What is the appropriate diagnostic evaluation of fibroids?

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EVIDENCE-BASED ANSWER

Although transvaginal sonography (TVS) has inconsistent sensitivity (0.21–1.00) and specificity (0.53–1.00), its cost-efficiency and noninvasiveness make it the best initial test for ruling in fibroid disease (strength of recommendation [SOR]: **B**, based on expert opinion, a systematic review, and prospective studies).

Sonohysterography (SHG) and hysteroscopy have superior sensitivity, specificity, and more discriminating positive and negative likelihood ratios for diagnosing fibroids than does TVS (SOR: **B**, systematic review). SHG is less painful, less invasive, and more cost-effective than hysteroscopy (SOR: **B**; single, prospective comparative study and cost comparison).

Magnetic resonance imaging (MRI) had comparable precision to TVS in a single study, but it is too expensive to be a good initial test for fibroids (SOR: **C**, expert opinion and an uncontrolled prospective study). One study reported a strong correlation between ultrasound and bimanual examination (SOR: **C**, retrospective case review).

CLINICAL COMMENTARY

When evaluating potential fibroids, a reasonable first step is a sonogram

In the asymptomatic patient with an enlarged, irregularly contoured uterus on routine exam, the differential includes fibroids, fibroids, and fibroids. My usual next step is to get a sonogram. The test is noninvasive, well-tolerated by patients, and significantly less expensive than the alternatives. It quickly and easily gives a great deal of useful information regarding the size, shape, consistency of the myometrium and the endometrium, from which we can reassure the patient regarding the benign natural history of this finding, especially in the perimenopausal woman. If the patient presents with symptoms of abnormal bleeding, pelvic pressure, or adnexal findings on exam, the review suggests that further workup may be indicated. However, the sonogram remains a very useful initial test even in this case.

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Evidence summary

Uterine myomas are usually diagnosed by incidental visualization during pelvic sonography or bimanual palpation of an enlarged, mobile uterus with irregular contours.[1] In a retrospective chart review of obese and nonobese patients with known uterine fibroids, clinical estimate of uterine size by bimanual examination correlated with both ultrasound fibroid sizing and posthysterectomy pathology analysis.[2] Additional diagnostic testing is indicated for patients with suspected fibroids and abnormal uterine bleeding, increased pelvic girth,

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FAST TRACK

With equivocal sonogram findings, or with abnormal uterine bleeding or other symptoms, further workup with SHG or hysteroscopy may be indicated

pelvic pressure contributing to urinary frequency or constipation, or pelvic pain with intercourse or other physical activity.[3]

TVS has high sensitivity for detecting myomas in a uterus of <10-week size. The use of high-frequency probes improves the sensitivity for diagnosing small myomas, although their precise location with respect to the uterine cavity often remains uncertain. Localization of fibroids in a larger uterus or when there are many tumors is limited.[4] Also, TVS may fail to detect small fibroids and subserosal myomas. A systematic review of 9 heterogeneous studies evaluating TVS found wide ranges for sensitivity and specificity (**TABLE**).[5] The cost of TVS is less than half of sonohysterography or diagnostic hysteroscopy, based on Medicare allowable pricing data.[6]

SHG uses an intrauterine saline contrast medium with transvaginal ultrasonography. This office-based procedure is more invasive than TVS but requires no anesthesia. SHG is more sensitive and specific than TVS in detecting submucous myomas and focal endometrial lesions.[7] In a prospective study of 81 symptomatic patients, using a gold standard of surgical pathology, SHG demonstrated more discriminating positive and negative likelihood ratios (LR+, LR–) for detecting myomata than did TVS or hysteroscopy.[8] A prospective study of 56 symptomatic patients with a gold standard of hysteroscopic or surgical pathology similarly found SHG to be superior to TVS.[7] In a systematic review of 7 studies, SHG demonstrated a clinically significant LR+ of 29.7. There was too much heterogeneity in the data to calculate an LR– (**TABLE**).[5]

Hysteroscopy is as accurate but more invasive than SHG in evaluating uterine myomata. In a systematic review of 4 studies, hysteroscopy had a pooled LR+ of 29.4 for diagnosing fibroids. Due to study heterogeneity, a pooled LR– could not be calculated.[5] A prospective, blinded comparative study of SHG and hysteroscopy for diagnosing fibroids in 117 women found SHG to have a higher failure rate (22% vs 6%) but a statistically significant lower median pain score: 1.6 (interquartile range 0.48–3.03) vs 3.2 (1.58–5.18) (P<.001)—than hysteroscopy.[9] Failure of SHG was most commonly due to cervical stenosis.

In a double-blinded comparative study of 106 consecutive premenopausal women undergoing hysterectomy for benign reasons, MRI and TVS detected myomas with equal precision (**TABLE**). MRI is preferred in cases for which exact myoma mapping is necessary and those with multiple myomas or large uteri who are scheduled for advanced surgical procedures.[4] MRI costs up to twice as much as sonohysterography or diagnostic hysteroscopy, when comparing Medicare allowable pricing data.[6]

Recommendations from others

A 1994 American College of Obstetrics and Gynecology (ACOG) bulletin stated that uterine fibroids can be diagnosed with 95% certainty by examination alone.[10] ACOG recommends augmenting physical examination with ultrasonography in cases involving obese women or when adnexal pathology cannot be excluded based on examination alone. This bulletin also points out that routine ultrasonography does not improve long-term clinical outcomes for fibroids. A more recent bulletin (2000) addressed management but not evaluation or diagnosis of leiomyomas.[11]

A 2003 guideline from the Society of Obstetrics and Gynecology of Canada recommends against routine ultrasonography, since it rarely affects the clinical management of uterine fibroids. However, it emphasizes the importance of ruling out underlying endometrial pathology in women with abnormal uterine bleeding.[12]

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TABLE

Evaluations of diagnostic tools for fibroids

DIAGNOSTIC TOOL	PASRIJA ET AL[7]	BONNAMY ET AL[8]	DUEHOLM ET AL[4]	FARQUHAR ET AL[5]	ROGERSON ET AL[9]
Summary characteristics of trial	Prospective, 56 pts, symptomatic, gold standard hysteroscopy or hysterectomy pathology	Prospective, 81 symptomatic pts, gold standard of "clinical survey" or histopathology	Double-blind, 106 premenopausal pts undergoing hysterectomy for benign reasons	Systematic review including 19 studies with significant heterogeneity	117 women; SHG compared with outpatient hysteroscopy (gold standard)
TVS				(9 studies)	
Sensitivity	84.8	65 (43–84)	99 (92–100)	21–100	
Specificity	79	94 (79–99)	91 (75–98)	53–100	
PPV	82.4		96 (88–99)		
NPV	82		97 (82–100)		
LR+	*4.0*	10 (2.6–4.1)	*11 (3.0–50)*	1.61–62.25	
	0.19	0.4 (0.2–0.7)	*0.01 (0.11–0)*	0.03–0.80	
SHG				(7 studies)	
Sensitivity	94.1	91 (72–99)		57–100	85.2
Specificity	88.5	94 (79–99)		96–100	87.3
PPV	91.4				74.3
NPV	92				93.2
LR+	*8.2*	15 (3.8–56)		29.7 (17.8–49.6)	*6.7*
LR_	*0.067*	0.1 (0.02–0.4)		0.06–0.47	*0.17*
Hysteroscopy				(4 studies)	
Sensitivity		88 (62–98)		53–100	
Specificity		94 (79–99)		97–100	
LR+		14 (3.5–52)		29.4 (13.4–65.3)	
LR–		0.1 (0.04–0.5)		0.08–0.48	
MRI					
Sensitivity			99 (92–100)		
Specificity			86 (71–94)		
PPV			92 (83–97)		
NPV			97 (85–100)		
LR+			*7.1 (03.2–16.7)*		
LR–			*0.012 (0.11–0)*		

Italicized values were not reported in the original studies, but calculated for this review. Numbers in parentheses represent 95% confidence levels.
LR+ = positive likelihood ratio (a value greater than 10 is clinically significant and the higher the value, the more helpful the test at ruling in the diagnosis); LR– = negative likelihood ratio (a value less than 0.1 is clinically significant and the lower the value, the more helpful the test at ruling out the diagnosis).
PPV, positive predictive value; NPV, negative predictive value; TVS, transvaginal sonography; SHG, sonohysterography; MRI, magnetic resonance imaging.

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Should a nylon brush be used for Pap smears from pregnant women?

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EVIDENCE-BASED ANSWER

Use of a nylon brush (Cytobrush and others) with spatula to obtain Papanicolaou (Pap) smears from pregnant women is more likely to obtain sufficient endocervical cells, without adverse consequence for the mother or for the fetus. This method is also most likely to be cost-effective. However, current evidence does not support any superiority of the nylon brush with spatula for any patient-oriented outcomes (eg, fewer procedures, less cancer, etc) during or after pregnancy (strength of recommendation: **A**; based on multiple randomized controlled trials).

CLINICAL COMMENTARY

Use the spatula and brush for Pap smears from pregnant women

The evidence for safety and efficacy supports the use of the spatula and brush for obtaining Pap smears from pregnant women. You will have fewer inadequate smears that need to be repeated, but you will need to warn the patient of spotting that may occur after the specimen is obtained. For ThinPrep Pap smears, remember to follow the same recommendations as for nonpregnant women—turn the spatula the full 360° in contact with the cervix and only turn the brush a half-turn. Being overly aggressive to collect endocervical cells by twirling the brush may cause more bleeding.

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Evidence summary

A Cochrane review of Pap smear sampling devices for nonpregnant women concludes that the cervical brush with spatula is more effective at collecting endocervical cells and producing adequate Pap smears.[1] Based on more limited evidence, the higher rate of adequate smears is associated with the detection of more cytologic abnormalities. However, the manufacturer of Cytobrush (Medscand) recommends that the device not be used after the first 10 weeks of pregnancy, raising issues of both effectiveness and safety in this population.

Upon review of the literature, these concerns appear to be unfounded. In multiple studies involving more than 25,000 pregnant and nonpregnant patients, the brush was consistently shown to be the method obtaining the highest rate of adequate smears—ie, those containing endocervical cells.[2–10] Furthermore, in studies including about 1900 pregnant patients, the brush with spatula caused no significantly increased risk of serious adverse outcomes, nor any trend in that direction.[5–7,9–11] The device did cause a slight increase in self-limited vaginal spotting.

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FAST TRACK

The nylon brush yields the highest rate of adequate smears throughout pregnancy, despite the manufacturer's concern about the post-10-week period

In theory, a more accurate Pap smear could lead to patient-oriented outcomes, such as less need for procedures to diagnose and treat cervical cytologic abnormalities, reduced incidence of invasive cervical cancer, and fewer patient deaths from cervical cancer. No data on these outcomes is available. Some studies did look for differences in the detection of cytologic abnormalities between the brush with spatula and the swab with spatula methods. Most small studies and a meta-analysis showed no difference.[2,3,8,9] One study showed a trend towards improved yield; in another study, the brush with spatula significantly improved the ability to detect cytologic abnormalities in pregnant patients.[7,10]

Three studies addressed cost-effectiveness of the brush in pregnancy.[3,9,12] Especially when including the cost of repeat Pap smears for inadequate specimens, the brush with spatula was rated most cost-effective in all 3 studies.

Comparison of the use of conventional Pap smear collection techniques with newer liquid-based cytology or human papilloma virus (HPV) typing has not yet been addressed in the literature.

Recommendations from others

"The Working Group's Recommendations for Women in Low Risk Pregnancy" through the Veterans Health Administration lists use of a nylon cervical brush—no type is specified—as the appropriate sampling device in the late first trimester of pregnancy.[13] No recommendations specific to the Cytobrush were found.

The following organizations have made no recommendations for or against the use of the Cytobrush in pregnancy: US Preventive Services Task Force, American College of Obstetricians and Gynecologists, American Academy of Family Physicians, or the American Academy of Nurse-Midwives.

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What is the best approach to the evaluation of hirsutism?

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EVIDENCE-BASED ANSWER

The evaluation of hirsutism should begin with a history and physical examination to identify signs and symptoms suggestive of diseases such as polycystic ovarian syndrome (PCOS), hypothyroidism, hyperprolactinemia, hyperandrogenic insulin-resistant acanthosis nigricans (HAIR-AN) syndrome, androgenic tumors, Cushing's syndrome, or congenital adrenal hyperplasia (CAH). Findings suggestive of these diseases include rapid or early-onset hirsutism, menstrual irregularities, hypertension, severe hirsutism, virilization, or pelvic masses (strength of recommendation [SOR]: **B**, based on a cohort study in a referral population) (**TABLE**). Hirsutism with unremarkable history and physical exam findings should be evaluated with a serum total testosterone and dehydroepiandrosterone sulfate (DHEAS) level (SOR: **B**, based on a cohort study in a referral population).

CLINICAL COMMENTARY

Early work on expectations by physician and patient leads to a better outcome

Primary care physicians field questions about nonspecific findings on a day-to-day basis. Hirsutism is a common complaint and physical finding in women. Most diagnoses related to hirsutism are not life-threatening and have a relatively straightforward workup. There is the occasional patient with a zebra-type diagnosis that demands more detailed evaluation. As with most physical findings that have a large subjective component, I find that early management of expectations both on the part of the physician and patient leads to a better outcome whether or not a million-dollar workup shows any definitive pathology.

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Evidence summary

Hirsutism is the presence of excess terminal hairs in androgen-dependent areas on a female, and can be measured objectively using a scoring system such as the modified Ferriman-Gallway (mF-G) score. This test is done by adding hair scores (0=none, 4=frankly virile) in 9 different body locations. A total score >8 is considered hirsute. The incidence of hirsutism in the US is about 8%, based on a prospective study of 369 consecutive women of reproductive age seeking pre-employment physicals in the southeastern US using the mF-G criteria.[1]

The causes of clinically apparent androgen excess, including acne and hirsutism, were evaluated in 1281 consecutive patients presenting to a university endocrinology clinic.[2] Researchers excluded 408 subjects due to the inability to assess hormone status or ovulatory function. The remaining 873 women were assessed by clinical exam, mF-G score, serum total and free testosterone, DHEAS, and 17-hydroxy-

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FAST TRACK

With an unremarkable history and exam, order serum total testosterone and dehydroepiandrosterone sulfate levels

progesterone (17-HP). Hyperandrogenism was defined as an androgen value above the 95th percentile of 98 healthy control women (total testosterone ≥88 ng/dL, free testosterone ≥0.75 ng/dL, or DHEAS ≥2750 ng/dL). Those with a 17-HP level >2 ng/mL had either a repeat 17-HP or adrenocorticotropic hormone (ACTH) stimulation test. Those with at least 2 total testosterone levels above 250 ng/dL or those with signs of an androgen-secreting neoplasm (eg, virilization) underwent a transvaginal sonogram and a CT scan of the adrenals. Patients with ovulatory dysfunction had a thyroid-stimulating hormone (TSH) and prolactin level drawn. If Cushing's syndrome was suspected clinically, the subjects underwent an overnight 1-mg dexamethasone suppression test (**TABLE**). Of 873 patients, 75.5% had hirsutism and 77.8% had hyperandrogenemia. An identifiable disorder of androgen excess was found in 7%; functional androgen excess (principally PCOS) was identified in the remainder.

The incidence of endocrine disorders among patients presenting with hirsutism or androgenic alopecia was evaluated during a prospective study of 350 consecutive patients referred to an endocrine clinic in the UK.[3] Testing included serum total testosterone, androstenedione, 17-HP, and DHEAS on 2 occasions. Patients also underwent high-resolution pelvic ultrasound. Further investigations were done only for those with abnormal hormone levels or clinical findings suggestive of a tumor. Of 350 women tested, 13 had a markedly elevated serum total testosterone level >5 nmol/L (150 ng/dL). A single total testosterone test identified 6 of 8 patients with an underlying endocrine disorder. The other 2 had either acromegaly or prolactinoma. The researchers concluded that clinical assessment and a single serum total testosterone level were sufficient to exclude enzyme deficiencies and virilizing tumors.

A retrospective study of 84 consecutive women presenting to an endocrinology clinic in the Netherlands was conducted to determine hormone level sensitivity and specificity to identify virilizing adrenal tumors.[4] Hormone levels of 14 women with either an adrenal carcinoma (n=12) or an adrenal adenoma (n=2) were compared with the hormone levels of the women with hirsutism (n=73) as well as to the controls (n=31). Serum levels of total testosterone, androstenedione, DHEAS, DHEA, and cortisol were measured. A 24-hour urinary 17-ketosteroid excretion was also measured. A 5-day dexamethasone suppression study was conducted and a urinary sample was obtained between 8 and 9 A.M. on Day 6. An elevated basal total testosterone (normal range, 29–84 ng/dL) or DHEAS level (normal range, 118–431 ng/dL) detected all 14 women with adrenal carcinomas or adenomas and 36 of 73 women with hirsutism of non-neoplastic origin. The combined test sensitivity was 100% (95% confidence interval [CI], 77–100) and specificity was 50% (95% CI, 38–62) for the detection of adrenal tumors.

A prospective study of the incidence of late-onset CAH among hirsute women evaluated 83 consecutive patients with hirsutism from an endocrinology clinic in California with an ACTH stimulation test.[5] They found 1 patient with late-onset CAH. Because CAH had an incidence of only 1.2% (95% CI, 0.0–3.4), the authors concluded that routine testing with the ACTH stimulation test is not cost-effective for the evaluation of hirsutism.

Recommendations from others

The American College of Obstetrics and Gynecology 1995 technical bulletin recommended using the clinical examination to guide the evaluation, and laboratory testing to rule out androgen-producing tumors including a serum total testosterone and DHEAS.[6] The Society of Obstetricians and Gynaecologists of Canada advised using the clinical examination to guide the assessment, and a total serum testosterone level and a DHEAS level.[7]

Referral is recommended in the presence of virilism or if the total testosterone or DHEAS level is over twice the upper limit of normal or if there are signs of Cushing's disease.

TABLE

Differential diagnosis of clinically apparent androgen excess

DIAGNOSIS	INCIDENCE	KEY HISTORY/EXAM FINDINGS	ADDITIONAL TESTING
Polycystic ovarian syndrome	82.0%	± irregular menses, slow-onset hirsutism, obesity, infertility, diabetes, hypertension, family history of PCOS, diabetes	Fasting glucose, insulin and lipid profile, blood pressure, ultrasound positive for multiple ovarian cysts
Hyperandrogenism with hirsutism, normal ovulation	6.8%	Regular menses, acne, hirsutism without detectable endocrine cause	Elevated androgen levels and normal serum progesterone in luteal phase
Idiopathic hirsutism	4.7%	Regular menses, hirsutism, possible overactive 5 alpha-reductase activity in skin and hair follicle	Normal androgen levels, normal serum progesterone in luteal phase
Hyperandrogenic insulin-resistant acanthosis nigricans (HAIR-AN)	3.1%	Brown velvety patches of skin (acanthosis nigricans), obesity, hypertension, hyperlipidemia, strong family history of diabetes	Fasting glucose and lipid profile, BP, fasting insulin level >80 µIU/mL or insulin level >300 on 3-hour glucose tolerance test
21-hydroxylase non-classic adrenal hyperplasia (late-onset CAH)	1.6%	Severe hirsutism or virilization, strong family history of CAH, short stature, signs of defeminization, more common in Ashkenazi Jews and Eastern European decent	17-HP level before and after ACTH stimulation test >10 ng/dL, CYP21 genotyping.
21-hydroxylase-deficient congenital adrenal hyperplasia	0.7%	See *Late-onset CAH.* Congenital virilization	17-HP levels >30 ng/dL
Hypothyroidism	0.7%*	Fatigue, weight gain, history of thyroid ablation and untreated hypothyroidism, amenorrhea	TSH
Hyperprolactinemia	0.3%†	Amenorrhea, galactorrhea, infertility	Prolactin
Androgenic secreting neoplasm	0.2%	Pelvic masses, rapid-onset hirsutism or virilization, over age 30 with onset of symptoms	Pelvic ultrasound or abdomen/pelvic CT scan
Cushing's syndrome	0%‡	Hypertension, buffalo hump, purple striae, truncal obesity	Elevated blood pressure, positive dexamethasone suppression test

*Five patients were previously diagnosed with hypothyroidism and 1 patient was diagnosed as part of the work-up for a total prevalence of 6 in 873 or 0.7% although the de novo incidence was only 0.1%.
†Two patients were previously diagnosed with hyperprolactinemia and 1 was detected during the work-up for a total prevalence of 3 in 873 or 0.3% although the de novo incidence was 0.1%.
‡No patients were identified with Cushing's syndrome in this study. Other published reports vary from 0-1% (3).
Source: Azziz et al, *J Clin Endocrinol Metab* 2004[2]; Azziz, *Obstet Gynecol* 2003.[8]

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Is DEET safe for children?

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EVIDENCE-BASED ANSWER

Reported evidence suggests that DEET use is safe for children older than 2 months, with only very rare incidence of major adverse effects (strength of recommendation [SOR]: **C**). Typically, a topical concentration between 10% and 30% should be used (SOR: **C**). Increasing DEET concentration does not improve protection, but does increase the duration of action (SOR: **A**).

CLINICAL COMMENTARY

Counsel parents to take 3 steps to prevent bites—avoid, cover up, and repel

The emergence of West Nile virus has heightened awareness of mosquitoes, and I often field questions about how to protect children from bites. I counsel parents to take 3 steps to prevent bites—avoid, cover up, and repel. Mosquitoes are active at dawn and dusk, so staying indoors during these times is protective. Covering up with long sleeves, pants, and socks protects from most bites. Lastly, DEET repellent protects exposed areas from mosquitoes. Lotions make it easier to apply DEET to children. Commonly, parents express fear of DEET due to media reports. This review will help me ease their fears.

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Evidence summary

The increasing prevalence of mosquito-borne diseases, including West Nile virus, has raised concerns about safe and effective forms of prevention. For decades, parents have used the insect repellent DEET (N,N-diethyl-metatoluamide), but questions remain regarding adverse effects, including seizures, particularly when used in children.

Two large case series suggested that the risk of DEET is low. The first collected poison control center reports during the 1980s. The report concluded that DEET exposure rarely led to adverse effects and that the route of administration (ie, ingestion) was more closely linked to toxicity than age or gender.[1] There were 5 major adverse reactions reported from 9086 exposures to DEET (0.05%); these included hypotension, hypotonic reaction, and syncope, and 1 death (a suicide ingestion).

The second series, also collected from poison control centers, included roughly 21,000 reports of DEET exposures during the 1990s. The authors concluded that the risk of toxicity was low and that there was no clear dose-dependent relationship between exposure and extent of severity of neurologic manifestations.[2] This report found a rate of major adverse reactions (0.1%) from DEET that was similar to the first case series. The major reactions reported included hypotension, seizures, respiratory distress, and 2 deaths (0.01%). When limiting the data to infants and children only, there were 10 major events among 17,252 reported exposures (0.06%), and no deaths. Although infants and children accounted for 83.1% of all reported exposures, the majority of the serious outcomes (including the deaths) occurred in adults. About half of all those exposed reportedly had no ill effects, the

other half had minor effects (transient effects that resolved without treatment). Only 4% experienced moderate effects (non–life threatening problem, but one that would likely require treatment). There were no data presented on the overall size of the exposed population, eg, users of DEET in the US.

Two recent narrative reviews also concluded that DEET toxicity is rare in children. The first review found that DEET posed essentially no risk in children.[3] The second review was sponsored by SC Johnson and Company, the makers of OFF! brand insect repellent. It assessed animal studies, epidemiologic data, and case reports, and supported the safety of DEET in children.[4]

A theoretical risk is that DEET toxicity could be enhanced by coapplication with other agents. Some studies have uncovered dangerous interactions with military and industrial chemicals, but such exposures are unlikely in most children. The most practical concern regards sunscreen. One study reported that use of sunscreen increased the penetration of DEET.[5] However, since the poison control center studies indicated that toxicity did not occur in a dose-dependent manner; the clinical significance of increased penetration is not clear.[1,2]

Increasing the concentration of DEET does not improve protection but does provide longer duration. Concentrations of 6.65% protect for about 2 hours while 23.8% DEET can last about 5 hours.[6] By understanding this relationship, parents can apply lowest concentration necessary to provide the protection needed.

Recommendations from others

The American Academy of Pediatrics recommends avoiding DEET in children under 2 months of age. For all other children, it advises using DEET with a concentration between 10% and 30%.[7]

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What are Clinical Inquiries?

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

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

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- Finally, a practicing family physician or other clinician writes an accompanying commentary to provide a clinical perspective.

CONTINUED

FAST TRACK

DEET at 10%–30% concentration is safe for children older than 2 months; increased concentration prolongs action but does not improve protection

What is angular cheilitis and how is it treated?

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EVIDENCE-BASED ANSWER

Cheilitis is a broad term that describes inflammation of the lip surface characterized by dry scaling and fissuring. Specific types are atopic, angular, granulomatous, and actinic. Angular cheilitis is commonly seen in primary care settings, and it specifically refers to cheilitis that radiates from the commissures or corners of the mouth. Other terms synonymous with angular cheilitis are perlèche, commissural cheilitis, and angular stomatitis.

Evidence reveals that topical ointment preparations of nystatin or amphotericin B treat angular cheilitis (strength of recommendation [SOR]: **A**, 2 small placebo-controlled studies).

Improving oral health through regular use of xylitol or xylitol/chlorhexidine acetate containing chewing gums decreases angular cheilitis in nursing home patients (SOR: **B**, 1 cluster randomized, placebo-controlled trial).

CLINICAL COMMENTARY

To prevent recurrence, use xylitol gum or lip balms/petroleum jelly in the skin folds

Angular cheilitis is often mistakenly thought to be caused by a vitamin deficiency. As noted in this Clinical Inquiry, *Candida* infections in the moist skin folds around the mouth are the cause in elderly patients. The controlled trials show that antifungal preparations clearly work. In my experience, most topical anti-candidal agents work. To prevent recurrence, xylitol gum or aggressive use of lip balms or petroleum jelly in the skin folds is needed since these areas will invariably stay moist.

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Evidence summary

There is some evidence demonstrating that antifungals effectively treat angular cheilitis. A prospective, double-blind, placebo-controlled study of 8 patients compared the efficacy of nystatin with placebo ointment. These patients were referred to a Department of Oral Diagnosis for sore lips with detected *Candida albicans* lesions located bilaterally.[1] All of the patients were instructed to use one ointment on the right side and the other on the left side. Contamination was prevented by the use of gloves changed between applications. All 8 patients demonstrated complete healing after 1 to 4 weeks of treatment by nystatin, whereas only 1 patient had complete healing after the placebo, giving a number needed to treat (NNT) of 1.14 ($P<.001$).

A second study compared antifungal treatments with placebo. This randomized-controlled trial from 1975 studied lozenge use of nystatin or amphotericin B in 52 patients with red palate, angular cheilitis,

or both.[2] These patients were identified through screening of 600 consecutive patients attending the prosthetic clinic for examination or treatment. Patients were randomly given a 1-month supply of nystatin, amphotericin B, or placebo and instructed to dissolve 4 lozenges a day in their mouth. The study did not describe any blinding procedure. Both nystatin and amphotericin B had statistically significant cures rates at 1 month compared with placebo (P=.05 and P=0.01, respectively). The NNT was 2.7 for the nystatin group and 2.0 for the amphotericin B group at 1 month. A comparison of the 2 antifungals found no difference in cure rate. Recurrence rates at 2 months after discontinuing therapy were the same. The only adverse effect reported was the unpleasant taste of the lozenges, especially nystatin.

Improving oral health is another method proposed to treat angular cheilitis. Many modalities have been suggested including emphasis on denture cleaning, mouthwashes, or medicated chewing gums.

A randomized controlled, double-blind study, performed in 21 English nursing facilities, enrolled 164 patients aged 60 years and older with some natural teeth and evaluated the effects of medicated chewing gum on oral health.[3] At the end of 1 year, the 111 patients (67%) completed the study. Fifty-seven percent of the participants wore dentures.

Several aspects were measured including the presence of angular cheilitis. There were 3 arms: no gum, xylitol gum, and chlorhexidine acetate/xylitol gum. The gums were used after breakfast and the evening meal and consisted of 2 pellets to be chewed for 15 minutes. Adherence was described as chewing gum at least 12 times per week for 12 months. A blinded investigator examined patients at baseline, 3, 6, 9, and 12 months.

The results demonstrated a decrease in angular cheilitis in both the xylitol and chlorhexidine acetate/xylitol group at 12 months when compared to the no gum group (P<.01). Cheilitis was found in 14% of the xylitol group (compared with 27% at baseline), 7% of the chlorhexidine acetate/xylitol group (a reduction from 28%), and 32% of the no gum group (no change). The NNT was 7.7 for the xylitol group and 4.8 for the chlorhexidine acetate/xylitol group. This effect size may be exaggerated as the study randomized by nursing home not individual patients, and there was no statistical adjustment for the cluster randomization.

Chewing gum impregnated with chlorhexidine is not readily available in the United States, whereas xylitol-containing gums are available in many retail stores and on-line centers.

Recommendations from others

We found no clinical guidelines regarding the treatment of angular cheilitis. The American Dental Association does mention topical antifungal creams for the treatment of angular cheilitis when discussing oral health and diabetes.[4] In addition, Taylor's *Family Medicine* recommends antifungals, including nystatin pastilles, clotrimazole troches, or a single 200-mg dose of fluconazole.[5] *Geriatric Medicine* also recommends topical antifungals to treat angular cheilitis.[6]

FAST TRACK

Dry scaling and fissuring of the lip respond to topical nystatin or amphotericin B

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CONTINUED

Do beta-blockers worsen respiratory status for patients with COPD?

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EVIDENCE-BASED ANSWER

Patients with chronic obstructive pulmonary disease (COPD) who use cardioselective beta-blockers (beta$_1$-blockers) do not experience a significant worsening of their short-term pulmonary status as measured by changes in forced expiratory volume in 1 second (FEV$_1$), or by changes in patients' self-reported symptoms. If such harmful effects do exist, they are likely to be less clinically important than the substantial proven benefits of beta-blockade for patients with concomitant cardiovascular disease (strength of recommendation: **A**, based on a high-quality meta-analysis of controlled trials).

Limited evidence suggests that most patients with congestive heart failure and COPD without reversible airflow obstruction tolerate carvedilol, which causes both nonselective beta- and alpha-adrenergic blockade (SOR: **B**, based on limited-quality cohort studies).

CLINICAL COMMENTARY

Benefits outweigh risks for beta-blockade for patients with CV disease, comorbid COPD

It appears that the benefits outweigh the risks for the use of cardioselective beta-blocker therapy in patients with cardiovascular disease and comorbid COPD. Prudent management of these patients dictates that beta-blocker therapy should be initiated with a low-dose cardioselective beta-blocker, that the respiratory status of these patients should be monitored closely, and that any otherwise unexplained decline in respiratory status should warrant a reevaluation of the appropriateness of beta-blocker therapy.

Evidence summary

In recent years, beta-blockers have been shown to substantially decrease mortality in patients with congestive heart failure, coronary heart disease, and hypertension. Patients with both cardiovascular disease and COPD, however, are much less likely to receive beta-blocker therapy than comparable patients without COPD. Clinicians may be fearful of using beta-blockers in these patients because of the possibility of worsening respiratory function from the potential side effect of bronchoconstriction.[1]

A 2004 meta-analysis synthesized the data of 19 clinical controlled trials that compared active therapy with either placebo or prior-to-treatment controls, assessing differences in FEV$_1$, response to a beta$_2$-agonist, and patient-reported respiratory symptoms.[2] Trials included in the meta-analysis used cardioselective beta-blockers and evaluated either single-dose treatments or therapy of longer duration

(2 days to 3.3 months). The authors concluded that patients with COPD who received cardioselective beta-blockers (such as metoprolol, atenolol, or bisoprolol) did not experience a statistically significant short-term deterioration in FEV_1, worsening of COPD symptoms, or decreased responsiveness to $beta_2$-agonists. The authors reported similar results for an analysis restricted to only those patients with severe COPD.

This meta-analysis was limited by the relatively small number of participants (N=141 in single-dose treatment studies; N=126 in studies of longer duration treatment) in the handful of eligible studies. Consequently, rare or minimally harmful effects could have gone undetected.

A retrospective analysis of a cohort study analyzed the tolerability of carvedilol, a nonselective beta- and alpha-adrenergic blocker, in patients with COPD who had been taking the medication for at least 3 months. Eighty-five percent of the 89 patients with COPD tolerated carvedilol. The authors of the study (which was funded by the manufacturer of carvedilol) did not state why the other 15% of patients did not tolerate carvedilol, nor did they mention whether the patients with COPD had reversible airflow obstruction.[3]

One of the sites that participated in this study subsequently published a smaller retrospective analysis of a cohort study that examined the outcomes of 31 patients with heart failure and COPD without reversible airflow obstruction who were started on carvedilol therapy. Over the 2.4 years that the patients were followed, 1 patient stopped taking carvedilol (mean dose 29 ± 19 mg daily) due to wheezing.[4] Whether these 31 patients were also included in the larger study is unclear.

A 2004 narrative review article cited these 2 studies and concluded that carvedilol was well-tolerated in patients with COPD without reversible airflow obstruction, but no evidence exists regarding its tolerability in patients with reversible airflow obstruction.[5]

Recommendations from others

A 2002 evidence-based clinical guideline on the diagnosis and management of COPD reported that the use of cardioselective beta-blockers in patients with COPD did not significantly worsen respiratory status, citing a previous version of the meta-analysis reviewed above as its source of evidence.[6] The American College of Cardiology and the American Heart Association recommended the cautious administration of low-dose, short-acting cardioselective beta-blockers for acute coronary syndrome in patients with COPD.[7]

A recent consensus workshop summary report issued by experts convened by the National Heart, Lung, and Blood Institute, cited continuing uncertainty regarding the use of beta-blockers for COPD patients with heart disease, and called for additional studies of management strategies for these often-coexisting conditions.[8] ■

FAST TRACK

Cardioselective beta-blockers do not significantly worsen short-term pulmonary status in COPD

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