivity for TST was 71.5% at a 10-mm cutoff and 31.3% with a 15-mm cutoff (with total cohort TST specificity 64.5%).

The CDC recommends using either TST or IGRA in combination with risk assessment. IGRA testing is preferable to TST if a patient is not likely to complete the TST or if a person has received BCG. TST is preferred in children <5 years.

**TABLE 1**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>QuantiFeron-TB-Gold In Tube assay</td>
<td>83%</td>
<td>99%</td>
</tr>
<tr>
<td>T-Spot.TB assay</td>
<td>90%</td>
<td>88% (limited data)</td>
</tr>
<tr>
<td>Tuberculin skin test</td>
<td>89%</td>
<td>85%</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Specificity among BCG-vaccinated participants</th>
<th>Specificity among non-BCG-vaccinated participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>QuantiFeron-TB-Gold In Tube assay</td>
<td>70%</td>
<td>98%</td>
<td>96%</td>
<td>99%</td>
</tr>
<tr>
<td>T-Spot.TB assay</td>
<td>90%</td>
<td>93%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Tuberculin skin test</td>
<td>77%</td>
<td>N/A</td>
<td>59%</td>
<td>97%</td>
</tr>
</tbody>
</table>

N/A = not available.


What is the etiology and significance of otherwise asymptomatic temporomandibular (TMJ) joint popping and clicking?

**Evidence-Based Answer**

The etiology is unknown. Asymptomatic TMJ noises tend to have a waxing and waning course and do not need evaluation or treatment. (SOR: C, based on expert opinion.)

TMJ noises are common in the general population. Various authors estimate that audible sounds occur in 17% to 40% of adult patients (up to 80% if auscultated with a stethoscope) and nonpainful clicking occurs in 16% to 65%. In adolescents, audible popping occurs in 1% to 5% and clicking is present in 5% to 34%. Many authors consider the nonpainful clicking and popping to be a normal variant. Crepitus or loud cracking with popping sounds are thought to be clinically more significant and occur in 10% to 24% of the adult population.

The sources of TMJ noise have been hypothesized to include poor chewing coordination, articular cartilage dislocation, irregular articular surfaces, and prior injury; however, none has been shown to be the definitive cause.

The natural history of the syndrome was investigated in an observational study of 402 randomly selected patients, aged 7, 11, and 15 years old, who were interviewed at baseline and re-interviewed 5, 10, and 20 years later (80% of the initial 402 were followed through the whole study). Symptoms appeared to come and go with time, with 55% reporting TMJ sounds at baseline, but only 5% of patients reporting sounds at all 4 evaluations.

Other studies have investigated progression of TMJ associated with intervention. A retrospective chart review identified 190 patients from a university TMJ clinic and several private practices with a chief complaint of jaw clicking. A variety of treatments had been prescribed, including relaxation, physical therapy, and TENS (transcutaneous electrical nerve stimulation) unit therapy. The patients were contacted by phone 3 to 15 years later to assess resolution or progression of symptoms. Of the university clinic patients, 73% had a resolution of symptoms and 26% were unchanged (1% worsened); of the private patients, 51% had a resolution of symptoms and 45% were unchanged (4% worsened).

A separate study followed 94 patients who presented to a TMJ clinic. At initial assessment all patients were taught jaw-opening exercises. No other interventions were provided; a follow-up was conducted 1 to 10 years after the initial appointment to assess if clicking had resolved or progressed to pain. Over a 10-year period, 70% of patients eventually progressed to pain with the clicking, at a rate of approximately 6% per year. Eleven percent had persistent clicking without pain and in 19% the clicking resolved.

Most authors agree that treatment is not necessary for isolated popping and clicking of the jaw.

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“Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.”

Is acupuncture an effective treatment for generalized anxiety disorder?

Summary

Some evidence suggests acupuncture may be beneficial in the treatment of generalized anxiety disorder (GAD), but there is insufficient high-quality data to demonstrate its efficacy over placebo or standard pharmacologic management.

The evidence

GAD is the most common anxiety disorder encountered in primary care, affecting between 5.3% and 7.6% of patients, and almost half of patients with GAD are first diagnosed by a primary care physician.¹

A systematic review of acupuncture for anxiety examined 12 studies: 4 RCTs and 2 nonrandomized controlled trials of patients with GAD or anxiety neurosis, and 6 studies of patients with situational anxiety.² Of the studies on GAD or anxiety neurosis, 2 found no difference between acupuncture and control groups, 3 favored acupuncture, and 1 showed benefits for acupuncture and behavioral therapy combined.

In 1 of the RCTs, 39 patients with GAD received either electroacupuncture 45 minutes a day or trazodone 100 to 150 mg daily for 6 weeks. The Hamilton Anxiety Scale was given pre- and posttreatment, and scores <8 were defined as “cure,” while a score reduction of ≥50% was defined as “marked effect.” No significant difference was noted between the groups. In the acupuncture group, 2 of 20 were cured and 11 attained a marked effect. In the control group, 1 of 19 was cured and 10 attained a marked effect.²

Another RCT compared traditional semistandardized acupuncture methods, one of which included herbal remedies, with doxepin in 296 patients with anxiety neurosis. A treatment group received any 2 of 4 different acupuncture methods daily for 30 sessions and a control group received doxepin 25 mg PO 3 times daily. Symptomatic improvement (not clearly defined) was evident in 94.3% of the treatment group and 96.4% of the control group.²

In another RCT, 43 patients with minor depression and 13 patients with GAD were randomly assigned to receive 10 sessions of acupunture or 10 sessions of sham acupuncture. In the acupuncture group 60.7% showed a treatment response (measured by Clinical Global Impression score), compared with 21.4% of the control group (P<.01). Among patients diagnosed with GAD, 6 of 7 subjects in the acupuncture group showed improvement, versus only 2 of 6 in the sham group.²

A controlled clinical trial compared three 10-day sessions of acupuncture combined with flupentixol (a typical antipsychotic), melitracen (a tricyclic antidepressant), and oryzanol (rice bran oil) to therapy with this drug regimen alone for 100 patients with anxiety neurosis. More patients were cured in the combined group than the group that received drug therapy alone (96% vs 64%, respectively; P<.01). Duration of the trial was 2 months to 30 years. Cure was determined by subjective assessment by physicians, the process of which was not described.²

In a large RCT, 240 patients with anxiety neurosis were randomly assigned to receive acupuncture, behavioral desensitization (BD), or a combination of acupuncture and BD. The patients received between 10 and 40 treatment sessions. Clinical symptoms and Zung anxiety rating scale scores (possible scores between 20 and 80) were administered pre- and posttreatment. “Cure” was defined as the absence of clinical symptoms and Zung scores <45. Cure was reported by 20% of the acupuncture-only group, 26.3% of the BD group, and 52.5% of the combined therapy group. The combined therapy group had a significantly greater improvement rate than either treatment alone after a course of 10 sessions (P<.01).² The trial duration was 2 weeks to 16 years.

Most of the studies reviewed used problematic methodology or data analysis, or both. In the studies using drug therapy as controls, the drug regimens were not first-line for anxiety treatment and suboptimal dosing was used. Additionally, measures of clinical outcome were not consistent or well described and various methods of acupuncture were used.

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REFERENCES


Football-related injuries

The most popular sport in America based on participation numbers in high school. Participants are both male and female (at high school level), and the most common injuries they encounter are knee, ankle, and head injuries.

Factors affecting injury rates

- Grass versus artificial turf
  - Injuries on grass are more common than on artificial turf
- Footwear
  - Length of cleats affects torsion forces on ankle, leading to knee and ankle injuries
- Protective equipment
  - Helmet, mouth guard, shoulder pads, hip pads, knee pads all reduce risk of injury

Most common injuries

1. Knee injuries (internal derangement): Most common injury in games (18%) and practice (12%)
2. Foot and ankle injuries: Second most common football injury
3. Shoulder injuries: Account for 10% of football injuries
4. Exertional heat illness: Most common during preseason, accounting for 6% of preseason injuries
5. Concussion rate: 0.72 per 100,000 athletes

Cervical spine injuries

Usually from tucking chin at impact. Encourage coaches to teach “heads up” tackling

MRSA in athletes

High MRSA transmission rates among players in practice and games

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Editor: Carol Scott, MD, U of Nevada, Reno, NV

Anal fissure

A tear of the lining of the anal canal, distal to the dentate line, causing pain and bleeding. Chronic anal fissures are present more than 6 weeks; fibrosis at the base.

Incidence, prevalence

- Difficult to establish
- 87.5% of patients with benign anorectal diseases do not consult a physician
- During a 1990s German study in unselected neurological patients, prevalence was 1.6% in males and 2.2% in females

Therapeutics

Acute treatment (SOR C):

- Conservative therapy has 43%–87% cure rate
- Fiber supplementation keeps stools formed and soft
- Sitz baths after bowel movements relax anal sphincter
- Anesthetic creams no more helpful than sitz baths and fiber

Medical therapies (SOR A):

- Meta-analysis showed nitroglycerin ointment significantly better than placebo (49% vs 37%), but recurrence about 50%
- Botulism toxin injections, diltiazem, and nifedipine equal to nitroglycerin ointment, with fewer adverse effects
- Major adverse effects: headache (nitroglycerin and calcium channel blockers), flushing (nitroglycerin)

Prognosis

- 75% heal without treatment or with sitz baths

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Editor: Robert Marshall, MD, MPH, Capt MC USN, Puget Sound FMR, Naval Hospital, Bremerton, WA

To review complete topic monograph visit www.fpin.org/page/ebpemedref
How prevalent is fluoroquinolone resistance in gonorrhea?

**Bottom line**
Fluoroquinolone resistance among isolates of *Neisseria gonorrhoeae* is increasing. (SOR: C, based on multiple patient-oriented studies.) Surveillance studies are ongoing; as yet, no evidence of increased resistance has been found to cephalosporins or azithromycin.

**Evidence summary**
From 1993 through 2000, fluoroquinolones were the drug class of choice for treating *Neisseria gonorrhoeae*, the second most common sexually transmitted disease (STD) diagnosed in the United States, due to their high efficacy, availability, and convenience of single-dose therapy. However, in the last decade, resistance has become more prevalent in the United States and many parts of the world.¹

**Fluoroquinolone resistance increasing in Canada**
A Canadian epidemiologic investigation using public health laboratory records exhibited fluoroquinolone resistance to gonorrhea increasing from 4% to 28% between 2002 and 2006. Examination of fluoroquinolone-resistant isolates (n=695) and fluoroquinolone-sensitive (control) isolates (n=688) demonstrated more resistance in men (OR 3.1; 95% CI, 2.3–4.1) and those older than 30 years (OR 3.1; 95% CI 2.4–3.8). This study found fluoroquinolone resistance in Ontario to be similar to the resistance reported in the West Coast of the United States.²

**Resistance increasing in United States, too: Gonococcal Isolate Surveillance Project**
Antibiotic resistance to gonorrhea is monitored in the United States by the Gonococcal Isolate Surveillance Project (GISP), a national surveillance system of STDs in 25 to 30 clinics, coordinated within 5 regional laboratories and the Centers for Disease Control and Prevention (CDC). From 1988 to 2003 the GISP collected 82,604 urethral gonococcal isolates from men (mean age 26 years; 74% black, 13% white, 11% Hispanic, 1% Asian, 1% American Indian). Among all patients studied, 42% were from the West Coast, 22% from the Midwest, 8% from the Northeast, and 29% from the South.³

From 1990 to 2003 the percentage of isolates resistant to ciprofloxacin increased from 0% to 4.1% (P<.001 for trend) and the presence of fluoroquinolone-resistant isolates increased from 39% to 70% of cities, with Hawaii and California accounting for 75% of these resistant isolates. Isolates with resistance to ciprofloxacin have demonstrated resistance to other fluoroquinolones as well.³

Generalizability of GISP data is debated, because it tests less than 2% of gonococcal infections reported in the United States, obtains all isolates from public clinics, and oversamples the West Coast (which is more proximal to Asia, where new resistant strains of *N gonorrhoeae* have often been first detected). In the GISP sample, resistance to cephalosporins, azithromycin, and spectinomycin was rare.³

**Recommendation**
The CDC currently recommends that fluoroquinolone antibiotics no longer be used as treatment for gonococcal infections, and that a cephalosporin be prescribed (ceftriaxone or cefixime).¹⁴

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**REFERENCES**
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1. What is the role of progesterone measurement in the evaluation of threatened abortion?
   a. Progesterone level <5 ng/mL indicates an ectopic pregnancy
   b. Increasing serial progesterone levels in the face of continued bleeding indicate viability
   c. There is no role for progesterone in the evaluation of threatened abortion
   d. Progesterone level <5 ng/mL indicates an abnormal, nonviable pregnancy

2. Problems arise in trying to generalize data from the Gonococcal Isolate Surveillance Project because
   a. Samples are obtained only in the southern United States
   b. No reference labs are used
   c. Only infections in women are included
   d. <2% of cases are sampled

3. Patients with nonpainful temporal mandibular joint sounds may be reassured that this condition:
   a. Has a well-defined cause
   b. Never progresses to joint dysfunction
   c. Is present in up to 90% of the adult population
   d. May go away on its own

4. Which oral antiviral medication has been shown to improve healing of herpes labialis lesions the fastest?
   a. Acyclovir
   b. Famciclovir
   c. Valacyclovir
   d. None of the above

5. The QuantiFeron tuberculosis (TB) assay
   a. Differentiates latent from active TB
   b. Is recommended in patients who received Bacillus Calmette-Guérin (BCG) vaccination
   c. Is more convenient to perform than the T-Spot assay
   d. Is more sensitive than the tuberculin skin test in all studies

6. Based on heterogeneous study results, complete right bundle branch block (RBBB) in patients with coronary artery disease (CAD) likely confers:
   a. The same risk of mortality as CAD patients with incomplete RBBB
   b. An increased risk of mortality versus CAD patients without RBBB
   c. An increased risk of mortality versus CAD patients with left bundle branch block
   d. A decreased risk of mortality versus CAD patients without RBBB

7. A patient who takes hydrochlorothiazide presents with a sodium level of 124 mEq/L. Further testing reveals a serum uric acid level of 5.1 mg/dL. This clinical situation is most consistent with which of the following conditions?
   a. Isolated total body water depletion
   b. Syndrome of inappropriate diuresis
   c. Extracellular volume depletion
   d. Gout

8. In which one of these acute ischemic stroke patients should the blood pressure (BP) be treated?
   a. BP of 210/115 mmHg and not receiving tissue plasminogen activator (tPA)
   b. BP of 180/100 mmHg and receiving tPA
   c. BP of 225/117 mmHg and not receiving tPA
   d. BP of 160/90 mmHg and receiving tPA

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