

## TYPE I CLINICAL INQUIRIES

### Are antibiotics effective in preventing pneumonia for nursing home patients?

#### ■ EVIDENCE-BASED ANSWER

Antibiotics should not be used for prophylaxis of pneumonia in nursing homes. We found no studies testing the effectiveness of antibiotics in preventing pneumonia in any population, including persons with predisposing conditions such as influenza. Three measures effectively prevent pneumonia in nursing home patients: influenza vaccination of residents (strength of recommendation [SOR]: **B**, based on systematic review of homogenous cohort observational studies); influenza vaccination of caregivers (SOR: **B**, based on individual randomized controlled trial); pneumococcal vaccination of residents (SOR: **B**, based on randomized, nonblinded clinical trials and consistent case-control studies).

Two other suggested interventions have not been extensively tested: antiviral chemoprophylaxis during an influenza outbreak in the nursing home, and oral hygiene programs for nursing home residents.

#### ■ EVIDENCE SUMMARY

Overuse of antibiotics is already a problem in nursing homes. A large portion of bacterial pneumonia in the nursing home population results from aspiration of oropharyngeal bacteria, which is more likely to be drug-resistant if the resident has been on antibiotics.<sup>1</sup> We found no studies that testing antibacterial agents for prevention of pneumonia in nursing home patients. However,

3 measures are clearly helpful in preventing pneumonia in nursing home patients:

1) *Influenza vaccination of residents*: A meta-analysis of 20 cohort studies showed a 53% efficacy (95% confidence interval [CI], 35–66)—defined as 1 minus the odds ratio—for influenza immunization in preventing pneumonia.<sup>2</sup>

2) *Influenza vaccination of caregivers*: A cluster randomized trial in British long-term care facilities demonstrated that influenza vaccination of health care workers (61% of 1078 workers) reduced the total nursing home mortality rate (odds ratio [OR]=0.56 [95% CI, 0.4–0.8]) for a drop in mortality rate from 17% to 10% (number

### 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](http://www.fpin.org)).

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- FPIN librarians and editors identify questions recently answered in best evidence sources (e.g. Cochrane Reviews, Clinical Evidence, the US Preventive Services Task Force, Evidence Based Guidelines, a published systematic review).
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- Finally, a practicing family physician or other clinician writes an accompanying commentary to provide a clinical perspective.

TABLE

### Available treatment and prophylactic regimens for influenza

Drug name	Regimen for treatment*	Regimen for prophylaxis†	Comments	Cost‡
<b>Oseltamivir (Tamiflu)</b>	75 mg orally twice daily for 5 days	75 mg orally once daily for >7 days	Influenza A and B	10 tabs \$59.99 (no generic)
<b>Rimantidine (Flumadine)</b>	100 mg orally twice daily (100 mg orally once daily in elderly)	100 mg orally twice daily (100 mg orally once daily in elderly)	Influenza A only	14 tabs \$33.45 (no generic)
<b>Amantadine (Symmetrel)</b>	100 mg orally twice daily (100 mg orally once daily in elderly)	100 mg orally twice daily (100 mg orally once daily in elderly)	Influenza A only (consider lower doses in debilitated patients)	60 tabs \$75.58 (brand), \$18.99 (generic)
<b>Zanamivir (Relenza)</b>	2 inhalations (10 mg) every 12 hours for 5 days	Not indicated	Influenza A and B (inhalations may be difficult to administer to debilitated patients)	20 inhalation doses \$54.41 (no generic)

Source: Epocrates RX: Online and PDA-Based Reference, June 12, 2004.  
 \* Start treatment within 48 hours of onset of symptoms.  
 † Start prophylaxis immediately or within 48 hours of exposure.  
 ‡ Approximate retail price from www.drugstore.com, June 2004.

needed to treat [NNT]=14.3).<sup>3</sup>

3) *Pneumococcal vaccination of residents*: This evidence was reviewed in a prior Clinical Inquiry.<sup>4</sup> The evidence comes primarily from 2 clinical trials in which the NNT to prevent 1 episode of pneumonia was about 35.

Two other proposed interventions require further study to evaluate their role in prophylaxis. Antiviral prophylaxis to prevent pneumonia during nursing home outbreaks of influenza has not been evaluated in controlled trials. Observational studies strongly suggest that amantadine, rimantadine, and oseltamivir are all effective in reducing spread of influenza during outbreaks in nursing homes (**Table**). Oseltamivir acts against influenza B as well as A and has fewer side effects, but it is more expensive.<sup>5,6</sup> Presumably, decreasing the rate of influenza also reduces the rate of subsequent pneumonia.

Oral hygiene programs for nursing home residents may also reduce pneumonia. In a single study, 366 patients in 11 Japanese nursing homes were divided into controls (self-care) and those treated with rigorous oral care (by staff). The intervention group had a relative risk of 0.6 (95% CI, 0.36–0.99; NNT=12.5) for pneumonia over a 2-year period.<sup>7</sup> The NNT for preventing a death by pneumonia was 11 ( $P<.01$ ). This intriguing result merits follow up in larger groups in US nursing homes to see if this approach is feasible.

#### ■ RECOMMENDATIONS FROM OTHERS

There are no recommendations about the use of antibiotic prophylaxis for pneumonia in either the nursing home or in the outpatient settings; however, there are clear recommendations against the overuse of antibiotics.<sup>8</sup>

The CDC Advisory Committee on Immunization

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Practices (ACIP) recommends:

- annual influenza vaccine for persons residing in nursing homes<sup>9</sup>
- annual influenza vaccine for health care workers in long-term care facilities<sup>9</sup>
- pneumococcal vaccine for persons residing in a nursing home (the schedule for an immunocompetent adult is a single dose, followed by a booster after age 65 if the first dose was before age 65, or after 5 years for persons <65 years with compromised immune status)<sup>10</sup>
- chemoprophylaxis for influenza outbreaks in nursing homes.<sup>11</sup>

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## ■ CLINICAL COMMENTARY

### Prevention is key for reducing pneumonia mortality

Pneumonia is one of the most common causes of death for nursing home patients. While pneumonia can present with the classic fever, productive cough, and air hunger, it often presents with such nonspecific findings as altered mental status or mild tachypnea, which can significantly delay diagnosis. Additionally, many older adults poorly tolerate the metabolic demands of the disease and become critically ill very rapidly. Thus, prevention remains a key strategy for reducing mortality. Nursing home policies that facilitate vaccination and reduce disease transmission are critically important in this regard.

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## What is the best way to evaluate and manage diarrhea in the febrile infant?

### ■ EVIDENCE-BASED ANSWER

Routine infant diarrhea requires no lab work or cultures (strength of recommendation [SOR]: **C**); the degree of dehydration can be determined reliably by percent body weight change (SOR: **B**). However, bicarbonate may help rule out dehydration (SOR: **B**); electrolytes and blood urea nitrogen may be useful in evaluating complicated diarrhea with severe dehydration or when intravenous fluids are required; stool cultures are indicated for bloody or prolonged diarrhea, suspected food poisoning, or recent travel abroad (SOR: **C**).

Oral rehydrating solution is adequate fluid replacement for diarrhea associated with mild to moderate dehydration, followed by prompt refeeding with an age-appropriate diet (SOR: **A**); intravenous fluids are recommended for severe

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dehydration (SOR: C). Probiotics have been shown to safely reduce the duration and frequency of diarrhea (SOR: A).

## ■ EVIDENCE SUMMARY

Evidence is summarized in the **Table**. Evaluation of an infant with diarrhea usually requires only a thorough history and physical exam. While no clinical trials have tested the impact of blood or stool testing on patient outcome, a recent systematic review suggested the only blood test reliable for ruling out dehydration is a serum bicarbonate greater than 15 to 17 mEq/L.<sup>1</sup> Consensus reports have suggested laboratory studies are unnecessary unless dehydration is severe or IV fluids are required; stool cultures are necessary only for bloody or prolonged diarrhea, systemically ill infants, suspected food poisoning, or recent travel abroad.<sup>2,3</sup>

Effective management of infant diarrhea is based on the degree of dehydration, which can be estimated by percent body weight loss—the difference between the baseline and acute weights, divided by the baseline weight.<sup>3</sup> If the baseline weight is not known, prolonged capillary refill time, abnormal skin turgor, and abnormal respiratory pattern are more reliable indicators of dehydration; other physical findings are less precise.<sup>1</sup>

Infants with diarrhea who are not dehydrated should continue age-appropriate nutrition.<sup>4</sup> For infants with mild to moderate dehydration, however, rehydration using oral rehydrating solution is the initial therapy, followed by continued hydration to replace ongoing losses.<sup>2,3</sup> A meta-analysis of randomized controlled trials (RCTs) in developed countries demonstrated equivalent efficacy of oral fluids compared with IV fluids, with an overall failure rate of only 3.6% for infants and children treated with oral rehydrating solution (95% confidence interval [CI], 1.4–5.8). There was no significant difference between oral rehydrating solution of varying sodium concentrations, and no increased risk of hypernatremia or hyponatremia compared with the IV treatment arm.<sup>5</sup> Continued breastfeeding during the rehydrating phase significantly reduced dehydration

**Probiotics have been shown to safely reduce the duration and frequency of diarrhea**

(based on case control studies; odds ratio [OR]=5.23; 95% CI, 1.37–19.99;  $P=.016$ , limited by sample size).<sup>3,6</sup> Breastfeeding also significantly reduced the number of diarrheal stools (found in a small-scale RCT).<sup>7</sup> For obtunded or severely dehydrated infants, or those with an ileus or persistent vomiting, expert opinion suggested IV fluids.<sup>2,4</sup>

In a systematic review of RCTs comparing lower-concentration oral rehydrating solution with standard World Health Organization solution, lower-concentration solution showed superior efficacy. These resulted in fewer unscheduled infusions of IV fluids (OR=0.59; 95% CI, 0.45–0.79) and less stool output without increasing the incidence of hyponatremia.<sup>8</sup>

Unrestricted diets may reduce the duration of diarrhea compared with oral or IV fluids alone, and age-appropriate diets should be resumed immediately after hydration (based on a review of variable-quality RCTs and prospective trials or case series).<sup>2</sup> No studies supported the effectiveness of BRAT (bananas, rice cereal, applesauce, toast) diets over the infant's usual diet.<sup>2,4</sup> A meta-analysis of variable-quality RCTs demonstrated no significant difference in stool frequency between lactose-containing and lactose-free diets.<sup>9</sup> Comparisons of undiluted lactose-milk with diluted milk or delayed reintroduction of milk revealed no significant differences in treatment failure or duration of diarrhea, although stool output increased slightly with the undiluted diet. However, undiluted milk was superior for restoring body weight.<sup>9</sup>

Multiple RCTs showed that *Lactobacillus* supplementation shortened the duration of diarrhea for infants and young children<sup>10,11</sup> and reduced the risk of diarrhea persisting more than 3 days (relative risk [RR]=0.43; 95% CI, 0.34–0.53;  $P<.001$ ; number needed to treat [NNT]=4).<sup>11</sup> This probiotic can be reconstituted in oral rehydrating solution and administered 1 to 8 times daily,

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**TABLE**

**Evaluative strategies and therapeutic interventions for infant diarrhea**

Evaluation	Routine diarrhea*		Complicated diarrhea†		SOR	
	Recommended	Not recommended	Recommended	Not recommended		
Serology		X	X		B <sup>1</sup> , C <sup>2-3</sup>	
Stool culture		X	X		C <sup>2-3</sup>	
Intervention	<b>WHO ORS</b> (Osm 311 mmol/L)		X	X <sup>‡</sup>	A <sup>8</sup>	
	<b>ORS</b> (Osm ≤250 mmol/L)	X		X	A <sup>8</sup>	
	<b>Age-appropriate diet after hydration</b>	X		X	C <sup>2</sup>	
	<b>Continued breast-feeding</b>	X		X	B <sup>6,7</sup>	
	<b>BRAT diet</b>		X		X	C <sup>2,4</sup>
	<b>Lactose-free or dilute lactose diet</b>		X		X	B <sup>9</sup>
	<b>Lactobacillus (probiotic)</b>	X		X		A <sup>10,11</sup>
	<b>Antidiarrheal agents</b>		X		X	C <sup>2,4,12</sup>

\* Mild to moderate dehydration, diarrhea of short duration without bloody stools, severe systemic illness, suspected food poisoning, or recent foreign travel.  
 † Severe dehydration, prolonged diarrhea, or diarrhea with bloody stools, severe systemic illness, suspected food poisoning, or recent foreign travel.  
 ‡ Recommended for treatment of cholera.  
 ORS, oral rehydration solution; SOR, strength of recommendation; BRAT, bananas, rice cereal, applesauce, and toast.

depending on the formulation.

Antidiarrheal agents are not recommended (based on limited reviews and consensus reports).<sup>2-4,12</sup>

**RECOMMENDATIONS FROM OTHERS**

The Centers for Disease Control and Prevention (CDC) recommends oral rehydrating solution for mild to moderate dehydration, and boluses of normal saline or Lactated Ringer's (20 cc/kg) for severe dehydration. For frail or malnourished infants, boluses of 10 cc/kg should be given until hydrated.

The CDC also recommended against nutrition containing simple sugars (soft drinks, juice, gelatin desserts) due to high osmotic loads, but noted that diets containing some fats may have a beneficial effect on intestinal motility. They also recommended age-appropriate use of complex carbohydrates, meats, yogurt, fruits and vegetables. Zinc supplementation may also be beneficial (SOR: C).<sup>12</sup>

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## ■ CLINICAL COMMENTARY

### Exam should note fever, weight loss, abdominal tenderness, blood in the stool

The evaluation and management of an infant with diarrhea as always, begins with history. The length and severity of the illness, sick contacts, oral intake, travel, and characteristics of the stool are all important factors to consider. The physical exam should note presence of fever, weight loss, abdominal tenderness, and blood in the stool. Laboratory studies such as electrolytes, stool culture, and Wright stain are really only indicated if the child is severely dehydrated, unable to maintain hydration with oral intake and requires IV fluids, or if the episode is unusually protracted or the stool bloody.

A regular age-appropriate diet is essential, but parents should be counseled to avoid adding too much juice to the diet in an effort to rehydrate.

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## Is antibiotic prophylaxis effective for recurrent acute otitis media?

### ■ EVIDENCE-BASED ANSWER

For children who have recurrent episodes of clinically diagnosed acute otitis media (AOM), antibiotic prophylaxis significantly reduces recurrence, although the effect is not large (strength of recommendation: **A–**, based on 1 systematic review of randomized controlled trials [RCTs] with below-average quality and 1 subsequent RCT with conflicting results). Evidence is insufficient to suggest which antibiotic is most appropriate, the optimal length of prophylaxis, or the number of episodes of AOM needed to justify prophylactic treatment. Possible harms of antibiotics include vomiting, diarrhea, rash, and infection with antibiotic-resistant organisms.

### ■ EVIDENCE SUMMARY

A systematic review of antibiotic prophylaxis for recurrent AOM examined 9 RCTs with a total of 958 children. Recurrent AOM was defined as 3 or more episodes per 6 to 18 months. The studies were low to moderate in quality (mean methodologic quality score of 11.8 out of 29 possible points). The most commonly used antibiotics were amoxicillin, cotrimoxazole, and sulfamethoxazole, given for 3 to 24 months (dosing not reported).

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Children taking antibiotics had 0.11 (95% confidence interval [CI], 0.03–0.19) fewer episodes of recurrent AOM per patient-month than those taking placebo. The rate in the control group was 0.19 (95% CI, 0.13–0.26). Nine children would have to be treated per month to prevent 1 ear infection (NNT=9; 95% CI, 5–33). Only 2 of the 9 studies had statistically significant results; both used sulfisoxazole for 10 to 12 weeks and were of similar methodologic quality (12.5 out of 29 points).

A trend towards a better outcome in studies that used sulfisoxazole did not reach significance compared with those using other medications (ie, ampicillin, amoxicillin, cotrimoxazole). Shorter treatment intervals (<6 months) trended toward being more effective than longer intervals, but this also did not reach significance. Children with more frequent episodes of AOM did no better than those with less frequent episodes.<sup>1</sup>

Since that review was published, another study of prophylaxis for ear infections had been published. This randomized, double blind, placebo-controlled study enrolled 194 children aged 3 months to 6 years with at least 3 documented AOM episodes in the preceding 6 months. The children were given amoxicillin (20 mg/kg/d) either once daily (n=55) or divided twice daily (n=44) or placebo (n=59). Excluding 36 noncompliant subjects, the percentages without a recurrent episode were 63% for the placebo group, 64% for the once-daily amoxicillin group, and 61% for the twice-daily amoxicillin group. There was no significant difference in the incidence of new AOM episodes among the children in the 3 groups.<sup>2</sup>

A review article states: “Many children with acute otitis media do not benefit from antimicrobial therapy because the cause of their illness is not bacterial or the infection is cleared by the immune system without use of a drug. At present, we do not have clinical criteria for distinguishing which children are in need of antibiotic therapy for AOM.”<sup>3</sup> The lack of criteria for determining which children need antibiotic therapy for AOM makes it more difficult to select children for antibiotic prophylaxis against recurrent AOM.

## ■ RECOMMENDATIONS FROM OTHERS

The American Academy of Pediatrics and the American Academy of Family Physicians do not address antibiotic prophylaxis for recurrent episodes of otitis media in their guidelines. Both groups recommend modification of risk factors to decrease recurrent AOM, including promoting breastfeeding during the first 6 months, avoiding bottle-propping, reducing or eliminating pacifier use in the second 6 months of life, and eliminating exposure to secondhand smoke.

They also recommend pneumococcal conjugate vaccine to reduce vaccine-serotype pneumococcal otitis and live-attenuated influenza vaccine during respiratory virus season for children aged >2 years.

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## ■ CLINICAL COMMENTARY

### **Treatment options include observation, antibiotic prophylaxis, tympanostomy tubes; no option is ideal for all**

Treatment options for children with recurrent acute otitis media include observation with treatment of recurrences, antibiotic prophylaxis, or tympanostomy tubes. No option is ideal for all children.

Multiple factors can be weighed to choose more or less aggressive treatment including frequency and severity of infections, exposure to secondhand smoke, day care enrollment, sibling history, parental comfort and anxiety, presence of serous otitis media between episodes, time of year, and effect on overall hearing. Measures to prevent otitis media and reserving the diagnosis of acute otitis media for “true” purulent infections can help limit the number of children diagnosed with recurrent disease.

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## What is the diagnostic approach to a 1-year-old with chronic cough?

### ■ EVIDENCE-BASED ANSWER

Very few studies examine the evaluation of chronic cough among young children. Based on expert opinion, investigation of chronic cough should begin with a detailed history, physical examination, and chest radiograph (strength of recommendation [SOR]: C, expert opinion).<sup>1</sup>

Before pursuing additional studies, remove potential irritants from the patient's environment. Work-up for persisting cough should consider congenital anomalies and then be directed toward common causes of chronic cough like those seen in older children and adults, including postnasal drip syndrome, gastroesophageal reflux disease (GERD), and asthma (SOR: C).

### ■ EVIDENCE SUMMARY

The data on which expert opinion is based comes from case series of chronic cough in adults and older children in the setting of a specialty clinic.<sup>2,3</sup> A detailed history should attend to the neonatal course, feeding concerns, sleep issues, potential for foreign-body aspiration, medications, infectious exposures, family history of atopy or asthma, and exposures to environmental irritants such as tobacco smoke.<sup>1</sup> A dry,

barking, or brassy cough in infants suggests large airway obstruction; in older children, it is likely psychogenic. A wet, productive cough is associated with an infectious cause. A cough associated with throat clearing suggests GERD or postnasal drip syndrome.<sup>3</sup>

Chest radiography, although universally recommended, was only abnormal for 4% of older patients (age 6 years through adult) from one series.<sup>2</sup> Chest radiography may be most helpful for infants at increased risk for foreign-body aspiration. Cough from passive smoke exposure should improve with removal of exposure. There is no information on how long to wait for improvement.<sup>1</sup>

If the initial evaluation is not revealing, further investigation should focus on congenital anomalies, asthma, postnasal drip, and GERD. Aberrant innominate artery and asthma were the most frequent diagnoses among children aged <18 months old referred for otolaryngology consultation.<sup>3</sup> Because pulmonary function testing is not practical for infants, a trial of aggressive therapy in combination with a "cough diary" kept by the parents may be used to diagnose asthma.<sup>1</sup> Sinus computed tomography films are not routinely recommended to evaluate for postnasal drip, as sinusitis among children does not correlate well with postnasal drip.<sup>1</sup> GERD may present with chronic cough; however, there is insufficient evidence for a uniform approach to diagnosis of cough associated with reflux.<sup>4</sup>

After evaluating infants for common causes of chronic cough (or if suggested by the history or physical), less common causes should be explored (Table). Consider a sweat chloride test first, followed by tuberculin testing. More than one cause for chronic cough was found 23% of the time in adults.<sup>2</sup> Multiple causes of cough may be less common among infants, though no data confirm this.

Though it includes a mixture of adults and older children, a case series from pulmonary specialists finds pulmonary function tests with methacholine challenge the most helpful test.<sup>2</sup>

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TABLE

### Causes of chronic cough among children with normal chest radiograph

Category	Diagnoses
<b>Asthma</b>	Cough-variant asthma, hyperactive airways after infection
<b>Infectious</b>	Chronic sinusitis, otitis media with effusion, chronic bronchitis, bronchiectasis, chronic Waldeyer's ring infection, pertussis, parapertussis, adenovirus, tuberculosis
<b>Congenital</b>	
Narrowing airway	Aberrant innominate artery, vascular rings, bronchogenic cyst, esophageal duplication, subglottic stenosis, tracheomalacia, tracheal and bronchial stenosis
Aspiration	Gastroesophageal reflux, esophageal incoordination, tracheoesophageal fistula, cleft larynx, vocal cord paralysis, pharyngeal incoordination, achalasia, cricopharyngeal achalasia
Other	Tracheobronchial tree abnormalities, cystic fibrosis, immotile cilia syndrome, congenital heart disease, bronchopulmonary dysplasia
<b>Psychogenic</b>	Psychogenic cough
<b>Traumatic</b>	Foreign bodies of bronchus, trachea, larynx, nose, external auditory canal
<b>Environmental</b>	Tobacco exposure, low humidity, overheating, allergens, industrial pollutants
<b>Otologic</b>	Cerumen, foreign body, infection, neoplasm, hair
<b>Neoplastic</b>	Larynx: Subglottic hemangioma, papillomatosis Tracheobronchial tree: Papillomatosis, bronchial adenoma Mediastinal tumor causing tracheobronchial compression
<b>Cardiovascular</b>	Rheumatic fever, congestive heart failure, mitral stenosis

*Adapted from:* Holinger 1986.<sup>3</sup>

Case series from otolaryngology find endoscopy to be the most helpful, but it also includes a mix of older patients.<sup>3</sup> Therefore, it seems likely that primary care physicians already appropriately refer patients to the correct specialists for evaluation. The optimal time to refer patients is unknown. We identified no reports from primary care settings. The question is an appropriate topic for primary care research.

#### ■ RECOMMENDATIONS FROM OTHERS

A guideline from Finaldn suggests referral for investigations of asthma, allergy, and GERD.

Infectious diseases, the presence of foreign bodies, and psychogenic causes should also be considered.<sup>5</sup>

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### ■ CLINICAL COMMENTARY

#### **Inquire about exposure to irritants, feeding habits, infection, family history of asthma**

A comprehensive detailed history is the first important diagnostic step in the approach to a chronic cough in a 1-year old. The primary care provider should inquire about the infant's exposure to environmental irritants such as tobacco smoke, their feeding habits, possible foreign-body aspiration, infectious exposure, and the family history of asthma. Environmental pollution in areas such as where I practice (Houston, Texas) can be a significant factor in evaluating infant with chronic cough. A chest radiograph should be considered after a thorough physical examination.

After an initial evaluation, further investigation should focus on the common causes of chronic cough such as postnasal drip, asthma, and GERD. Because of the high frequency of postnasal drip, the patient can be empirically started on antihistamine/decongestion combination. The primary care provider may consider an empirical treatment for gastroesophageal reflux disease if suggested by the history and physical examination. If no improvement is seen after several weeks, the patient should be referred to the appropriate specialist for evaluation of asthma, congenital anomalies, or other less common cause of chronic cough.

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## **Can transvaginal ultrasound detect endometrial disease among asymptomatic postmenopausal patients?**

### ■ EVIDENCE-BASED ANSWER

Transvaginal ultrasound should not replace endometrial biopsy for detection of endometrial disease among asymptomatic postmenopausal patients. Endometrial biopsy has been considered a standard for the clinical diagnosis of endometrial disease among asymptomatic patients, but it is invasive, may be uncomfortable, and may not be able to be performed for some patients with cervical stenosis. Ultrasound evaluation is less invasive and more comfortable and can be performed for patients with cervical stenosis. The positive predictive value of ultrasound is not adequate to allow it to replace endometrial biopsy for screening of asymptomatic women (strength of recommendation: **B**, based on cohort studies).

### ■ EVIDENCE SUMMARY

In a trial of postmenopausal estrogen use, 448 asymptomatic postmenopausal women were monitored with both endometrial biopsy and transvaginal ultrasound.<sup>1</sup> Biopsy detected 11 cases of serious disease. At a threshold of 5 mm for endometrial thickness, ultrasound had a positive predictive value of 9% for detecting any abnormality with 90% sensitivity and 48% specificity. At this threshold, more than half of women evaluated with ultrasound would require endometrial biopsy as well, and only 4% of these patients would have serious disease. This study concludes that transvaginal ultrasound has a poor positive predictive value but a high negative predictive value for detecting serious endometrial disease for this asymptomatic population.

An additional study evaluated 1926 asymptomatic postmenopausal women with trans-

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vaginal ultrasound.<sup>2</sup> Of these, 1833 had endometrial thickness <6 mm and 1750 of this cohort underwent biopsy. Five cases of serious endometrial abnormality were identified in this group (1 adenocarcinoma and 4 atypical hyperplasia). Specificity in this group was 98%, but sensitivity for accurately detecting an abnormality was low at 17%.

The negative predictive value was greater than 99%. An inadequate number of patients with endometrial thickness >6 mm were biopsied (45%) to allow for accurate calculation of positive predictive value in those with a >6 mm stripe. The study concludes that transvaginal ultrasonography may not be an effective screening procedure for this population.

The relevance of several other studies is affected by small sample size (range, 36–85).<sup>3–6</sup> Other studies did not attempt to biopsy all patients screened with ultrasound.<sup>7,8</sup>

## ■ RECOMMENDATIONS FROM OTHERS

The National Cancer Institute states finds the evidence insufficient to recommend any routine screening for endometrial cancer with either endometrial biopsy or transvaginal ultrasound. The American Cancer Society does not recommend routine screening of asymptomatic patients for endometrial cancer. They recommend prompt recognition and evaluation of abnormal uterine bleeding. The US Preventive Services Task Force and American Academy of Family Physicians have not issued recommendations related to endometrial cancer screening.

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## ■ CLINICAL COMMENTARY

### No need to screen postmenopausal women for endometrial disease

This Clinical Inquiry appears to draw appropriate conclusions to the question as presented. However, the question implies tacit approval of the notion of screening asymptomatic postmenopausal women. As pointed out above, *no* major organization recommends screening of these women. When reviewing a study we must also ask if the original study question is similar to our own clinical question. A critical piece of information regarding this answer is that references 1 and 2 are “nested” studies done within the context of large drug trials originally designed to answer very different questions. These asymptomatic women were being screened as part of the study protocol to ensure drug safety. Any effort on our part to apply this data to our asymptomatic patients should be considered with this significant limitation in mind.

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## TYPE II CLINICAL INQUIRIES

### How useful is ultrasound to evaluate patients with postmenopausal bleeding?

#### ■ EVIDENCE-BASED ANSWER

Using a threshold of  $\leq 5$  mm, transvaginal ultrasound (TVUS) can be used to identify those patients with postmenopausal bleeding who are at low risk for endometrial cancer, polyps, or atypical hyperplasia at a sensitivity comparable with that of endometrial biopsy and dilatation and curettage (D&C) (strength of recommendation: **B**, based on systematic reviews of consistent exploratory cohort studies.)

#### ■ EVIDENCE SUMMARY

A 1998 meta-analysis of 35 exploratory cohort studies published between 1966 and 1996 included a total of 5892 women with postmenopausal bleeding.<sup>1</sup> TVUS evaluations were followed by endometrial tissue sampling and results were compared. Using endometrial thickness of  $\leq 5$  mm as the threshold, ultrasound was very accurate at *ruling out* patients with endometrial cancer but only fair at *diagnosing* cancer (likelihood ratio for a positive test [LR+]=2.5; LR for a negative test [LR-]=0.06). In addition, the 5-mm threshold was accurate at ruling out any endometrial abnormality (cancer, polyp, atypical hyperplasia: LR- = 0.01). The authors suggested that TVUS can reliably rule out significant endometrial disease among postmenopausal women with vaginal bleeding.

A 2002 meta-analysis of 57 cohort studies, without consistently applied reference standards, published between 1966 and 2000 included a total of 9031 women with postmenopausal bleeding.<sup>2</sup> Because many of the studies were felt to use inadequately stringent criteria for diagnosis, the authors limited their final analysis to

TABLE

#### Differential diagnosis of postmenopausal bleeding

Histologic diagnosis	Incidence (n=1138)
Atrophy	59%
Endometrial polyp	12%
Hyperplasia	10%
Endometrial cancer	10%
Hormonal effect	7%
Cervical cancer	2%
Other	<1%

Source: Karlsson et al 1995.<sup>4</sup>

only 4 studies. They concluded that a negative result using a 5-mm threshold rules out endometrial pathology with fair certainty (LR- = 0.21).

#### ■ RECOMMENDATIONS FROM OTHERS

A Consensus Conference Statement from the Society of Radiologists in Ultrasound recommended that either TVUS or endometrial biopsy could be used in the initial evaluation of patients with postmenopausal bleeding.<sup>3</sup> Using a threshold of  $>5$  mm as abnormal, they concluded that the sensitivities of TVUS and endometrial biopsy are comparable when "sufficient tissue" is obtained with endometrial biopsy. They felt that data was currently insufficient to clearly state which technique is more effective.

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**The false negative rate for TVUS compares favorably with endometrial biopsy and D&C**

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**CLINICAL COMMENTARY**

**TVUS is an effective, relatively noninvasive way to rule out significant pathology**

Postmenopausal women need accurate diagnostic evaluation when they have abnormal bleeding. While the majority have a benign cause of bleeding, such as atrophic endometrium, many have significant pathology, including cancer (**Table**). Many older patients are reluctant to undergo invasive sampling studies. Cervical stenosis, a common occurrence in this age group, further complicates matters. Evidence suggests that TVUS with a full endometrial thickness of 5 mm or less, full visualization of the cavity, and no other abnormal findings, can identify patients at low risk for significant abnormalities. The false negative rate for TVUS (8%) compares quite favorably with endometrial biopsy (5%–15%) and even D&C (2%–6%).<sup>1</sup> TVUS is an effective and relatively noninvasive strategy for ruling out significant pathology. Given the false negative rates of these techniques, all patients with postmenopausal bleeding require close follow-up.

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